Report of the Workgroup on Blood and Blood Products

Background and Progress Since Coolfont

AIDS was first recognized to be transmissible through blood transfusions in late 1982, well before the discovery that the HIV causes this syndrome. Early in 1983, blood collecting agencies, supported by PHS recommendations, introduced the practice of asking potential donors whose behavior put them at increased risk for HIV infection to exclude themselves voluntarily. After the discovery of HIV, serological tests for HIV antibody were rapidly developed and licensed by the Food and Drug Administration (FDA). By mid-1985, these tests were used for screening virtually all donated blood and plasma in the United States. These advances have resulted in a blood supply that is among the safest in the world. Nevertheless, there remain unresolved issues in transfusion-related AIDS and HIV infection.

By late September 1988, more than 74,000 AIDS cases among adults and adolescents had been reported to the CDC, as well as more than 1,100 cases in children under age 13. Included among the totals were 1,833 cases of transfusion-associated AIDS and 695 cases of coagulation factor-associated AIDS in the adult/ adolescent population, and 152 cases of transfusion-associated AIDS and 70 cases of coagulation factor-associated AIDS in the pediatric population. Thus transfusion-associated AIDS represented 3 percent of the total AIDS cases in adults and 14 percent in children, while cases related to hemophilia/coagulation disorders represented 1 percent of adult and 6 percent of pediatric AIDS cases.

Whereas transfusion-associated AIDS represents only 2 percent of AIDS cases among adult males, it represents 11 percent among adult females. The proportion of total cases that have been transfusion-associated has remained relatively constant over the past 3 years.

Only 13 cases of HIV infection associated with transfusion of screened blood have been reported to CDC since 1985. However, depending on the prevalence of infection in the donor population, estimates of the risk for transfusion-associated transmission range from 4 per million to 25 per million (representing a maximum of 1 for every 40,000 units of blood transfused). Also, at least 7 cases of HIV transmission have occurred from use of dry-heated antihemophilic Factor VIII made from screened plasma, and approximately two dozen additional suspected cases are under study.

These estimates, while representing a risk that is low in comparison with many accepted medical risks, necessitate a comprehensive effort to improve the current system of donor exclusion and blood testing. In particular, there are recognized deficiencies in the systems used by blood and plasma establishments to educate donors about risk behaviors and thus elicit their cooperation in voluntary deferral. Because a disproportionate number of HIV positive donors are black or Hispanic, blood and plasma centers must carefully establish the best methods to reach these populations and educate these donors about the need to refrain from donating if they practice high-risk behavior.

Attempts to improve laboratory screening of donated blood rest on the scientific effort to better define the duration of the time period between infection and seroconversion--the incubation period--and to develop tests for other virus markers that can be detected during this interval. More generally, there is a continued need to improve our understanding of not only the risks currently associated with transfusion but also the degree to which existing programs have been effective in reducing these risks. For example, the practice of confidential unit exclusion, in which donors are able to indicate confidentially that their blood should be used only for laboratory purposes and not transfusion, has been recommended by FDA and universally adopted. However, the practice is not standardized, nor is it known to work equally well in all systems.

Another issue of concern is quality control. Routine FDA inspections of blood-collecting establishments found instances in which, because of testing or clerical errors, components prepared from units that tested positive for HIV or other infectious agents were released for transfusion or further manufacture. Although, to date, followup evaluations of the donors of these units have shown that they were not true-positive for antibodies to HIV, these incidents have led to a demand for improvements in laboratory quality assurance and test proficiency, as well as upgraded systems for monitoring quarantined inventories.

A related concern involving the safety of workers who may come in contact with infectious donated blood has developed in the wake of reported HIV seroconversions in three health care workers after accidental cutaneous exposure to blood, and in two laboratory workers involved in handling industrial-

scale virus concentrates. A set of overlapping efforts to define the requirements for worker safety has emerged. In particular, the Occupational Safety and Health Administration (OSHA) and the FDA are both involved in monitoring blood-handling establishments.

New issues that have arisen related to testing include the need to assess the sensitivity and specificity of screening tests that utilize recombinant DNA-derived and synthetic peptide antigens as substrates for antibody detection. Also, the potential benefit of a test for viral antigen needs to be evaluated on a large scale.

The discovery of a second class of AIDS virus, HIV-2, as a common infection in some regions of West Africa, with secondary spread to countries of Western Europe, indicates a need for a new test since the existing tests for HIV-1 antibodies are not fully cross-reactive with HIV-2. So far, surveillance studies in the United States have included tests on 8,500 random donors and more than 14,000 individuals at increased risk of infection with HIV-1. Although no cases of HIV-2 infection have been found in these groups to date, continued surveillance is needed. To reduce the risk of drawing units infectious for HIV-2, FDA has recommended donor exclusion criteria based on geographic origin--that is, donors from areas of the world where HIV-2 is endemic.

Disease transmission can also be reduced by decreasing the use of homologous blood transfusions. Alternatives that already exist include autologous donations, intraoperative blood salvage, and blood substitutes. Pilot evaluations around the country have shown the practicality of autologous donation for elective surgery. Other programs have demonstrated that homologous blood use can be markedly reduced by perioperative and emergency blood salvage. Although still under clinical study, the use of a drug known as Desmorpressin acetate (DDAVP) can provide a transient boost in the levels of Factor VIII and Von Willebrand factor in patients with mild to moderate hemophilia, and may possibly produce significant benefit in nonhemophilic surgical patients. In the future, hematopoietic growth factors may be useful in augmenting autologous donations and/or replacing some homologous transfusions. Major impact could also be achieved by enhancing physician awareness of the indications for and hazards of transfusion, and of potential alternatives to the use of homologous blood.

New methods of purification and viral inactivation have virtually eliminated the risk of transmitting HIV (as well as hepatitis B and hepatitis non-A non-B) through clotting factor concentrates, which are derived from plasma (although comparable methods have yet to be developed to remove or inactivate infectious agents in cellular blood products). In addition, recombinant Factor VIII may soon be available. However, the benefits of these new products to patients is threatened by their scarcity and/or markedly increased cost. Special efforts will be needed to address these problems. In addition, continued research is needed to define the pathogenesis of HIV infection in hemodialysis and the role of transfusion or the presence of viruses other than HIV in blood products as potential cofactors for progression of HIV-related disease.

Responses to the Coolfont Recommendations

The Coolfont report *(1)* contained several recommendations designed to prevent the transmission of HIV in blood and blood products. The recommendations addressed the following areas: (1) deferral of persons at risk for HIV infection; (2) establishment of registries of deferred donors; (3) serologic tests for HIV infection; (4) testing of donated organs, tissues, and semen for antibody to HIV; (5) elimination of unnecessary transfusions; (6) studies of the role of anti-HIV immunoglobulin in passive immunization; and, (7) approaches to treatment and prevention.

Donor deferral

Various approaches have been taken to increase the effectiveness of deferral measures for all persons at risk for HIV infection. CDC, FDA, and NIH have all undertaken studies to elucidate demographic and other information relating to donation by persons at risk of HIV infection.

CDC, for example, has conducted a study of HIV seropositive blood donors at three blood collection centers. More than 80 percent of these donors had a known risk factor for HIV infection. Compared with seronegative donors, the seropositive donors--especially men who described themselves as bisexual--were more likely to be black or Hispanic. CDC is initiating studies with more than 20 blood collection centers to define more specifically the reasons for blood donation by seropositive persons. Study results should help in the design of more effective donor deferral strategies.

FDA completed a followup study of blood donors with repeatedly reactive enzyme-linked immunosorbant assay (ELISA) screening tests and variable Western blot (WB) test results. The study confirmed that WB is important as a specificity test, and suggested the importance of improving efforts to exclude donors with known risk factors. The NIH Clinical Center's Department of Transfusion Medicine is conducting a similar study, comparing donors who are ELISA positive and WB variable with ELISA-positive, WB-negative subjects. The Clinical Center's findings have been similar to those of FDA.

Information is also being obtained from a transfusion safety study and other research supported by NIH's National Heart, Lung, and Blood Institute (NHLBI). In general, most donors with HIV antibodies have engaged in the behaviors known, since the beginning of the epidemic, to increase the risk of HIV infection, but data suggest that the epidemiology of infected donors may be gradually changing.

An important element in donor deferral is communication by the blood banking community with potential donors. FDA is supporting a contract to develop a strategy to improve communication with donors about self-deferral, simplified donor education materials, and effective mechanisms for reaching target populations. In 1987 NHLBI began a National Blood Resource Education Program (NBREP) with a workshop to identify areas of concern. A key theme of the initial workshop was: "The public needs to understand:...Who should exclude themselves from donating and why." A subcommittee of the Coordinating Committee for NBREP is developing goals and priorities for public education. NHLBI is also investigating the relative benefits of developing strategies that focus efforts on individuals with risk behavior versus strategies based on laboratory testing of the donated blood itself.

Two other issues associated with self-deferral have been addressed since Coolfont. The first has to do with providing a way for donors who do not self-exclude, but who have doubts about the suitability of their blood, to indicate that their blood should not be used for transfusion. Methods to achieve confidential exclusion have been recommended to blood establishments by FDA and are in place voluntarily in all blood banks.

The second issue is implementing the use, in all blood banks, of a signed donor consent form in which the donor specifically states that he or she has no known risk factors for transmission of infections. Such forms are now being used in all blood establishments, in compliance with FDA recommendations.

Maintaining donor deferral registries

In keeping with the Coolfont recommendations, FDA has continued to require all blood and plasma establishments to maintain deferral registries of donors with repeatedly positive tests for HIV antibody and other markers of transmissible diseases, and to check the registries at each donation. The reason for permanent donor deferral need not be indicated on the registries, nor is it routinely available outside the establishment where the testing is performed.

Serologic tests

NHLBI has amended seven contracts to develop new and more sensitive tests to measure HIV antibodies, antigens, or nucleic acids in blood. One year into the course of these 5-year contracts several approaches seem promising, but none has yet been brought to the level where it can be used in blood banking.

FDA has also supported the development of more sensitive screening tests for HIV by continuing to give high priority to reviews of investigational new drug applications, product applications, and product amendments in this area. One new product and five product amendments have been approved since June 1987. In March 1988, FDA, CDC, and NIH cosponsored a public workshop on the uses of recombinant and synthetic antigens of HIV for antibody detection. FDA and CDC have collaborated on a study to determine whether HIV-2 infections are present in blood donors or other U.S. populations at high risk for HIV infection.

CDC has studied the occurrence of HIV infection in persons who received blood from seronegative donors. These studies indicate that a small number of persons donate blood soon after they are infected with HIV but before they develop antibody detectable by commercial test kits. These findings provide an impetus for development of more sensitive serologic tests. CDC, FDA, and NIH will participate in a large-scale study by the American Association of Blood Banks to determine the potential value of testing donated blood for HIV antigen.

Testing of donated organs, tissues, and semen

Although the Coolfont Report recommended that HIV antibody testing for donors of organs, tissues, and semen be made mandatory, FDA has no current responsibility for transplantation medicine. FDA has, however, instituted several other measures. It has supported a recommendation made by CDC *(2)* for serologic screening of sperm donors at the time of donation, a retest after 6 months, and a 6-month quarantine of sperm donations. FDA has recommended a similar system of 6-month quarantine and donor retesting for red cell immunization. FDA is currently preparing to initiate actions to regulate sperm banks. The operating policies of the Organ Procurement and Transplantation Network require HIV testing of organs to be transplanted.

Eliminating unnecessary transfusions

Efforts to eliminate unnecessary transfusions have been stepped up. Nearly 5 years ago, NHLBI started a program of academic awards to improve the teaching of transfusion medicine in medical schools and during postgraduate training. This program has focused on the training of medical students and house officers in the proper use of blood and blood components, as well as continuing education programs for physicians already in practice. Also, NHLBI has organized national consensus conferences on the use of plasma, platelets, and red cells.

NHLBI's National Blood Resource Education Program has, as its second goal, to "ensure that blood and blood components are transfused only when therapeutically appropriate." A paper is being developed to provide scientific support for transfusion decisions concerning red cells, platelets, and fresh frozen plasma. The paper will provide a basis for undergraduate, postgraduate, and continuing medical education, as well as for audits and quality assurance activities at blood-handling establishments.

Through special labeling, FDA has facilitated the use of autologous donations as an alternative to homologous transfusions. Most of the FDA effort in the last year has concerned an attempt to guarantee that units collected for autologous use are not "crossed over" for homologous use without meeting all of the usual donor suitability criteria. To build an information base, FDA has conducted a 10-year retrospective review of the adverse consequences of transfusion.

Anti-HIV immunoglobulin

Under an NHLBI contract, an HIV hyperimmune globulin was prepared from the plasma of donors who had an anti-HIV neutralizing titer of at least 1:256. This hyperimmune globulin was administered to chimpanzees, but failed to protect them from a challenge dose of HIV. As part of this study, a panel of sera was assembled from individuals who were at various stages of HIV infection, and whose sera demonstrated varying titers of antibodies to HIV. This panel was submitted to a number of laboratories for analysis of neutralizing antibodies, antibody-dependent cell cytotoxicity (ADCC), and other anti-HIV activities. Evaluation of the results of this multi-laboratory study is incomplete at this time, but some preliminary observations can be made. There is general agreement among the laboratories as to which specimens were strongly reactive, weakly reactive, and negative. Nevertheless, the level of agreement is not as good as one would expect if one were to use a well-defined and standardized test. It is difficult at this time to determine the meaning of any assays with regard to the clinical significance or protective effect of antibodies to HIV.

Treatment and prevention

The Coolfont report recommended that all treatment and prevention approaches should include information and counseling on sexual and perinatal transmission of HIV, availability of family planning services, and availability of voluntary serological testing for HIV.

Cooperative efforts by the National Hemophilia Foundation, the Health Resources and Services Administration's Bureau of Maternal and Child Health, and CDC have established regionalized teams whose goal is to reduce risk and to alleviate stresses on the family. These teams, which work within the existing network of 25 Federally funded Comprehensive Hemophilia Treatment Centers, have identified the issues most important to the hemophilia community and have designed and implemented an intensive education campaign to address them.

The Federal Government has an important role to play in addressing the many problems associated with the safety of the Nation's blood supply. There is a need for the Government to support studies that will result in better scientific understanding of HIV transmission and methods of prevention relevant to transfusion. Support is also needed for developing methods to improve the current level of communication with donors and to educate physicians. Government involvement in monitoring laboratory safety and testing proficiency will need to continue. Government efforts will include FDA regulation to maintain standards for testing and transfusion practices and to provide rapid review of new products; continued epidemiologic studies and surveillance by CDC to define new elements of risk and focus increased attention on laboratory proficiency; and continued funding, by NIH, of research proposals in multiple areas, including new technology and studies to evaluate the current blood collection, screening, and transfusion system.

Issue: Transfusion-Associated AIDS/HIV Infection

Goal: Further define the epidemiology of transfusion-associated AIDS and HIV infection.

Objectives:

- Initiate a national program to upgrade the computer base of the major blood centers and to centralize collation of the cumulated data. The data base should include information on the demographics of the donor population and the frequency of blood donation. Since information on transfusion recipients is not readily available to blood centers, it must be obtained independently, for instance, through a large- scale epidemiologic study.

- Continue to utilize available information on transfusion-associated HIV infection to calculate the projected incubation period between infection and disease.

- Refine determination of the risk of a person becoming infected if exposed to an HIV antibody-positive blood unit.

- Better define the duration of the "window" between time of infection and presence of HIV antibody in blood.

- Support additional studies to determine the current risk that a blood recipient will develop HIV infection following receipt of a unit from a donor who at the time of donation tests negative for HIV antibody, but who is potentially infectious.

- Continue the current program of surveillance of transfusion-associated AIDS cases. Donor and recipient tracing should continue.

- Continue to support "look-back" programs (which attempt to identify recipients of blood from a donor later found to be HIV antibody-positive), including specific cross-checking between AIDS case lists and donor lists by State Health Departments, consistent with applicable law.

Goal: Determine the risk of HIV infection and AIDS among recipients of clotting factor concentrates.

Objectives:

- Continue long-term investigations of hemophilia cohorts to determine the contribution of inactivated HIV inoculation to the total immune response in the HIV-infected hemophiliac and to determine the role of cofactors in infection outcome.

- Continue to evaluate the effectiveness of processes to inactivate virus in clotting factor by surveillance for instances of HIV seroconversion occurring as a result of administration of these products, and also by *in vitro* quantitation, including assessments of the role of protein concentration and various additives.

Issue: Continued Efforts to Improve the Safety of the Blood Supply

Goal: Improve early detection of HIV infection.

Objectives:

- Support the study of HIV antigen and other markers of infection in 500,000 blood donors.

- Support independent review of the issue of "zero risk" in the blood supply, using HIV antigen as the model. Because "zero risk" can never be a practical reality, there is a need to define a level of acceptable risk.

- Evaluate antibody tests employing recombinant and synthetic antigens both as screening and as confirmatory assays.

- Encourage further development of other methods of virus detection such as gene amplification by the polymerase chain reaction

(PCR) technique, while recognizing that its application to blood bank screening is not practical at this time.

- Reassess the donor reentry algorithm, a tool for screening out potentially infectious donors, to determine whether it can be simplified without compromising blood safety.

- Improve the Western blot test and/or develop alternatives:
  - Continue to refine the Western blot test to enhance standardization and increase specificity.
  - Evaluate new technologies, including the use of multiple recombinant antigens or synthetic peptide antigens and PCR, as substitutes for the Western blot.
  - Establish long-term clinical and serologic followup of people with indeterminate Western Blot results.
  - Evaluate the infectivity of individuals with indeterminate Western blot results.

Goal: Improve the effectiveness of donor deferral.

Objectives:

- Conduct studies of seropositive blood donors in order to identify characteristics that could be used to improve current donor exclusion criteria.

- Determine the usefulness of a history of sexually transmitted diseases as a surrogate marker for HIV infection.

- Determine whether there is an increased risk of recent seroconversion with first-time blood donors.

- Determine whether donor education can diminish donations by persons likely to be in the "window" between infection and seropositivity.

- Support objective studies of donor education, enlisting the assistance of advertising and marketing experts, to improve the effectiveness of education efforts and donor compliance with self-deferral.
  - Develop messages targeted to high-risk population groups or subgroups.
  - Let donors know that testing is not always 100-percent effective.

- Obtain and analyze data that will determine the benefit of a nationwide donor deferral registry.

- Assess and standardize methods of confidential unit exclusion.

- Sustain volunteerism in blood donation, reducing pressures that may induce unsuitable donors to donate and providing incentives to encourage donations by persons with low risk for HIV infection.
  - Encourage members of low risk populations to donate blood.
  - Encourage consideration of the medically appropriate use of iron as an adjunct to frequent donation, specifically in some women who may readily become iron-deficient.
  - Devise and implement measures to increase the availability of alternative test sites for HIV antibody testing and counseling. In particular, the waiting time for testing at these sites must be decreased.

Goal: Remove or inactivate viruses in cellular blood products.

Objective:

- Support studies of virus removal and/or inactivation in cellular blood components, especially platelets.

Goal: Develop alternatives to blood transfusion.

Issue: Medical Practices Surrounding HIV Testing and Notification

Goal: Standardize medical practices related to HIV testing and notification.

Objectives:

- Advise physicians that ELISA and Western blot tests are available as clinical diagnostic tests, and that individuals at increased risk of HIV infection should be tested and counseled. Specifically they should consider testing persons who received blood transfusions between 1978 and 1985.

- Develop standard HIV testing sequences for use in clinical decision-making.

- Ensure that all blood and plasma collection facilities provide confirmatory testing and coun-

seling for persons with positive tests. Counseling should include consideration of partner referral or notification.

Issue: HIV-2 Risk to the Blood Supply

Goal: Monitor the epidemiology of HIV-2.

Objective:

- Continue surveillance for monitoring the prevalence of HIV-2. This should be done in multiple geographic areas, and should particularly assess persons recently emigrating from Africa, persons sharing needles, and persons with multiple sexual contacts.

Goal: Continue specific efforts to protect the blood supply from HIV-2 infection.

Objectives:

- Continue to exclude donors from areas of the world where HIV-2 infection is endemic, and consider whether the exclusionary areas should be broadened.

- Develop a specific practical serologic test for HIV-2 infection that could be used should surveillance data indicate the need for it.

Issue: Monitoring Procedures in Blood and Plasma Collection Facilities to Prevent Errors in Testing or Inappropriate Release of Units

Goal: Assess the effectiveness of current management systems to prevent the inadvertent release of potentially infectious products.

Objectives:

- Direct particular attention to the management of recovered plasma and autologous donations.

- Support appropriate systems research studies, such as uses of computer software, equipment for automation, and standardized bar codes.

- Validate and monitor quality control procedures used for serologic testing by blood collection establishments.

Issue: Ensuring the Safety of Workers in Blood and Plasma Collection Facilities

Goal: Establish appropriate safety procedures.

Objective:

- Cooperate with the Department of Labor in developing biosafety standards for blood collection establishments and assess compliance with these standards.

Goal: Define risks to workers.

Objectives:

- Address the need for employee serum banks or for periodic serologic testing of employees of blood collection establishments, as part of the development of comprehensive PHS policies regarding serologic testing and management of employees with an occupational risk of HIV infection.

- Define and address the specific hazards to personnel in different areas of blood and plasma establishments.

Issue: Reducing the Risk of HIV Transmission by Donated Tissue

Goal: Strongly support donor testing for HIV and other transmissible agents as a standard of practice in organ and tissue transplantation and sperm banking.

Goal: Assess the value of rapid screening tests for HIV antibody in the transplantation setting.

Issue: Enhancing Use of Alternatives to Homologous Transfusion

Goal: Initiate studies to define the medical indications for autologous donation.

Objectives:

- Encourage insurance carriers to accept valid indications for autologous transfusion, with the associated costs.

- In the absence of an anticipated need, such as elective surgery, discourage long-term storage of autologous blood.

- In the absence of data showing increased safety, initiate studies to better define the role of directed donation in comparison with routine homologous donation.

- Establish methods to ensure the safety of autologous collections for cross-over to homologous use.

- Support the medical practice of obtaining informed consent for homologous transfusion.

- Support research into the use of hematopoietic growth factors to enhance the use of autologous donation and/or substitute for homologous transfusion.

Goal: Identify ways to reduce neonatal exposure to the blood of multiple donors.

Issue: Problems Related to Care of Hemophilia Patients

Goal: Seek ways to minimize the cost of clotting factor products for hemophilia patients.

Objectives:

- Encourage additional mechanisms to cover the costs to patients for Factor VIII and Factor IX therapy that are not met by the insurance industry.

- Encourage the use of the least expensive available products made with techniques known to inactivate HIV and hepatitis viruses.

- Encourage investigations of methods to increase the production of Factor VIII, including recombinant DNA technology.

Goal: Sustain the supply of Factor VIII and Factor IX concentrates.

Objectives:

- In view of rapidly changing technology and market forces, sustain a 3-month inventory of Factor VIII and Factor IX concentrates for US distribution.

Goal: Improve overall care of the hemophilia patient.

Objectives:

- Support efforts to prevent discrimination against HIV-infected hemophiliacs.

- Encourage additional resources for comprehensive hemophilia care, including the costs of monitoring the immune system of HIV-infected patients, dealing with HIV-related disease, and responding to increased needs for family counseling and support.

- Target funding for outreach efforts, and counseling and testing for sexual partners of HIV-infected hemophilic men.

Issue: Addressing Misconceptions About the Safety of Blood Donation

Goal: Continue ongoing educational efforts to dispel misconceptions surrounding blood donation and blood safety.

References

1. Coolfont report: A PHS plan for prevention and control of AIDS and the AIDS virus. Public Health Rep 101:341-348, July-August 1986.
2. Centers for Disease Control: Semen banking, organ and tissue transplantation, and HIV antibody testing. MMWR 37:57-58,63, Feb. 5, 1988.