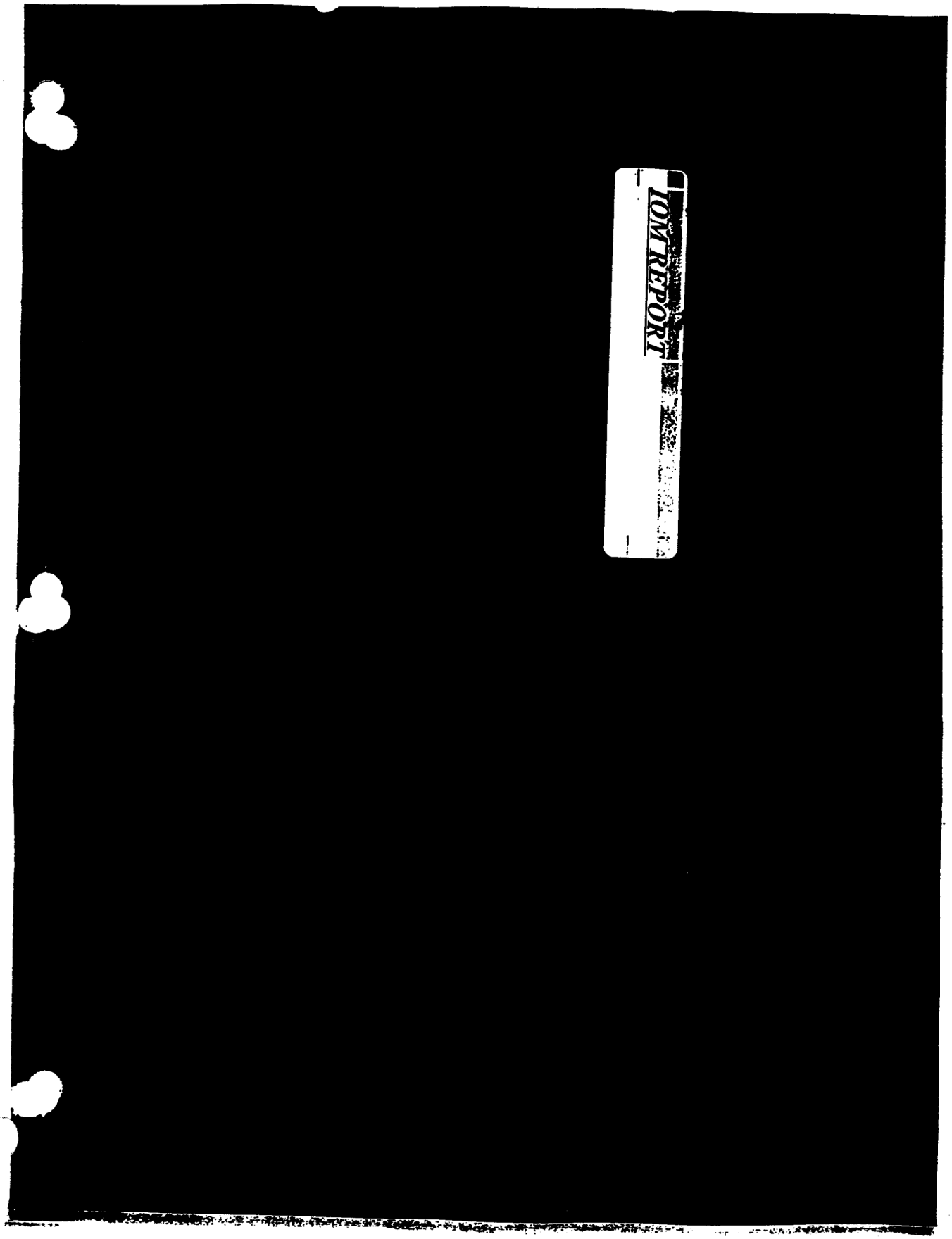

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Introduction

A nation's blood supply is a unique life-giving resource and an expression of its sense of community. In 1993, voluntary donors gave over 14 million units of blood in the United States (Wallace, et al. 1993). However, the characteristic that makes donated blood an expression of the highest motives also makes it a threat to health. Derived from human tissue, blood and blood products can effectively transmit infections such as hepatitis, cytomegalovirus, syphilis, and malaria from person to person (Institute of Medicine 1992). In the early 1980s, blood became a vector for HIV infection and transmitted a fatal illness to approximately half of the 16,000 hemophiliacs in the U.S. and to over 12,000 blood transfusion recipients (CDC, MMWR, July 1993).

Each year, approximately four million patients in the United States receive transfusions of over 20 million units of whole blood and blood components. The blood for the transfused products is collected from voluntary donors through a network of nonprofit community and hospital blood banks. Individuals with hemophilia depend upon blood coagulation products, called antihemophilic factor (AHF) concentrate to alleviate the effect of an inherited deficiency in a protein that is necessary for normal blood clotting. Bleeding due to this deficiency can cause serious damage to muscles, tissues, and joints, and can be fatal when there is bleeding into the brain. The AHF concentrate is manufactured from lots of "pooled" plasma derived from 1,000-20,000 or more, donors, exposing individuals with hemophilia to the high risk of infection by blood-borne viruses.

The safety of the blood supply is a shared responsibility of many organizations—the plasma fractionation industry, community blood banks, the federal government, and others. Public concern about the inherent risks of blood and blood products has led the federal government, through the agencies of the U.S. Public Health Service, to take the lead in ensuring blood safety. The Food and Drug Administration (FDA) has regulatory authority over plasma collection establishments, blood banks, and all blood products. The Centers for Disease Control and Prevention has responsibility for surveillance, detection, and warning of potential public health

risks within the blood supply. The National Institutes of Health (NIH) supports these efforts through fundamental research.

AIDS emerged as a threat to the safety of the blood supply in the early 1980s because of a unique confluence of events. Medical breakthroughs in cardiac surgery and other areas resulted in greater use of whole blood and its components. A new treatment for hemophilia, home infusion of AHF concentrate, grew rapidly and significantly improved the health and increased the life span of individuals with hemophilia. In addition, much of the medical community, as well as the country as a whole, believed that epidemics of infectious disease were a thing of the past. There were also many changes occurring in the government and society, such as a presidential mandate to lessen the regulatory role of government and increased public awareness that the homosexual population was enduring stigmatization and discrimination (Bayer 1983).

As evidence for blood-borne transmission of AIDS accumulated in 1982 and 1983, the Public Health Service had to deal with a very difficult problem. On the one hand, the U.S. blood supply was barely adequate to meet the urgent needs of day-to-day patient care. On the other hand, there was growing evidence that a blood transfusion posed a risk of causing a disease that was proving to be fatal for many. However, both the magnitude of the risk and the prognosis were still unknown. An examination of the efforts of the Public Health Service and others to cope with this problem provides a remarkable window into the making of public policy under duress and uncertainty.

The syndrome that came to be called AIDS was first noticed in homosexual men in 1981, but within a year epidemiologic evidence suggested that AIDS might also be a threat to recipients of blood and blood products. Several blood banks, blood collection agencies, and blood product manufacturers (i.e., plasma fractionators) took some actions to increase blood safety (e.g., donor education and screening to exclude known high risk groups; terminating plasma collection from prisons; and encouraging autologous donations to reduce the risk of infection as early as January 1983) yet thousands of individuals and members of their families became infected before the implementation of a blood test for HIV in 1985.

Perhaps no other public health crisis has given rise to more lasting anger and concern than the contamination of the nation's blood supply with HIV. In response, blood recipients and individuals with hemophilia who were infected during this period, their families and their physicians, and public and private officials with responsibility for blood safety have asked a series of questions: Could this tragedy have been averted? What institutions, policies, or decision processes, had they been in place in the early 1980s, could have helped to reduce the number of people infected with HIV? What should be done now to thwart future blood-borne infections? Mindful of the risks of retrospective analysis, this report attempts to answer these questions.

HIV INFECTION VIA BLOOD TRANSFUSION

Transmission of HIV occurred via fresh blood (whole blood, packed cells) and fresh blood components (platelets, fresh frozen plasma, etc.) as well as antihemophilic factor (AHF) concentrate. Most of the individuals were tested when the HIV test became available in 1985 and thus, the number of those that became infected is well documented. In December 1987, the CDC reported that of the estimated 15,500 hemophiliacs in the United States, approximately

9,465 (63%) were infected with HIV (CDC, MMWR, 1987b). Estimates of HIV infection in other patients (medical and surgical) due to transfusion are more difficult to obtain. A study by the CDC summarized data up to June 1992, by which time 4,619 persons (excluding hemophilia patients) had been reported with transfusion-associated AIDS. This number is thought to be an under-reporting because patients die from their basic disease before developing AIDS (as 50 percent of patients receiving transfusion die within six months) (Barker and Dodd 1989). On the other hand, some patients that are infected may not have been tested up to this day.

In addition to the documented cases of transfusion-associated AIDS, the CDC routinely estimates the transmission of HIV to blood recipients, as there continue to be a few cases each year (even since the implementation of the ELISA test). According to the CDC,

> the number can be approximated using prevalence of infection in donors, the efficiency of transmission, and the number of units transfused per year. In 1985, 0.04 percent of donations were positive for HIV antibody by Western blot assay. If 0.04 percent had been the seroprevalence among donors the years prior to screening, if all seropositive units had transmitted infection, and if each unit had gone to a different recipient, then 7,200 of the approximately 18 million components transfused in 1984 might have transmitted infection. If 60 percent of these recipients have died from their underlying disease, then approximately 2,900 living recipients who acquired transfusion-associated HIV infection in 1984 would remain. Most of these would be asymptomatic. . . . Mathematical projections from reported transfusion-associated AIDS cases estimate that approximately 12,000 people now [1987] living in the United States acquired a transfusion-associated HIV infection between 1978 and 1984 [CDC, MMWR, 1987a].

COMMITTEE CHARGE

Individuals with hemophilia, transfusion recipients, and their families have raised serious concerns about why there were not better safeguards and warning systems to protect them from viruses transmitted by blood products. Could viral inactivation processes for blood products have been developed more rapidly? Were appropriate measures taken to eliminate high-risk donors from the blood supply? Were the necessary regulations to ensure the safety of blood and blood products enforced? Were consumers of blood and blood products appropriately informed of the possible risks associated with blood therapy and were alternatives clearly communicated?

In response to these concerns, the Secretary of Health and Human Services asked a Committee of the Institute of Medicine (IOM) to review the scientific evidence that was available to decision makers during the early 1980s when the AIDS epidemic emerged, to examine the decision-making processes, and to evaluate the actions taken to contain the epidemic. Of equal importance, the Secretary asked the Committee to recommend a framework for steps that could prepare the nation to deal effectively with future threats to the blood supply. The IOM established a committee whose charge was to review and evaluate the following areas: the history of efforts to assure blood and blood product safety, efficacy, and availability; the regulatory process for governing blood and blood products; the history of the transmission of the AIDS virus through the blood supply; the roles and responses of government and other agencies, health organizations, plasma fractionators, and medical care providers; research on blood and blood products; and the decision-making processes that followed the first suspicions

that the blood supply was a vector for transmitting AIDS. The Committee's charge did not include the development of assertions about what should have been done at the time, nor did it include conducting a comprehensive organizational analysis.

Within the emotion-laden and potentially adversarial atmosphere of a public health tragedy, the Committee engaged in a systematic inquiry. The Committee framed its approach by examining four topics that are essential components of a focused strategy for ensuring the safety of the blood supply: blood product treatment; donor screening and deferral; regulation of removal of contaminated products from the market; and communication of risk to physicians and patients. The Committee then tested a range of hypotheses to explain why decision makers acted as they did. These hypotheses take account of the legal authority of relevant organizations; the information available to them; the countervailing public health considerations and scientific knowledge that influenced particular decisions; the resource limitations that constrained organizations; the institutional, social, and cultural obstacles; the public or private interest motivations of organizations; and the economic and political incentives that influenced decisions.

To understand how events unfolded over the course of the AIDS epidemic and develop a chronology, the Committee sought to identify the critical events that would illuminate the decision making process. The Committee asked each of the major organizations to list several events that they felt were the most important and to give the reasons for their choices. The Committee used this information to develop a chronology and focus its analysis on specific events.

Historical information was obtained from the key contacts at each of the organizations. The Office of the Assistant Secretary of DHHS identified sources of information within the federal service; and others representing non-government agencies made themselves known to the IOM Committee and staff. Among the topics for literature searches were: history of hemophilia; history of blood collection activities; scientific knowledge about HIV; viral inactivation processes; hepatitis; risk communication; social and ethical implications of AIDS; and regulations concerning blood products. The Committee obtained, largely through requests and voluntary contributions, court depositions, congressional hearings, internal office memoranda, minutes of meetings, and scientific articles.

The evaluation of policy decisions and actions taken over a decade ago is a problematic enterprise. On one hand, the historical record consists primarily of contemporaneous notes and explanations that make the decisions appear inevitable. On the other hand, the difficulties that beset decision makers at the time do not appear so compelling in light of our current knowledge—exemplifying the risk that hindsight knowledge can easily and anachronistically be transposed back to the period in question. Finally, the documentary record is often incomplete, ambiguous, or vague, and current testimony about past events may be filtered by years of subconscious reinterpretation in the light of new knowledge. Even when the record is reasonably complete and apparently "clear on its face," interpreting its meaning demands the reconstruction of an always elusive historical context, without which no individual actions or statements can properly be understood.

In addition to these difficulties, the events under discussion are highly charged emotionally, as pointed out above. The infection of individuals with HIV through the use of blood and blood products has created almost unimaginable suffering among those who were infected and their families (some of whom themselves became infected). Many, particularly in the hemophiliac

community, believe that they were betrayed by the very scientific establishment, nonprofit organizations, physicians, and governmental agencies on whom they relied to assist them in managing their chronic conditions and acute episodes. Those in official positions, by contrast, almost uniformly believe that they did everything that could and should have been done given the scientific uncertainty and public health considerations that constrained the range of realistic options.

ORGANIZATION OF THE REPORT

Chapter 2 describes institutions and organizations that comprise the national blood supply system and presents an overview of how blood is collected and distributed. Chapter 3 presents the history of the unfolding AIDS epidemic and the evolving knowledge base about the risk of AIDS from blood and blood products.

The main analysis of this report appears in Chapters 4–7. Chapter 4 provides a review of the development of processes to inactivate viruses in blood products such as AHF concentrate, examining the efforts made by the FDA, NIH, and the plasma fractionators, going back to the 1970s when it first seemed possible to inactivate hepatitis B virus and thereby enhance the safety of blood products. Chapter 5 addresses strategies for protecting the safety of the blood supply by screening potential donors, examining closely the factors that influenced decisions regarding the implementation of donor screening measures. Chapter 6 examines the role of the FDA in regulating blood and blood product safety, highlighting several critical events, such as the FDA's guidance for implementing donor screening practices, recall of potentially contaminated products, and procedures to inform recipients of contaminated products. Chapter 7 describes how the risks of HIV and the options for risk reduction were communicated to individuals with hemophilia, to transfusion recipients, and to physicians. The chapter also addresses the institutional, social, and cultural obstacles to effective communication about risk. In Chapter 8, the Committee presents conclusions and makes several recommendations that draw upon the analysis in the preceding chapters.

REFERENCES

Barker, Lewellys F., Dodd, Roger Y. "Viral Hepatitis, Acquired Immunodeficiency Syndrome, and Other Infections Transmitted by Transfusion," from Petz, Lawrence D., Swisher, Scott N. Clinical Practice of Transfusion Medicine (second edition) Churchill Livingsone, Inc., New York, NY; 1989.

Bayer, Ronald. Gays and the Stigma of Bad Blood. Hastings Center Report; April 1983.

Centers for Disease Control. *Morbidity and Mortality Weekly Report*. July 23, 1993.

Centers for Disease Control. *Morbidity and Mortality Weekly Report*. March 20, 1987a.

Centers for Disease Control. *Morbidity and Mortality Weekly Report*. December 1987b.

Institute of Medicine. Emerging Infections. National Academy Press, 1992.

Wallace, E.L., et al. Collection and Transfusion of Blood and Blood Components in the United States. Transfusion, vol. 33; 1993.

The U.S. Blood Supply System

CONTENTS

The U.S. Blood Supply System

INTRODUCTION

The U.S. blood supply system is comprised of many organizations with different management structures and philosophies. Table 2.1 lists each of the major organizations that function to meet the nation's blood needs. To provide the context for the Committee's analysis, this chapter provides information on blood and blood products, the organizations that collect, manufacture and distribute them, and the professional and trade associations that represent these organizations. Because of the special role of hemophilia in its analysis, this chapter also provides background information on the National Hemophilia Foundation and related organizations. Finally, this chapter also presents information on the federal agencies responsible for blood safety, the history of blood and blood product regulations, and the regulatory authority of the FDA.

BLOOD AND BLOOD PRODUCTS

There are two different types of blood collection activities. One blood collection and supply system involves the cellular elements and plasma obtained from whole blood, and the other involves large-scale collection of the plasma portion of whole blood and the subsequent manufacture of derivatives produced from that plasma as a raw material. Before describing these two types of activities, a brief summary of the products produced from whole blood and plasma is helpful.

Blood is composed of plasma and several cellular elements which include red cells (erythrocytes), five kinds of white cells (leukocytes, many with important subtypes), and platelets. Either whole blood can be collected, or the plasma portion of the blood can be collected with the cellular portion returning to the donor. Whole blood is collected by blood banks, which prepare the cellular products and unprocessed plasma used directly for transfusion. Plasma is collected and used as raw material to commercially produce plasma "derivatives," which are concentrated forms of selected plasma proteins (Figure 1).

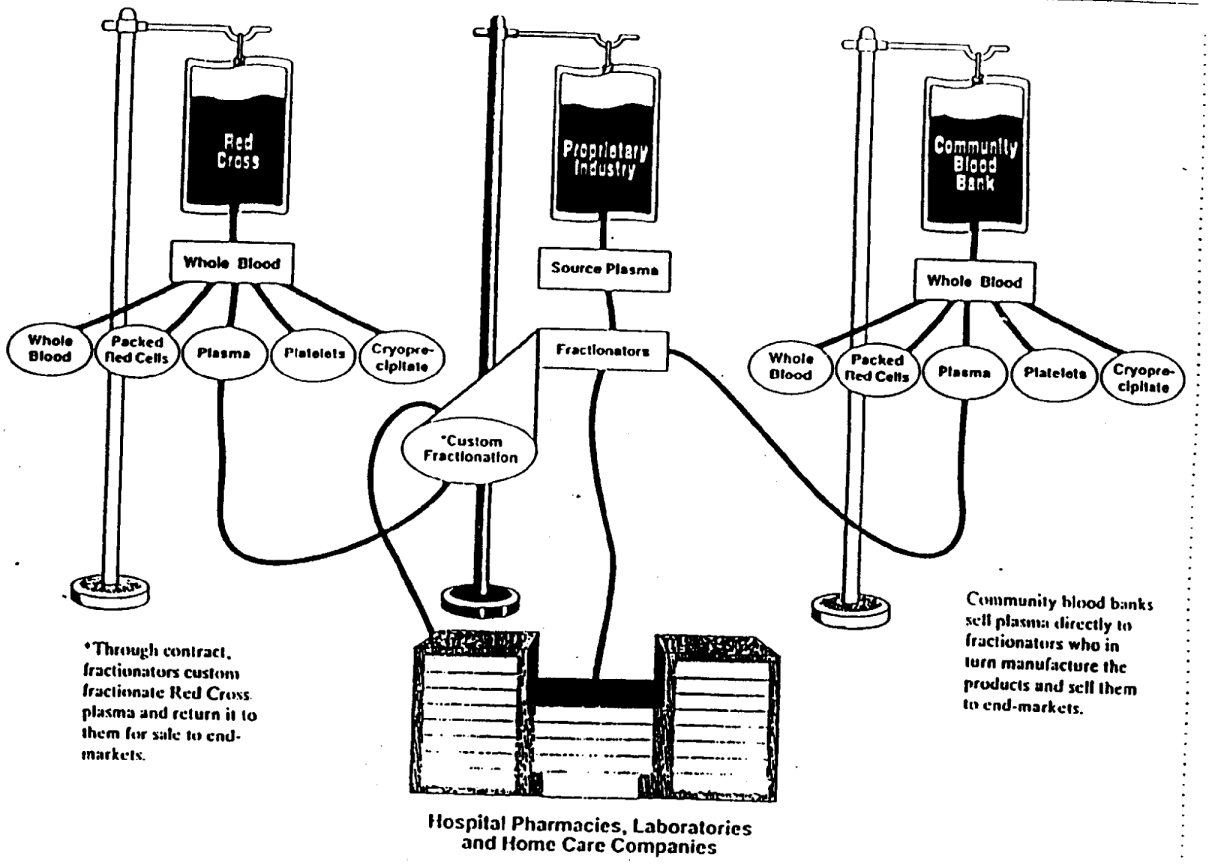

Figure 1. Organization of the plasma and plasma products industry. Reprinted with permission of the American Blood Resources Association.

Table 2.1 Major Organizations Comprising the Blood Supply System and Their Functions

Organization	Function
Federal Agencies	
Department of Health and Human Services	Direction and Oversight
Public Health Service	Direction and Oversight
Food and Drug Administration	Regulation and Review
Center for Biologics Evaluation and Review	Regulation, Review, Research
Blood Products Advisory Committee	Scientific Advice
Centers for Disease Control and Prevention	Surveillance, Investigation, Information Dissemination
National Institutes for Health	Biomedical Research
Blood Collection Organizations	
American Red Cross	Blood Collection and supply, Research
Community blood banks	Blood Collection and supply, Information Exchange
Hospital blood banks	Blood Collection and Patient Care.
For-Profit	
Plasma Fractionation Industry	Plasma Collection and supply, Manufacturing, Research
Professional and Trade Associations	
American Association of Blood Banks	Representing Blood Collection and Transfusion Services Organizations, Standard Setting (Inspection and Accreditation Program), and Education
American Blood Resources Association	Advocacy for Plasma Fractionation Industry, Education
Council of Community Blood Centers	Representing Blood Collection, Information Exchange
Nonprofit-Patient Advocacy	
National Hemophilia Foundation	Advocacy, Education, Information Dissemination
Medical and Scientific Advisory Council	Medical and Scientific Advice

Whole Blood and Components

Whole blood is collected by venipuncture from healthy adults into plastic bags containing a liquid anticoagulant preservative solution. About 450 milliliters of blood can be collected as often as every 56 days without harm to the donor. The whole blood is separated into components within eight hours after collection. The components are red blood cells, platelet concentrate, and fresh frozen plasma. The fresh frozen plasma can be used in one of three ways: (1) for transfusion; (2) for further processing into cryoprecipitate (i.e., fresh or frozen plasma) to be used for transfusion, and cryoprecipitate poor plasma, which serves as a source of raw material for further manufacture of plasma derivatives; or (3) as a source of raw material for subsequent manufacture of plasma derivatives as described below.

As shown in Table 2.2, among the components prepared from whole blood are red blood cells, platelets, fresh frozen plasma, and cryoprecipitate. Blood banks make many modifications of these components to obtain blood products that will be effective for specific purposes. In addition, blood banks distribute many of the plasma derivative products as part of their total supply program for transfusion medicine therapy, but most of these other plasma products are actually manufactured commercially by plasma fractionation companies.

Table 2.2 Components Produced by Blood Banks and the Medical Use of the These Components

Component	Medical Use
Red blood cells	Oxygenate tissues
Platelets	Prevention or stopping of bleeding
Fresh frozen plasma	Stop bleeding
Cryoprecipitate	Stop bleeding
Cryoprecipitate poor plasma	Plasma exchange
Granulocytes	Treat infection
Frozen red blood cells	Store rare blood
Leukocyte-depleted red blood cells	Prevent reactions and certain diseases

Because the United States has a pluralistic system of blood collection, there is no central repository of data about the number of units of blood collected or the components produced or transfused. The American Red Cross (ARC) collects about 45 percent of the 14 million units of whole blood available for use annually in the United States. Other community blood banks collect about 42 percent, hospitals collect about 11 percent, and the remaining 2 percent is imported. In 1989, a total of 12,544,000 units of whole blood were collected by 190 blood centers and 1,685,000 units were collected by an estimated 621 hospitals (Wallace, et al. 1993).

Plasma and Derivatives

For the manufacture of derivatives, plasma can be obtained as the by-product from whole blood (plasma) or by plasmapheresis (source plasma). Plasma that is a by-product from whole blood collected by community blood banks or hospitals is sold to commercial companies in the plasma fractionation industry, who in turn manufacture the plasma derivatives and sell them in the pharmaceutical market. See chapter 4 for a description of the role one such product—antihemophilic factor—in the treatment of hemophiliacs. The blood banks' sale of their plasma to the commercial plasma fractionator may, but usually does not, involve an agreement to provide some of the manufactured derivatives back to the blood bank. For example, plasma from whole blood collected by the American Red Cross is fractionated through a contract with Baxter Healthcare, which then returns all of the derivatives produced to the ARC for sale through their blood provision system.

The amount of plasma obtained from whole blood is not adequate to meet the needs for raw material to produce plasma derivatives. Therefore, much of the plasma that will be made into derivatives is obtained by plasmapheresis. This plasma is called source plasma, which is "the fluid portion of human blood collected by plasmapheresis and intended as the source material for further manufacturing use" [C.F.R., 1992]. Automated instruments are usually used to obtain 650 to 750 milliliters of plasma up to twice weekly from healthy adult donors (approximately 225 cc of plasma can be obtained from 450 ml of whole blood but most plasma is obtained directly through plasmapheresis). An individual can donate up to about 100 liters of plasma annually in the United States if the plasma protein levels and other laboratory tests and physical findings remain normal. The plasma is used as raw material for the manufacture of the derivatives shown in Table 2.3. The production of these plasma derivatives is a complex manufacturing process usually involving large batches of plasma (up to 10,000 liters) from as many 1,000-20,000, or more, donors.

The high demand for plasma products and the lengthy and often uncomfortable procedure of plasmapheresis led to the justification and legalization of compensation for plasma in the United States. Up to the early 1980s, plasma collection centers could be located in prisons and other areas where there was a high prevalence of hepatitis and other chronic infections. With the possible emergence of AIDS in the blood supply, plasma fractionators began closing their prison collection sites in December 1982 and in essence all were closed by January 1984.

Organizations and facilities need licenses for plasma collection (if shipped interstate) and the manufacture of AHF concentrate and other products from plasma.

Table 2-2 Plasma Derivative Products and Their Uses

Plasma Derivative	Medical Use
Albumin	Restoration of plasma volume subsequent to shock, trauma, surgery, and burns
Alpha 1 proteinase inhibitor	Used in the treatment of emphysema caused by a genetic deficiency
Anti-inhibitor coagulant complex	Treatment of bleeding episodes in presence of Factor VIII inhibitor
Anti-thrombin III	Treatment of bleeding episodes associated with liver disease, anti-thrombin III deficiency, and thromboembolism
Cytomegalovirus immune globulin	Passive immunization subsequent to exposure to cytomegalovirus
Factor IX complex	Prophylaxis and treatment of hemophilia B bleeding episodes and other bleeding disorders
Fibrinogen	Treatment of hemorrhagic diathesis in hypo-, dys-, and afibrinogenemia
Fibrinolysin	Dissolution of intravascular clots
Haptoglobin	Supportive therapy in viral hepatitis and pernicious anemia
Hepatitis B immune globulin	Passive immunization subsequent to exposure to hepatitis B
IgM-enriched immune globulin	Treatment and prevention of septicemia and septic shock due to toxin liberation in the course of antibiotic treatment
Immune globulin (intravenous and	Treatment of agamma- and hypogamma-globulinemia; passive immunization for hepatitis A and measles
Plasma protein fraction	Restoration of plasma volume subsequent to shock, trauma, surgery, and burns
Rabies immune globulin	Passive immunization subsequent to exposure to rabies
Rho(D) immune globulin	Treatment and prevention of hemolytic disease of fetus and newborn resulting from Rh incompatibility and incompatible blood transfusions
Rubella immune globulin	Passive immunization subsequent to exposure to German measles

Serum-cholinsterase	Treatment of prolonged apnea after administration of Succinylcholine Chloride
Tetanus immune globulin	Passive immunization subsequent to exposure to tetanus
Vaccinia immune globulin	Passive immunization subsequent to exposure to smallpox
Varicella-zoster immune globulin	Passive immunization subsequent to exposure to chickenpox

Plasma Collection

Data regarding the plasma fractionation industry are proprietary and thus not readily available. The Food and Drug Administration does not routinely collect data on the nature of plasma donors, the amount of plasma each organization collects, or the number of derivative products produced. According to the American Blood Resources Association (ABRA) the U.S. plasma and plasma fractionation industry employs over 12,000 people nation-wide (Scott 1990). U.S. plasma collection facilities perform approximately 13 million plasmapheresis donor collection procedures annually. Thus, if an average of 700 milliliters of plasma is obtained from each donation, it could be estimated that approximately nine million liters of plasma would be collected annually in the United States by plasma centers. Individuals who donate plasma to support the plasma fractionation industry receive between $15 and $20 per donation. According to the ABRA, donors receive compensation of more than $244 million from plasma collection facilities annually (ABRA 1994). This is in contrast to whole blood donors, who donate voluntarily and do not receive compensation. Much of the plasma obtained from whole blood collected by blood banks is also used for production. Blakestone has estimated that in 1990 approximately 12 million liters of plasma were consumed in the manufacture of plasma derivatives (Blakestone 1994).

It is estimated that plasma fractionation worldwide sales exceed $4 billion annually, with U.S. firms providing more than 60 percent of the plasma products or $2.4 billion in domestic and export sales annually (ABRA 1994). Of the $2.4 billion in domestic and export sales, $645 million is the estimated export revenue from sales of United States plasma products in Europe.

Plasma Processing

The collected plasma is sent from the collection site to a fractionation laboratory, which in the United States, is either owned by a pharmaceutical company or by an outside company that sells the fractionated plasma to the pharmaceutical company. Fractionation involves further separation of the plasma into proteins such as albumin, immunoglobulin and antihemophilic factor (AHF) concentrates. A pool size of at least 1,000 donors is required by the FDA for the

production of immunoglobulin products used in the treatment of infectious disease, because increasing the pool size concentrates the therapeutic antibody portion of plasma. Pooling was more efficient for production in the manufacturing process of AHF concentrates because clotting factor proteins are found in extremely small quantities in plasma. Pooling plasma also has the negative effect of increasing chances for contracting infectious disease (see Chapter 4).

Blood and Blood Components Distribution

Traditionally, some areas of the United States have been able to collect more blood than needed locally and have provided these extra units to other communities. The misalignment of blood use and blood collection is a long-standing phenomenon. To deal with these blood shortages, blood is "exported" from areas of oversupply and "imported" into areas of shortage—a practice called "blood resource sharing." The lack of an adequate local blood supply and the need to import blood causes several difficulties including complex inventory management, technical disparities, emergency donor recruitment, higher costs, decreased independence, and higher risk-management costs (Scott 1990). Some blood centers import blood because they can obtain this blood for less than their own costs of production (Anderson 1990). For years, blood banks have participated in systems to exchange blood among themselves to alleviate shortages. Blood banks in metropolitan areas that serve large trauma, tertiary, and transplantation centers most frequently experience shortages of whole blood, components, and type-specific blood units. Although experience has demonstrated that the American public is ever-willing to donate blood in times of local disaster or national emergency, this same public has often not donated blood in sufficient supply to meet the daily needs of the local community. Less than 5 percent of the U.S. population donates blood and in certain communities the percentage is even lower. Without resource sharing networks, many individuals would not receive the blood transfusions necessary to maintain or restore their health.

BLOOD COLLECTION ORGANIZATIONS

The United States blood collection system is heterogeneous owing to the "random development of blood centers without regard . . . to patient referral patterns" (Scott 1990). The American Red Cross (ARC) collects approximately half the blood in the United States. In the non-ARC covered areas, blood is collected by one or more community or hospital blood banks. In most areas of the United States, there is only one local organization that collects blood. However, in some communities, including these where the ARC operates a blood program, blood may be collected by more than one organization. When this occurs, usually several hospitals and a community blood center (ARC or non-ARC) are involved.

The adequacy of the nation's blood supply varies at different times of the year and in different parts of the United States, but, in general, the United States is almost 100 percent self-sufficient in its blood supply. Approximately 2 percent of the United States blood supply is imported from western Europe (Wallace, et al. 1993). Sufficiency, however, varies among geographic areas of the United States on a continual basis. The extent to which the adequacy

of the blood supply is related to the public image of blood banks and the association of blood with AIDS is not clear. Public opinion surveys indicate strong support for blood banks (Gallup 1991), and despite major public education efforts by blood banks, a high (35 percent) percentage of people believe they can contract AIDS or HIV by donating blood (CDC 1991).

Community Blood Banks

Blood is collected by blood centers and hospitals. Blood centers are freestanding organizations, virtually all of which are nonprofit. These centers are governed by a board of local volunteers and are organizations whose sole function is to provide the community's blood supply. Each blood center collects blood in a reasonably contiguous area and supplies the hospitals within the blood collection area. The blood center may or may not supply the total needs of the hospitals in its area or may supply hospitals in other areas as well. The area covered by each center is determined by historical factors and did not develop according to any overall plan. Rather, local interests dictated whether, how, and what kind of community blood program developed. Not every area of the United States is necessarily covered by a blood center. There are a total of approximately 180 blood centers in United States (Scott 1990). Approximately 45 of these (25 percent) are operated by the American Red Cross and the remainder are community blood centers as described above.

The American Red Cross Service

The American Red Cross (ARC) is the organization that collects the largest number of units of blood in the United States. The ARC Blood Service is one of many humanitarian programs operated by the ARC. The ARC is a nonprofit Congressionally chartered (but not government sponsored or operated) organization that conducts programs supported by donated funds and through cost recovery. The mission of the ARC Blood Service is to "fulfill the needs of the American people for the safest, most reliable, most cost-effective blood, plasma . . . services through voluntary donations." In addition, the organization attempts to be the "provider of choice for blood, plasma . . . services . . . by commitment to quality, safety, and use of the best medical, scientific, manufacturing, and business practices" (ARC 1994).

Hospital Blood Banks

Some blood is collected by blood banks that are part of hospitals. These blood banks usually collect blood only for use in that hospital and do not supply other hospitals. Very few (possibly no) hospitals collect enough blood to meet all their needs. They purchase some blood from a local or distant community blood center. Most U.S. hospitals do not collect any blood but acquire all of the blood they use from a community center. Of those that do collect blood, there are no good data available to define the proportion of their needs that they collect. This can be presumed to be quite variable.

PROFESSIONAL ASSOCIATIONS

There are three major professional associations involved with blood banking. These are the American Association of Blood Banks (AABB), the Council of Community Blood Centers (CCBC), and the American Blood Resources Association (ABRA). Other organizations such as the American Medical Association, College of American Pathologists, American College of Surgeons, and American Society of Anesthesiologists, may from time to time take positions on blood-bank-related issues and maintain blood-bank or transfusion medicine committees. The AABB and CCBC are the only professional organizations devoted exclusively to blood banking and transfusion medicine. The ABRA is the trade association representing the plasma fractionation industry. Each organization is described briefly in the following section.

American Association of Blood Banks

Established in 1947, the American Association of Blood Banks (AABB) is a nonprofit scientific and educational association for individuals and institutions engaged in the many facets of blood and tissue banking and transfusion and transplantation medicine. It is the only organization devoted exclusively to blood banking and blood transfusion services. Institutional members of the AABB are classified either as a community blood center, a hospital blood bank, or a hospital transfusion service. The community blood center collects blood and distributes it to several hospitals but does not transfuse blood. A hospital blood bank both collects and transfuses blood, a hospital transfusion service transfuses but does not collect blood.

Member facilities of the AABB collect virtually all of the nation's blood supply and transfuse more than 80 percent. Approximately 2,400 institutions (community, regional, and ARC blood centers; hospital blood banks; and hospital transfusion services) and 9,500 individuals are members of the AABB. The services and programs of the AABB include inspection and accreditation, standard setting, certification of reference laboratories, operation of a rare donor file, accreditation of parentage testing laboratories, group purchasing programs, certification of specialists (technologists) in blood banking, educational programs, legislative and regulatory assistance to members, participation in the National Marrow Donor Program, participation in the National Blood Foundation, which provides funds for research in transfusion medicine and blood banking, and participation in the National Blood Exchange, which facilitates the movement of blood among centers with surplus and those with shortages.

AABB Inspection and Accreditation Program

The AABB operates a voluntary accreditation system in which most blood collection and transfusion organizations participate. The AABB accreditation program involves a biannual inspection by AABB volunteers. The AABB Inspection and Accreditation (I&A) program was initiated in 1958. The I&A program is designed to assist directors of blood banks and transfusion services in determining that knowledge, equipment, and physical plant meet established requirements. It is also a means for detecting deficiencies in practices and provides,

when needed, consultation for their correction. The I&A program provides recognition through accreditation to those institutions functioning in accordance with existing published requirements of the AABB. While increased safety in obtaining and transfusing human blood and components is the major intent and benefit of the I&A program, certain ancillary benefits such as assistance in medico-legal problems may result. Inspection and accreditation by the AABB is a prerequisite for institutional membership in the association and for full participation in the AABB National Blood Exchange Program.

Council of Community Blood Centers

The Council of Community Blood Centers (CCBC) is an association of independent (non-ARC) not-for-profit community blood centers that serves the public by assisting its members in providing excellence in blood and related health services. The association was established in 1962 by the directors of six community blood centers who recognized the need for an organization that would represent the common interests of not-for-profit community blood programs and would provide a national forum to address the unique needs in the field of blood center operations. Its policies are determined by a board of trustees comprised of one voting representative from each institutional member.

Efforts to meet the goals of safety, quality, and efficiency in blood services are accomplished through a variety of activities and services that are developed and managed by volunteers. These efforts include group purchasing of supplies, services, and liability insurance; increasing volunteer blood donation; effective sharing of blood resources; strengthening of blood center management skills and the scope of services provided to the community; training programs to assure compliance with federal regulations; assuring fair and balanced resolution of disputes between blood centers and the public they serve; influencing federal and state regulations and policies; and promoting needed research and development in the blood services area.

The CCBC also promotes information exchange between members of operational practices, new programs, policies, and ideas through surveys, meetings of small working groups, and development of workable models. The weekly CCBC newsletter is a comprehensive chronicle of information about current government activities affecting blood centers as well as new developments in blood services and healthcare in general.

American Blood Resources Association

The American Blood Resources Association (ABRA) is a trade association founded in 1971 to represent the plasma collection and fractionation industry in both federal and state government relations. The ABRA's role is to educate the public at large about the commercial plasma and plasma products industry. The ABRA's mission is to promote and encourage research, to foster and monitor the promulgation of reasonable and just regulations, and to institute beneficial projects on behalf of the commercial plasma and plasma products industry. The ABRA provides facility and personnel certifications and develops industry manufacturing standards and guidelines. Its members operate under a strict code of ethics to ensure the high standards and

quality. Its memberships operate over 80 percent of the U.S. commercial plasma collection facilities, and includes all of the commercial plasma product manufacturers in the United States and a majority of the manufacturers worldwide. Members manufacture and collect plasma in 42 states across the country.

HEMOPHILIA ORGANIZATIONS

The Nature of Hemophilia

Hemophilia is a rare, inherited, sex-linked disorder characterized by a deficiency in blood clotting proteins. The estimated number of people with hemophilia in the United States population is approximately 15,000 to 16,000 (CDC, HRSA, MCHB, 1991, 1992, 1993). Hemophilia has been characterized by high mortality and a significantly lower mean age of death as compared to the general population (Chorba, et al. 1984).

There are two major types of hemophilia. The more common, hemophilia A, is characterized by a deficiency of antihemophilic Factor VIII clotting protein. The much less frequently occurring variety of hemophilia is hemophilia B, characterized by a deficiency of Factor IX clotting protein. About 85 percent of hemophilia cases are due to Factor VIII deficiency, about 14 percent to deficiencies of Factor IX. The remaining 1 percent involve the much more rare congenital clotting factors: V, VII, X, or XI (Hoffman, et al. 1994). The clinical severity of hemophilia is related to the degree to which the relevant factor is absent or deficient. The distinction of disease severity (i.e., mild, moderate, or severe) is critical in determining treatment of the disease. Mild or moderate hemophilia is rarely complicated by episodes of spontaneous bleeding (Hoyer interview). In severe cases, which are characterized by less than 1 percent of clotting factor activity, the disorder is accompanied by spontaneous bleeding into multiple joints of the body and muscles (Chorba, et al. 1984). This can be extremely painful, can lead to severe disabling musculoskeletal disease, and can be fatal. Most of the fatality associated with hemophilia results from central nervous system bleeding. Approximately 60 percent of hemophiliacs are classified as severe (Hoffman, et al. 1994).

Chapters 4 and 7 contain more detailed information on hemophilia treatment modalities available in the 1980s.

Hemophilia Treatment Centers

On July 29, 1975, Congress passed P.L. 94-63 authorizing federal funding to establish a network of comprehensive hemophilia treatment centers [Section 606 of P.L. 94-63 amended Title XI of the Public Health Service Act]. On October 1, 1976, a total of $3 million was appropriated to fund more than 20 regional hemophilia treatment centers [Federal Register, 1976, 1977] (Smith and Levine 1984). The Hemophilia Treatment Centers became a model program for the delivery of comprehensive care services for the diagnosis and treatment of hemophilia. The Centers provided education, medical, psychosocial, orthopedic, dental, and genetic counselling expertise, and the means for early application of treatment. The

comprehensive care provided was aimed at preventing or reducing the complications associated with hemophilia, as well as rehabilitation of those who already had severe musculoskeletal complications (Smith and Levine 1984).

National Hemophilia Foundation

The National Hemophilia Foundation (NHF) is a nonprofit health care organization founded in 1948. Its mission is to help meet the needs of all individuals with bleeding disorders. The NHF is organized into chapters, each of which has a locally elected board of directors and officers. Each chapter's president is the chief executive officer and serves without compensation. There are 46 chapters nationwide. Chapters are self-governed and determine their own priorities, programs, and uses of funds. They have the benefit and use of the NHF's advertising, public relations materials, publications, name, and affiliation. As an affiliated member, chapters pay a monthly participation fee to the NHF. There are several hemophilia societies not affiliated with the NHF.

The NHF provides financial support for particular programs and national legislative advocacy. The NHF board of directors serves as the policymaking body of the NHF, and the current board is comprised of 22 members. The Board serves to elect NHF officers, grant and terminate chapter charters, determine territorial jurisdictions for chapters, and establish and enforce uniform rules. The decision-making process of the NHF involves the four vice presidents, the president, the chairman of the board, the Medical and Scientific Advisory Council (MASAC) chair, and the executive director. The Board of Directors also approves all MASAC recommendations before they become "official" NHF MASAC recommendations for dissemination.

Medical and Scientific Advisory Council

One important national activity of the NHF is the MASAC. In 1982, the primary mission of the MASAC was to advocate for continued development and expansion of an accessible comprehensive care network, to advocate for quality treatment and care for hemophilia, to support and be involved in hemophilia research, to discuss timely issues of relevance to the hemophilia community and make recommendations concerning them, and to continue to provide technical information, educational materials, and publications. The MASAC also provided advice to the NHF board of directors concerning medical/scientific issues of relevance, and reviewed research activities. The MASAC membership included representatives from six other individual committees of NHF: research and review, nursing, mental health, social work, education, and musculoskeletal.

Membership of the MASAC is generally drawn from the regional treatment centers and represents both elected and appointed members (i.e., appointed members, regionally elected members, committee liaisons, and ex-officio members). The appointed members are generally elected for their expertise in a particular area (e.g., basic research in hemophilia, etc.). The chair of the MASAC is appointed by the NHF president and has a three-year term, and MASAC

members serve rotational two- and four-year terms.

In 1989, a committee of medical leadership was established by the NHF to facilitate more rapid communication about major issues in the hemophilia medical and scientific community. Members include the NHF vice president for medical and scientific affairs, the MASAC chair, the medical director, associate medical directors, the chair of the AIDS task force, the president of the NHF, the chairman of the NHF Board and the executive director.

ROLE OF THE U.S. PUBLIC HEALTH SERVICE

National Blood Policy of 1973

The federal government regulates blood banking, monitors the safety and efficacy of blood products, and promotes research on blood diseases (OTA 1985). In late 1972, the Department of Health, Education, and Welfare reported several problems within the blood supply system, including an inadequacy in the quantity of blood supplied, an unreliability in the quality of blood owing to the high rates of transfusion-related hepatitis, an inefficiency in the system itself owing to waste in some areas and shortages in others, and excessive costs of blood and blood services. On July 10, 1973, the assistant secretary for health announced the National Blood Policy, which became "the focal point around which blood banking policy has evolved over the past decade" (OTA 1985). The National Blood Policy recognized that reliance on "commercial sources of blood and blood components for transfusion therapy has contributed to a significantly disproportionate incidence of hepatitis, since such blood is often collected from sectors of society in which transmissible hepatitis is more prevalent." For this reason, the National Blood Policy encouraged efforts to establish an all-volunteer blood donation system and to eliminate commercialism in the acquisition of whole blood and whole blood components [Fed. Reg. 1975] (Hutt and Merrill 1991).

The National Blood Policy listed four primary goals: to provide an adequate supply of blood; to ensure a higher quality of blood; to facilitate maximum accessibility to services; and to achieve total efficiency (U.S. Senate 1979). The first actions taken to meet these goals included the adoption of an all-volunteer blood collection system (for whole blood); coordination of all costs and charges; regionalization of blood collection and distribution; and an examination of the standards of care for hemophiliacs and other special groups. The policy did not address the commercial acquisition of plasma, the preparation and marketing of plasma derivatives, and the commercial acquisition of blood for diagnostic reagents (Hagen 1982).

In 1975, the American Blood Commission (ABC) was established and funded by the National Heart, Lung, and Blood Institute and was charged with implementing the "lion's share" of the objectives set forth in the National Blood Policy (OTA 1985). The progress of the ABC was hindered by lack of funds, disagreement between the two largest blood suppliers, resistance to regionalization of blood collection and distribution, problems in obtaining data from blood banks, and a lack of knowledge of blood banking by lay members of the commission (U.S. General Accounting Office 1978). In 1985 the ABC was formally disbanded.

Public Health Service

Public health management is the responsibility of the federal government through the Public Health Service (PHS). The Public Health Service Act of July 1, 1944 [42 U.S.C. § 201], consolidated and revised substantially all existing legislation relating to the PHS. The mission of the PHS is to promote the protection and advancement of the nation's physical and mental health. The Office of the Assistant Secretary for Health in the Department of Health and Human Services plans and directs the activities of the PHS. The federal system by which public health policy decisions are made comprises the Centers for Disease Control and Prevention, the agency that conducts surveillance and reporting of disease; the National Institutes of Health, the organization that conducts research; and the Food and Drug Administration, the regulatory arm of the PHS.

Centers for Disease Control and Prevention

The Centers for Disease Control and Prevention (CDC) was established as an agency of the PHS in 1973. The CDC is charged with protecting the public health of the nation by providing leadership and direction in the prevention and control of diseases and other preventable conditions, and responding to public health emergencies. The CDC also administers national programs for the prevention and control of communicable and vector-borne disease which includes consulting with state and local public health departments. The CDC also collects, maintains, analyzes, and disseminates national data on health status and health services.

National Institutes of Health

The National Institutes of Health (NIH) is the federal government's principal biomedical research agency. Its mission is to pursue knowledge to improve human health. To accomplish this goal, the NIH seeks to expand fundamental knowledge about the nature and behavior of living systems, to apply that knowledge to enhance the health of human lives, and to reduce the burdens resulting from disease and disability. Two of the NIH institutes have a special role in protecting blood safety.

National Institute of Allergy and Infectious Diseases

The National Institute of Allergy and Infectious Disease conducts and supports broad-based research and research training on the causes, characteristics, prevention, control, and treatment of a wide variety of diseases believed to be attributable to infectious agents (including bacteria, viruses, and parasites), to allergies, or to other deficiencies or disorders in the responses of the body's immune mechanisms.

National Heart, Lung, and Blood Institute

In 1948 the National Heart Institute was established, and in 1969 it was reorganized as the National Heart and Lung Institute. In the 1960s, epidemiological evidence demonstrated a correlation between high rates of posttransfusion hepatitis and blood from paid donors. This, coupled with the advances in surgical techniques (especially cardiac) that increased the need for whole blood for transfusion, created a demand to increase safety measures regarding the blood supply. In addition, an increase in the use of platelets and plasma derivatives also occurred, primarily because of advances in new technologies. As a result, the National Blood Resources Program was established in 1967. The primary objective in establishing the program was to develop safe and efficient blood collection and distribution (U.S. General Accounting Office 1978).

In 1970, Congress amended the Biologics Act, which as discussed later in this Chapter, was originally enacted in 1902 to provide the framework for federal regulation of biological products for human use, to include vaccines, blood, blood components or derivatives, and allergenic products. As a result, the Blood Resources Program became the Division of Blood Diseases and Resources at the National Heart, Lung, and Blood Institute.

Food and Drug Administration

The name "Food and Drug Administration" was established by the Agriculture Appropriation Act of 1931 [46 Stat. 392], although similar regulatory functions had been in existence under different organizational titles since January 1, 1907, when the Food and Drug Act of 1906 [21 U.S.C. §§ 1–15] became effective. The FDA's activities are directed toward protecting the health of the nation against impure and unsafe foods, drugs and cosmetics, biologics, and other potential hazards. One of the FDA's responsibilities is to administer regulation of biological products under the biological product control provision of the Public Health Service Act and applicable provisions of the Federal Food, Drug, and Cosmetic Act. The FDA's legal authority is derived from the Food, Drug, and Cosmetics Act and related laws (Hutt and Merrill 1991).

Prior to 1972, regulation of the blood supply was carried out by the NIH (Hutt and Merrill 1991). Until 1947, the control of biological products had been under the supervision of the director of the Hygienic Laboratory of NIH. In 1948 it became part of the NIH National Microbiological Institute. In 1955, the NIH was reorganized and the Division of Biological Standards (DBS) for regulating biologics was created (Hutt and Merrill 1991).

In response to a 1972 General Accounting Office report that concluded that ineffective biologics were licensed under the Biologics Act because of the failure to apply the requirements for proof of effectiveness, the Secretary of Health Education and Welfare delegated concurrently to the FDA and the DBS the authority to administer the drug provisions of the Food, Drug, and Cosmetics Act for all biological products. On July 1, 1972, the responsibility for implementing the Biologics Act was transferred from the DBS to the FDA [37 Fed. Reg. 12,865, 1972]. Following its assumption of responsibility for administering the Biologics Act and the formation of the Bureau of Biologics, the FDA revoked NIH's announcement to review the effectiveness of all licensed biologics. The FDA then issued its own set of detailed procedures for the review

of the safety, effectiveness, and labeling of all licensed biologics. The Bureau of Biologics was given lead responsibility for overseeing blood collection, processing, testing, and marketing. It was at this point that all blood banks became federally regulated and state licensed [37 Fed. Reg. 17,419, 1972].

In 1982, through an FDA reorganization, the Center for Drugs and the Center for Biologics merged into one unit, and the Center for Drugs and Biologics (CDB) was established. The scientific director of the CDB was responsible for integrating the scientific and research activities for biologics between the NIH and FDA. The responsibilities of the Bureau of Biologics fell under this new center and the regulation for blood products and blood banking technologies was under the purview of the Office of Biologics Research and Review. The Office of Biologics in the Division of Blood and Blood Products was responsible for approval of license applications and amendments for new blood establishments and blood products, and for approval to market blood products and related technologies (OTA 1985).

In 1988, the CDB was reorganized again and the Office of Drugs and the Office of Biologics were separated into different centers. The Center for Biologics and Review assumed oversight for all activities that previously fell under the Office of Biologics and Review. In 1993, the Center for Biologics and Review was renamed the Center for Biologics Evaluation and Research (Fratantoni 1994).

The Center for Biologics Evaluation and Research (CBER) administers regulation of biological products under the biological product control provisions of the Public Health Service Act and applicable provisions of the Food, Drug, and Cosmetic Act. CBER plans and conducts research related to the development, manufacture, testing, and use of both new and old biological products to develop a scientific base for establishing standards designed to ensure the continued safety, purity, potency, and efficacy of biological products. It also coordinates with the Center for Drug Evaluation and Research regarding activities for biological drug products, including research, compliance, and product review and approval. CBER also plans and conducts research on the preparation, preservation, and safety of blood and blood products; the methods of testing safety, purity, potency, and efficacy of such products for therapeutic use; and the immunological problems concerned with products, testing, and use of diagnostic reagents employed in grouping and typing blood.

The CBER is the dominant focus for coordination of the Acquired Immune Deficiency Syndrome (AIDS) program, works to develop an AIDS vaccine and AIDS diagnostic tests, and conducts other AIDS-related activities. It inspects manufacturers' facilities for compliance with standards, tests products submitted for release, establishes written and physical standards, and approves licensing of manufacturers to produce biological products. In carrying out these functions, the CBER cooperates with other Public Health Service organizations, governmental and international agencies, volunteer health organizations, universities, individual scientists, nongovernmental laboratories, and manufacturers of biological products.

Blood Products Advisory Committee

The FDA makes extensive use of technical advisory committees in the support if its evaluation and regulation of drugs, biologics, and medical devices for human use. Advisory

committees are utilized by the FDA to obtain independent scientific and technical advice, opinions, or recommendations on a specific matter (FDA 1994). FDA advisory committees can be established in four ways: by order of the President of the United States; by congressional statute, by the Secretary of Health and Human Services, or by the FDA commissioner. The Secretary or the FDA commissioner must approve the establishment, renewal or rechartering, or amendment of all FDA public advisory committee charters (FDA 1994). Generally, the commissioner has direct authority to charter scientific and technical advisory committees, while the Secretary issues charters for committees advising on policy issues. All public advisory committees must be chartered, and their charters must be renewed biennially unless otherwise determined by law.

The CBER has four different standing advisory committees, one of which is the Blood Products Advisory Committee (BPAC), which provides evaluation of data related to safety, effectiveness, and labeling of blood and blood products and makes appropriate recommendations to the Secretary, the Assistant Secretary for Health, and the FDA commissioner (IOM 1992). Advisory committee nominations include candidates from relevant professional and scientific bodies, medical schools, academia, government agencies, industry and trade associations, and consumer and patient organizations. Committee members are appointed to terms not to exceed four years. Reappointment to a committee requires that one year elapse between appointments.

The general way in which an agenda is set for an FDA advisory committee involves two stages: (1) a meeting is formally scheduled and announced in the *Federal Register*; and (2) several days prior to the meeting, the FDA staff sends advisory committee members a detailed agenda and a list of specific questions on which their advice is sought. The FDA releases this list of questions to the public on the morning of the meeting (IOM 1992). An advisory committee meeting operates with the following separable portions: an open public hearing; an open committee discussion; a closed presentation of data; and closed committee deliberations. The BPAC's topics include investigational new drugs that meet the criteria of important diagnostic therapeutic, preventive, or other advances; novel and improved methods for product delivery; potential or apparently significant safety hazards; involvement of new biotechnology; and issues requiring additional expert review or clarification of study protocols. Product licensing agreements considered at BPAC meetings include those meeting the criteria of being a significantly new product; posing new uses for marketed products; having significant potential for risk compared to narrow therapeutic benefit; needing or being considered for postmarketing studies; presenting potential for withdrawal from market because of safety or questionable efficacy; and posing issues requiring additional expert review or clarification of study protocols.

The BPAC has 13 voting members and two nonvoting members. All voting members, consultants, and experts to advisory committees receive compensation for each day worked, travel, and per diem, unless waived. Industry and consumer representatives receive a salary if they have been cleared under the FDA's conflict of interest regulations as a special government employee. During the 1980s the BPAC was comprised of experts in relevant professional, scientific, and medical establishments, including academic blood banking, transfusion services, anesthesia and pharmacology, state public health departments, general medicine, biochemistry, pediatrics, laboratory medicine, infectious diseases, virology, hematology, and oncology.

BLOOD AND BLOOD PRODUCT REGULATION

Statutory Background

The history of blood and blood product regulation in the United States includes both congressional enactments (public laws) and rulemaking procedures of the FDA. The FDA regulates blood, blood components, and derivatives under two separate but overlapping statutes, one governing "biologics" and one governing "drugs." The biologics law requires that any "virus, therapeutic serum, toxin, anti-toxin, or analogous product" be prepared in a facility holding a federal license. A separate law, for food and drugs, includes drugs intended for the "cure, mitigation, or prevention of disease" and, thus, includes biologics such as blood and blood components or derivatives. Thus, blood banks and plasma product manufacturers are also subject to this drug regulatory process.

Biologics Act

In 1902, following several outbreaks of disease from contaminated vaccines, Congress enacted the Biologics Act [32 Stat. 728] which provided the framework for federal regulation of biological products for human use. The law required that biological drugs sold in interstate commerce must be licensed and produced in licensed establishments. The term *biologics* includes vaccines made from or with the aid of living organisms that are produced in animals or humans. Biologics also include antitoxins used to protect against diphtheria, tetanus, and whooping cough; serums for the treatment of disease; products for the treatment of allergies; and blood for transfusion and other medical purposes (Hutt and Merrill 1991).

In 1944, the Biologics Act was reenacted as part of the recodification of the Public Health Service Act, 58 Stat. 682, 702 (1944), and is now codified at 42 U.S.C. § 262 (Hutt and Merrill 1991). The recodification hearings focused on the issue of possible duplicative regulatory authority of biological products under the Federal Drug and Cosmetics Act. Under the original act, the Public Health Service (PHS) licensed and controlled the manufacturing of virus serums, toxins, and other biologics. At the hearings, while PHS control of biologics was viewed as effective, the wording of the new act was seen to be suggestive of duplicative administrative control of the PHS and the Federal Food and Drug Administration. In the event that some product dangerous to human life inadvertently entered the market, the FDA would have power of seizure [Section 351 of the PHS Act, referred to as the Biologics Act] (Hutt and Merrill 1991). Prior to 1970, the Biologics Act did not specifically include blood products. In 1970, Congress amended the Biologics Act "specifically to include vaccines, blood, blood components or derivatives, and allergenic products [84 Stat. 1297, 1308]" (Hutt and Merrill 1991).

Public Health Service Act

In 1974, the FDA promulgated regulations governing good manufacturing practices in the collection, processing, and storage of human blood components [39 Fed Reg. 18,614, 1974; 40

Fed Reg. 53,532, 1975]. By combining the jurisdictional and regulatory provisions of the Biologics Act and the Food, Drug, and Cosmetic Act, the FDA brought all blood and blood products produced and used in the United States under uniform federal requirements (Hutt and Merrill 1991).

Blood Shield Laws

During the 1950s and 1960s blood shield laws were adopted by 47 different jurisdictions. The blood shield laws were developed to exempt blood and blood products from strict liability or implied warranty claims on the basis that blood and blood products provide a service, not a sale. Accordingly (as stated in the California Health and Safety Code 1606),

> the procurement, processing, distribution, or use of whole blood, plasma, blood products, and any blood derivatives for the purpose of infusing the same, or any of them, into the human body shall be construed to be, and is declared to be, for all purposes whatsoever, the rendition of a service by each and every person, firm, or corporation participating therein, and shall not be construed to be, and is declared not to be, a sale of such whole blood, plasma, blood products, or blood derivatives, for any purpose or purposes whatsoever (Westfall 1986).

Only four jurisdictions (New Jersey, District of Columbia, Rhode Island, and Vermont) did not adopt statutes protecting hospitals or blood donor services from strict liability or breach of implied warranty (Lipton 1986). Even in these jurisdictions, however, the likelihood that a court would hold a hospital or blood donor service liable under either breach or implied warranty or strict liability theories was considered remote (Lipton 1986).

In 1976, blood banks received exemption from liability under protection of blood shield law as providing a service and not a product. The court ruled that there was a rational basis for blood bank's exemption from liability, based on weighing the need for an available blood supply for surgery and other medical procedures against the "relatively minor risk of hepatitis which the blood recipient must take" (Westfall 1986). In addition the court found that exemption of the blood bank from liability was constitutional because protection of blood banks was related to the state's purpose of encouraging the general blood supply.

In 1977, the courts extended this protection to blood product manufacturers on the same grounds: the distribution of blood products was a service and not a sale. In a wrongful death suit concerning a hemophiliac who had died from hepatitis after using a blood product [*Cutter vs. Fogo* 1977], the court reasoned that because the blood product was unavoidably unsafe, and because the risk of hepatitis could not be eliminated despite every attempt to screen donors (i.e., through both biological tests and avoidance of high-risk donors), the blood product manufacturers were protected from strict product liability since the blood product had been instrumental in helping many hemophiliacs (Westfall 1986).

Federal Licensure of Blood Collection Organizations

Federal licensure is thought to ensure that the facility in which the biologic is produced will insure its purity and quality. In addition to licensing the facility or establishment, this law requires that each biologic product itself be licensed by the government. Thus, to produce a licensed biologic, an organization must have an establishment license describing the facility in which the product is produced and a product license describing the specific product being produced. Over the years, this law has been specifically amended to include the terms *blood* and *blood component* or *derivative* to make it clear that blood and blood products are subject to the biologics regulation.

Establishment Licensure and Registration

Presently, there are 188 FDA-licensed organizations at 790 locations for collection and interstate shipment of blood and blood components. In addition, a total of 2,900 locations are registered to collect blood but not for interstate shipment. If an organization wishes to ship the components across state lines or engage in commerce by selling the products to other organizations, the organization must obtain an FDA license for this purpose. Even if an organization does not wish to produce blood components for interstate shipment, the FDA law requires that all organizations involved in "collection, preparation, processing, or compatibility testing . . . of any blood product" register with the FDA (McCullough 1995). This registration allows the organization to collect blood and prepare blood components for its own use. Thus, for practical purposes, most hospitals that collect blood or prepare blood components for their own use are registered but not licensed since they do not ship blood in interstate commerce. Most blood centers are licensed, since they supply multiple hospitals, some of which may be in other states. In addition, blood centers may wish to participate in blood resource sharing with blood centers in other states, and thus need to be licensed for interstate shipment of blood.

Product Licensure

Along with the establishment license, the organization must file a product license application for each product it plans to produce in the facility.

For whole blood and components, the product application involves basic information about the manufacturer (organization), establishment, product, standard operating procedures, blood donor screening tests, frequency of donation, donor medical history, presence of a physician, phlebotomy supplies, venipuncture technique, collection technique, allowable storage period, storage conditions, disposal of contaminated units, supplies and reagents, label control processes, procedures for reissue of blood, and a brief summary of experience testing 500 samples.

For the manufacture of plasma derivatives, the product license application involves the

manufacturer's (organization's) name; the establishment name; procedures for determining donor suitability including medical history, examination by physician, laboratory testing, methods of preparing the venipuncture site, and collecting the plasma; methods to prevent circulatory embolism and to assure return of red cells to the proper donor; minimum intervals between donation and maximum frequency of donation; techniques for immunizing donors; laboratory tests of collected plasma; techniques of preparing source plasma and storing it; methods to ensure proper storage conditions and identification of units; label control systems; and shipping conditions and procedures.

Blood banks and plasma derivative manufacturers must submit a report annually to the FDA indicating which products are collected, tested, prepared, and distributed.

Other Required Licensure

Blood banks are subject to several other requirements or licensure systems in addition to those of the FDA. Because blood banks carry out testing on human material that is in interstate commerce, and because they provide services to Medicare and Medicaid patients, they must comply with the Clinical Laboratories Improvement Act of 1988. Several states also require that blood banks have a license to operate or provide blood in that state. These licenses usually involve a specific application and inspection.

REGULATORY AUTHORITY OF THE FDA

Since 1972, the FDA has been the principal regulatory agency with respect to blood and blood products. Its statutory regulatory authority is extensive under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act [codified as 42 U.S.C. § 262].

Compliance with Regulations

The FDA depends on the regulated industry for some amount of self-regulation. However, the FDA's enforcement cannot be by self-regulation, and the FDA's General Counsel determines if a violation of legislative mandates constitutes grounds for legal action (Hutt and Merrill 1991) (See Chapter 6, which focuses on FDA's regulation of blood and blood products during the period 1982–1986 when HIV contaminated the blood supply and before the development of a test to detect antibody to HIV, for more information).

A formal compliance program for the plasma fractionation industry was established in 1977. The responsibility for annual inspections was transferred from the Bureau of Biologics to the FDA field investigation office (OTA 1985). In addition, there was no ban on commercial collection of plasma at this time because the voluntary donor system could not meet the demand for plasma. To reduce the risks of transmission of hepatitis, source identification (as to whether the donor was paid or volunteer) was required as a federal regulation imposed by the FDA in 1978, for both whole blood and its components. This requirement, however, did not apply to

source plasma or derivatives (OTA 1985).

In March 1980, a memorandum of understanding was established between FDA and the Health Care Financing Agency (HCFA) for coordination of the inspection of blood banks and transfusion services. The FDA exempted all transfusion services and clinical laboratories that are regulated by HCFA under Medicare [45 Fed. Reg. 64,601; September 30, 1980]. The HCFA adopted the FDA's blood regulation to assure uniform and efficient regulation of these facilities.

Recall Policy

The FDA's recall authority lies within the Public Health Service Act under the Biologics section [21 CFR Part 7]. The FDA can issue a mandatory injunction to place the blood bank back into compliance with the regulations (Falter, Foegel, Dubinsky interviews). The FDA's *Regulatory Procedures Manual* requires CBER's technical staff to prepare a health hazard evaluation of a product before a recall action is initiated (FDA 1988). (A less formal discussion of recall appears in Chapter 6 and focuses on FDA'S regulation of blood and blood products during the period 1982-1985 when HIV contaminated the blood supply and before the antiviral HIV test was developed.)

A recall is a method for removing or correcting marketed products that violate the laws administered by the FDA. They provide efficient and timely protection to the consumer, especially when a product has been widely marketed. Voluntary recalls may be undertaken at any time on the initiative of manufacturers to carry out their responsibility to protect the public health. The recall process is usually a voluntary action taken by a firm to remove a product from the market and may be taken as a result of FDA findings during inspections, reports from consumers, or scientific data indicating a risk (OTA 1985). If the firm decides against market withdrawal, the FDA can seize the product.

A market withdrawal is when a firm voluntarily removes a distributed product which involves a minor violation for which the FDA would not initiate legal action or which involves no violation. Requested recalls are initiated in response to a formal request from the FDA (FDA 1988). It is FDA policy that a recalling firm has the responsibility to determine whether the recall is progressing satisfactorily through the use of effectiveness checks. Because each recall is unique and requires its own strategy, the FDA reviews and/or recommends the firm's recall strategy and will develop its own strategy based on the agency's hazard evaluation and other factors, such as type or use of the product. The recall strategy is separate from, and not tied to, the class of recall selected (FDA 1988). Recall classification is a numerical designation assigned by the FDA to a product recall to indicate the relative degree of health hazard presented by the product being recalled. There are three classes of recall:

- Class I is defined as situations in which there is a strong likelihood that the use of, or exposure to, a violative product will cause serious, adverse health consequences, or death.
- Class II is defined as situations in which the use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote.

- Class III is defined as situations in which the use of, or exposure to, a violative product is not likely to cause adverse health consequences.

Once the recall has been classified, FDA determines the depth of the recall, which depends upon the product's degree of hazard and the extent of distribution. The recall strategy will specify the level to which the recall should extend as follows [see 21 CFR § 7.45]:

- consumer or user level, which may vary with the product, including any intermediate wholesale or retail level;
- retail level, including any intermediate wholesale level; or
- wholesale level.

The FDA issues a warning to alert the public that a product is being recalled and presents a serious hazard to health. This is usually reserved for urgent situations where other means for preventing the use of the recalled product may appear inadequate [21 CFR § 7.45]. The FDA also surveys and monitors recall actions for all biologics by following up to make sure that the recall message (i.e., a letter to the manufacturer) was received and acted upon.

The FDA can implement stronger enforcement actions if the manufacturer is not acting in accordance with the recall. However, there must be scientific and medical evidence to justify stronger enforcement actions such as a court injunction or product seizure. FDA staff must present evidence to the FDA general counsel and the Department of Justice on the necessity of such an action (Falter, Foegel, Dubinsky interviews).

SUMMARY

The nation's blood and plasma are collected by two distinct systems that are based on different donor sources and produce different products. The blood segment of the collection system is primarily not for profit, the plasma segment is primarily for profit. The federal government regulates blood banking, monitors the safety and efficacy of blood products, and promotes research on blood diseases. Both systems are regulated by the FDA in a similar manner, although the specific requirements differ because of differences between blood and plasma products.

Since the period 1982–1986, it appears that the number of units of whole blood collected in the United States has stabilized or slightly decreased. It also appears that the substantial increase in the collection of autologous blood that occurred during recent years is slowing. There is a slight decrease in the number of community blood centers and an increase in the average number of units collected, implying that the decrease in the number of centers may be due to mergers. Presently, members of the American Association of Blood Banks account for almost all blood collected in the United States. The number of AABB institutional members who collect blood has increased and those that transfuse blood has decreased. Because this could reflect the changing membership of the AABB, it is not proper to extrapolate these observations to changes in the blood collection or transfusion community. Membership in the Council of Community Blood Centers has increased substantially during the past decade.

It is not possible to provide accurate estimates of the amount of plasma or derivatives produced because this is proprietary information. There has been an increase in the kinds of plasma derivative products during the past decade. There has also been an increase in the number of plasma derivative manufacturers during the past decade. Although several companies that produced plasma derivatives in the early 1980s no longer do so, other companies have begun the production of plasma derivatives.

REFERENCES

American Blood Resources Association. Materials submitted to the Institute of Medicine; 1994.

Anderson, K. "The economics of importing vs collecting." In Adequacy of the Blood Supply, Council of Community Blood Centers conference proceedings; Clearwater, Florida. February 18, 1990.

Blakestone. MS Fractionation. Plasmapherisis, vol 5; 1994.

Centers for Disease Control, *Morbidity and Mortality Weekly Report*, July 3, 1981.

Centers for Disease Control, *Morbidity and Mortality Weekly Report*, July 16, 1982.

Centers for Disease Control, *Morbidity and Mortality Weekly Report*, March 20, 1987.

Centers for Disease Control, *Morbidity and Mortality Weekly Report*, December 18, 1987.

Centers for Disease Control, *Morbidity and Mortality Weekly Report*--HIV/AIDS Knowledge and Awareness of Testing and Treatment--Behavioral Risk Factor Surveillance. vol 40, p.704; 1991.

CDC, HRSA, and MCHB. *Minimal Data Set for Risk Reduction*; 1991, 1992, 1993.

Chorba, et al. Changes in Longevity and Causes of Death among Persons with Hemophilia A. American Journal of Hematology, Vol. 45; 1994.

Food and Drug Administration. Policy and Guidance Handbook for Advisory Committees; 1994.

Food and Drug Administration. Regulatory Procedures Manual; May 16, 1988.

Fratantoni, J., Food and Drug Administration, Division of Hematology. Presentation to Committee; May 16, 1994.

Gallup Organization. Attitudes of U. S. Adults Towards AIDS and the Safety of America's Blood Supply. Princeton, New Jersey; 1991.

Hagen, Piet J. Blood: Gift or Merchandise? Alan R. Liss, Inc., New York, New York; 1982.

Hoffman, et. al., editors. Hematology: Basic Principles and Practice. (Second Edition). Churchill Livingstone, New York, New York; 1994.

Hutt, Peter and Merrill, Richard. Food and Drug Law: Cases and Materials. The Foundation Press, Inc. Westbury, New York; 1991.

Institute of Medicine, Committee to Study HIV Transmission Through Blood Products. *Transcript of Public Meeting*; September 12, 1994.

Institute of Medicine. FDA Administration and Advisory Committees. National Academy Press, Washington, D.C.; 1992.

Lipton, K. Blood donor services and liability issues relating to Acquired Immune Deficiency Syndrome. Journal of Legal Medicine, Vol. 7, Issue 2; 1986.

McCullough, Jeffrey. The United States Blood Collection System, 1995.

Office of Technology Assessment. *Blood Policy and Technology* Washington, D.C: USGPO, OTA-H-260; January 1985.

Scott, E.P. "Why my blood center imports." In Adequacy of the Blood Supply, Council of Community Blood Centers conference proceedings, Clearwater, Florida; February 18, 1990.

Smith, Peter and Levine, Peter. The Benefits of Comprehensive Care of Hemophilia: A Five Year Study of Outcomes. American Journal of Public Health, Vol. 74; June 1984.

United States General Accounting Office [report to Congress]. Problems in carrying out the national blood policy. Washington D.C.: General Accounting Office; March 7, 1978.

United States Senate, Committee on Labor and Human Resources, Subcommittee on Health and Scientific Research. Hearing: Oversight on Implementation of National Blood Policy. June 7, 1979.

Wallace, E.L., et al. Collection and Transfusion of Blood and Blood Components in the United States. Transfusion, vol. 33; 1993.

Westfall, Pamela. Hepatitis, AIDS and the blood products exemption from strict products liability in California: a reassessment. Hastings Law Journal, Vol. 37, No. 6; July 1986.

Product Treatment

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Product Treatment

INTRODUCTION

Plasma products can be treated by a variety of physical and chemical processes to reduce the risk of contamination from viruses and other infectious agents, thus increasing the safety of their use. Currently available product treatment procedures use physical heat or chemical detergents to virally inactivate plasma products that will be used in medical treatment of clotting disorder diseases such as hemophilia. Owing to a variety of technical obstacles that remain today, there are no effective methods to inactivate viruses present in whole blood or in nonplasma blood components such as cellular blood products (e.g., red blood cells and platelets) used for transfusion purposes.

Shortly after the development of the technology to manufacture antihemophilic factor (AHF) concentrate, it was recognized that blood products carried a substantial risk of hepatitis to their recipients. Although some blood derivative products (e.g., albumin) have been treated with heat to destroy live viruses since the late 1940s, Factor VIII and IX AHF concentrates in the United States were not subjected to procedures of viral inactivation until 1983–1984. In fact, the methods used to manufacture AHF concentrate can also inadvertently concentrate certain viruses, present in the original plasma donation, within the final product preparation. The fact that AHF concentrate is prepared from pooled plasma from thousands of donors greatly increases its risks for transmitting disease.

This chapter describes the development and implementation of treatment methods used to inactivate viruses in AHF concentrate. The events leading to the development and implementation of these methods unfolded over the period from 1970 to March 1983, during which time AHF concentrate became widespread as the standard medical treatment for individuals with hemophilia. Although inactivation of hepatitis viruses was the goal of the first product treatment methods developed to increase the safety of AHF concentrate, review of the history of their development is important to consider for several reasons. First, because the product treatment methods used to inactivate hepatitis viruses also inactivate HIV, their availability prior to 1981 would have minimized, if not prevented, the widespread HIV infection of persons with hemophilia. Second, consideration of the development of viral inactivation

methods helped shed light on important aspects of the prevailing scientific, medical, and regulatory environments of the early 1980s. The Committee framed its analysis of the development and implementation of viral inactivation methods by four questions:

- When did the information that facilitated the development of viral inactivation methods become available?
- Could the technology to accomplish viral inactivation of AHF concentrate have been developed earlier to decrease the transmission of hepatitis and AIDS?
- What were the internal and external pressures that influenced the rate at which viral inactivation methods for AHF concentrate were developed and implemented?
- What was the role of the Food and Drug Administration and the National Institutes of Health in encouraging or supporting research on viral inactivation methods to improve the safety of AHF concentrate?

The Committee developed two hypotheses to explain the actions that were taken during the period from 1970 to 1983:

- Plasma fractionators and other organizations responsible for the safety of blood products did not begin research on viral inactivation of AHF concentrates until the onset of the AIDS epidemic.
- Hepatitis was viewed as an acceptable risk by the government regulatory agencies responsible for the safety of blood and blood products, the plasma fractionation industry, the physicians who treated the individuals with hemophilia, and the individuals with hemophilia. As a result, little incentive was available to improve AHF product safety through the expeditious development and implementation of viral inactivation technologies.

Testing these hypotheses against the evidence gathered through documents and fact-finding interviews, the Committee concluded they were able to reject the first hypothesis but unable to reject the second.

CRITICAL TIME PERIOD: 1970–1983

Two important elements frame the period from 1970 to 1983: (1) the discovery of hepatitis as an infectious agent associated with the use of blood and blood products, and (2) the development of viral inactivation procedures for increasing the safety of AHF concentrate. With respect to both elements, it is important to establish when certain scientific information was available in relation to decisions about blood and blood product safety.

Hepatitis

The transfer of blood and blood derivatives between humans is considered one of the greatest and most successful therapeutic practices in modern medicine. However, accompanying the development and increased use of blood transfusion practices, there has been a growth in rates of blood-borne diseases.

Iatrogenic transmission of hepatitis has a long history dating back to at least the 1880s when vaccination against smallpox, using glycerinated lymph of human origin was occasionally practiced. So-called serum hepatitis (now known to result from hepatitis B infection) was also seen in many individuals who received preparations of yellow fever vaccine that had been stabilized by the addition of human serum.

By 1943, hepatitis had been recognized as a complication following transfusion of whole blood and plasma. Supporting evidence accrued during World War II as the constant demand for blood and plasma administration during battle led to the recognition that a serious transmissible illness was affecting large numbers of soldiers following transfusion. Studies conducted in the United States and England following World War II identified two viruses, one with a short incubation period that could be transmitted both orally and parenterally, and the other with a long incubation period and transmissible only parenterally.

The identification of two viruses, made in the late 1940s, was confirmed two decades later with the availability of sera to distinguish between the two types of viruses responsible for the distinct clinical presentations (Seeff 1988). The virus causing hepatitis B (serum hepatitis) was discovered in 1965, and the virus causing hepatitis A in 1973. By 1968, a direct test for the presence of an antigenic component of hepatitis B, or HBsAg (hepatitis B surface antigen) was developed and used to detect individuals suffering from active chronic or acute hepatitis infections. Ultimately, a highly effective vaccine to prevent hepatitis B infection became available in 1982; a second generation recombinant vaccine has been available since 1986. An effective vaccine to prevent hepatitis A has recently been developed.

Despite the widespread use of diagnostic tests for hepatitis A and B, a significantly large number of cases of post-transfusion hepatitis continued to be observed. It was then realized, between 1976 and 1978, that other undiscovered agents were responsible for what became known as non-A, non-B (NANB) hepatitis.

Hepatitis A was found to be responsible for a transient infection that causes a self-limited disease of mild to moderate severity. A mortality rate of 0.2 percent or less is seen following hepatitis A infection and the infection never becomes chronic. Hepatitis A is commonly transmitted by a fecal-oral route, either the result of person-to-person transmission or ingestion of contaminated food or water. The virus usually appears in the bloodstream during the incubation period and the early acute phase of hepatitis A infection. Transmission by blood transfusion or by contaminated AHF concentrate has also been reported, however, such instances of blood-borne transmission are rare.

Hepatitis B (HBV) infection frequently causes a transient infection that in most cases is cleared by the host immune response and leaves the individual immune from reinfection by hepatitis B upon subsequent exposure (i.e., through development of immunity thought to be mediated primarily by antiviral antibodies). However, acute HBV infection can be severe and

sometimes fatal (i.e., there is a 0.2 to 2 percent mortality rate), and a minority of infected persons experience a persistent infection that is associated with progressive liver disease and a type of liver cancer known as hepatocellular carcinoma. Though HBV infection is less likely to be severe, it is more likely to become chronic in young persons, with 90 percent of infected newborns developing chronic infection while only 2 to 7 percent of infected adults do so. Transmission of HBV principally results from exposure to blood or blood products, although sexual transmission is also common. During the 1960s, up to 10 percent of persons who received massive transfusions acquired HBV infection and more than 80 percent of individuals with hemophilia were infected through their use of contaminated pooled AHF concentrate.

In 1977, another virus, the delta hepatitis virus (HDV) was discovered; HDV is an incomplete RNA virus that can be transmitted only in the company of HBV. Infection with HDV can occur either, as a co-infection with HBV, or as a "superinfection" in individuals with pre-existing chronic HBV infection. HDV infection is usually severe with complications of fulminant hepatitis and progressive chronic hepatitis. An overall mortality rate of 2 to 20 percent has been reported. Chronic HDV infections are seen in 1 to 3 percent of HBV infections and 70 to 80 percent of superinfections. The transmissible nature of HDV was established in 1980 by transmission of the virus to HBV-infected chimpanzees.

The identification of the viruses responsible for the hepatitis syndromes permitted the development of serologic tests to screen blood donors for potential infection and resulted in a substantial reduction of posttransfusion hepatitis B.

During the years 1970–1972, the HBsAg test was required and implemented in all blood and plasma collection organizations. In July 1975, the use of a third-generation test for HBsAg with a greater degree of sensitivity, utilizing radioimmunoassay or reversed passive hemagglutination, was required by the FDA. In 1977, the World Health Organization Committee on Viral Hepatitis adopted the terms *hepatitis A* for the hepatitis virus transmitted orally, and *hepatitis B* (HBV) for the virus transmitted sexually and through transfusion of blood or blood products.

As a result of the implementation of HBsAg testing during the period from 1972–1975, AHF concentrate testing positive for HBsAg decreased from 25 percent to 3 percent of Factor VIII lots tested by the FDA, and from 67 percent to 2 percent of Factor IX lots tested by the FDA. After 1975, according to Dr. Robert Gerety, chief of the Hepatitis Branch, Division of Blood and Blood Products in the Bureau of Biologics at the FDA at the time, no lots of either Factor VIII or Factor IX submitted to the bureau contained detectable HBsAg; but despite this, the problem of HBV infection following administration of the AHF concentrate would remain serious (Gerety and Barker 1976).

By 1975, even though third-generation testing was in practice, some donations of blood or plasma had levels of HBsAg that were below the level of assay detection and HBV-infected donations continued to enter the pools used in the plasma lots. Even though these lots contained undetectable levels of HBsAg, owing to the extraordinary infectivity of HBV, they were still able to transmit the infection to susceptible recipients of the affected blood products. However, in 1976, although 80 percent of individuals with hemophilia were identified as positive for the antibody to hepatitis B (evidence of previous infection with the virus), the majority did not develop clinically apparent hepatitis. The percentage of individuals with hemophilia with chronic HBV infection ranged from 2.5 to 7.8 percent and the percentage of those who had clinically

recognizable hepatitis ranged from 6 to 26 percent. Gradually, it was believed by the medical community treating individuals with hemophilia that many adults with hemophilia had developed an immunity to HBV as a result of prior exposure to the virus (Aledort, Dietrich, Levine interviews). Administration of the AHF concentrate to children and adolescents with hemophilia, however, often resulted in clinical and chronic HBV infections (Gerety and Barker 1976). Once screening for HBV markers resulted in the exclusion of HBV carriers in the donor pool, NANB virus was responsible for 80-90 percent of the hepatitis cases. Prospective studies performed in the late 1970s and early 1980s indicated that the incidence of post-transfusion hepatitis (HBV and HCV) was 7-21 percent in recipients of blood from volunteer donors (Barker and Dodd 1989). The infectious nature of NANB hepatitis was first established in 1978 by experimental transmission to chimpanzees. The virus itself was not identified until 1989, and is now referred to as hepatitis C (HCV).

Following the identification of the etiologic agent of the majority of cases of NANB hepatitis in 1988, the natural history and severity of this infection became better known. In prospective studies, 50-70 percent of persons with acute hepatitis C infection were shown to become carriers of chronic HCV. It is known now that chronic hepatitis C infection is often silent, is one of the major causes of cirrhosis, hepatocellular carcinoma, or both, in the United States, and is a common precipitant of liver failure necessitating liver transplantation.

Viral Inactivation of AHF Concentrate

Early Methods

According to a Department of Health, Education, and Welfare Conference on hemophilia in 1976, research at that time had already begun to develop alternate means, other than testing for HBsAg, of removing HBV from final products while maintaining the therapeutic activity of the clotting treatment. Pilot studies had been undertaken to evaluate two methods of viral removal: solid-phase immunoabsorption and polyethylene glycol precipitation. However, results of inoculating chimpanzees with the treated products were equivocal (Barker and Dodd 1989). In 1978, hepatitis continued to present a major risk in the use of pooled plasma products, including fibrinogen, AHF concentrates (i.e., Factors VIII and IX), and Factors II, VII, and X (Trepo, et al. 1978).

Two other methods of viral inactivation were also being developed during the 1970s. These methods provided the foundation for most of the subsequent development in this area. First, Dr. Edward Shanbrom, the codeveloper of Factor VIII concentrates, who by this time had left Hyland Laboratories (Baxter Healthcare) and was self-employed, developed a nonionic detergent method for treating plasma before it was fractionated into Factor VIII and the other plasma derivatives (Shanbrom interview). Second, a German pharmaceutical company, Behringwerke, A.G., initiated studies in 1977 on heat inactivation methods for AHF concentrate (Weidmann and Hoechst 1993).

Dr. Shanbrom's method required adding a detergent to the fractionation column, and was chosen for experimentation because it was known that viruses containing lipid membranes are

readily inactivated by detergent-induced disruption of membrane integrity (Shanbrom pers. com. 1995). The application of the inactivation process before the plasma was fractionated, however, would have required relicensure of all the products of fractionation (Shanbrom, Bacich interviews). Although Dr. Shanbrom tried to interest the various plasma fractionation companies in his detergent process, for several reasons none responded favorably (Shanbrom interview). According to one of the plasma fractionators, they were already involved with heat-treated viral inactivation research, and interrupting these research efforts to begin experimentation on the effectiveness of the detergent method would delay licensing (Bacich interview). There was also a question whether there were sufficient data to support the effectiveness of the detergent process against HBV (Mozen interview). Further, Dr. Shanbrom approached both Armour Pharmaceutical and the federal Centers for Disease Control to test the procedure in chimpanzees to confirm its ability to inactivate hepatitis viruses, but was told that there were too few chimpanzees and that confirming the efficacy of this process was not a priority (Favero 1992).

The process used by Behringwerke was (and still is) a pasteurization procedure that requires the heating of AHF concentrate at 60°C for 10 hours, using sucrose and glycine as stabilizers, before lyophilization. Behringwerke's "heat sterilized" Factor VIII was licensed in Germany in May 1981 (Weidmann and Hoechst 1993). Behringwerke claimed (at that time) that the loss of potency or yield (i.e., factor protein) of the treated Factor VIII was approximately 50 percent, but U.S. manufacturers claimed the loss was 90 percent or more according to their internal studies (Feldman pers. com. 1994).

The reasons for the discrepancies in the results obtained by different companies in testing this method are not clear. However, owing to the loss of activity resulting from this process, the cost of the Behringwerke product was approximately 10 times that of non-heat-treated concentrate (Feldman pers. com. 1994). Although Behringwerke's pasteurized Factor VIII was used in Germany upon its licensure, the company was simultaneously producing non-heat-treated material; also, Germany continued to import Factor VIII from the United States. The loss of yield due to the application of heat resulted in the need to obtain larger plasma volumes according to testimony from a Behringwerke representative. This led to significant supply problems, as larger plasma volumes were difficult to obtain at the time (Weidmann and Hoechst 1993). In 1981, there was only enough pasteurized product to treat about 50 patients, and in 1982 only 100. In addition, while the Behringwerke pasteurized product was shown to be effective against HBV, it remained unknown whether it was effective against non-A, non-B hepatitis.

The heat-treated Behringwerke product was not universally accepted for use among the German hemophilia population for several reasons, including the limited supply. One reason was the belief by some physicians that the stabilizer added to the product during the heating process would also stabilize the virus, hindering full viral inactivation (Feldman interview). There was also a concern about the risk of heat-induced alterations in the structure of the treated Factor VIII preparation (neoantigenicity). Neoantigenicity can lead to the formation of inhibitors, or antibodies, to the altered product after infusion into the patient. The medical community feared that the formation of such inhibitors to the product would render the patient more difficult to treat effectively (Aledort, Levine, Dietrich interviews). Behringwerke's heat-treated product was also considerably more expensive, and German insurance companies covered

its cost only for special circumstances (Weidmann and Hoechst 1993; Federal Minister of Health 1992). Behringwerke initiated testing the pasteurized product for inactivation of NANB hepatitis in 1985, and a successful clinical trial was completed during 1986–1987 (Weidmann and Hoechst 1993).

Studies by U.S. Plasma Fractionation Companies

There were basically three methods utilizing heat for viral inactivation used by U.S. manufacturers in the early 1980s. (1) In 1979, the Baxter Healthcare company initiated studies on heat inactivation of AHF concentrate using a "dry heat" process. The dry heat process involved the application of heat at a specified temperature and time to the concentrate in the lyophilized (freeze-dried) state (Persky pers. com. 1995). (2) The "wet heat" process, a term coined by Alpha Therapeutic, involved suspending powder of lyophilized concentrate in heptane solvent and heating at 60°C for 20 hours. Following the heating process, the solvent was removed and the concentrate revialed (McAuley pers. com. 1995). (3) In liquid pasteurization, Factor VIII, albumin, or other proteins in the completely soluble liquid state were heated with the addition of various stabilizers.

By the early 1980s, all of the plasma fractionators had initiated studies on inactivation by application of various amounts of heat for different durations of time (McAuley pers. com. 1995; Persky pers. com. 1995; Leahy pers. com. 1995; Hammes pers. com. 1995). They also began experimenting with the addition of different stabilizers and organic solvents to protect the protein and enhance the heat effect. There was, however, little if any communication between the different manufacturers regarding the results of the ongoing experiments, because of antitrust laws, regulations, and the normal business consideration of competitive advantage (Bacich pers. com. 1994; Feldman pers. com. 1994; Hammes pers. com. 1995).

Problems of Viral Inactivation Development

As the Behringwerke experience illustrates, to some extent the possibility of using heat to inactivate viruses in AHF concentrate, as used in other plasma derivatives (e.g., albumin), would be accompanied by three major concerns that impeded progress. The first concern was that heat would denature the labile factor protein to varying degrees depending on the amount and duration of the heat. Denaturing of the factor protein could cause the development of new antigens that would stimulate blocking antibodies (inhibitors) and reduce the amount of active factor protein in the recipients. Subsequently, this would further increase the amount of factor protein required to obtain a normal clotting response. The second concern was the potential additional cost of implementing the process. In addition to the heating process itself, a lower yield of active concentrate would increase the need for plasma, resulting in added cost. Finally, there was a concern about the adverse effects on the patient of a possibly unstable heat-treated product with varying degrees of purity. Higher-purity products, those in which extraneous proteins such as fibrinogen were removed (e.g., the Behringwerke product), were found to be

less stable at room temperature after reconstitution, according to the analysis conducted by one manufacturer (Feldman pers. com. 1994).

Impact of the First Reported Cases of AIDS in Individuals with Hemophilia

One of the purposes of the July 27, 1982, meeting of the PHS "Committee on Opportunistic Infections in Patients with Hemophilia" was the need to determine if certain blood products, particularly AHF, were risk factors for AIDS (See Chapter 3). The group issued a recommendation to urgently determine practical techniques for decreasing or eliminating the infectious risks from AHF concentrate. Meeting participants discussed several viral inactivation methods that were under study and that a meeting of the FDA's Blood Products Advisory Committee (BPAC) later in the year would discuss and evaluate the various approaches (Foege 1982). During a December 3-4, 1982 meeting of the BPAC there was discussion of a minimal criterion for virus inactivation in high-risk products such as AHF concentrate. Dr. Aronson, the director of FDA's Coagulation Branch in the Division of Blood and Blood Products, described several experimental methodologies, including heat inactivation, inactivation with propiolactone and ultraviolet irradiation, removal by affinity chromatography, antibody inactivation, immunoabsorbence by immobilized antibody, and polyethylene glycol precipitation. Hepatitis B was selected as a marker to determine the degree of inactivation per method because materials and methods were not yet available for NANB.

The CDC convened a meeting, held in Atlanta in early January 1983, to which those concerned with blood and blood products were invited (see also Chapter 3 and Chapter 5). The recommendations that stemmed from the meeting, however, made no mention of changing the current usage of AHF concentrate. On the other hand, it was mentioned that viral inactivation procedures for Factor VIII were on the horizon (Foege 1982).

Federal Research Support for Viral Inactivation

The National Institutes of Health is the major federal source of funding to support research in areas relevant to health. Within the NIH, the institute with primary responsibility for blood research is the National Heart, Lung, and Blood Institute, and in particular its Division of Blood Diseases and Resources (DBDR) (see Chapter 2). A charge of the DBDR is to support research to improve the quality, safety, and availability of blood and blood products for therapeutic use. Consistent with this charge, the five-year plan published by the DBDR in 1982 identified as a research priority, the development of methods to decrease the transmission of infectious pathogens, particularly the hepatitis viruses, via AHF concentrate and other blood products. However, the Committee did not find any evidence that the NHLBI actually provided any support for intramural or extramural research between 1982-1983 to develop viral inactivation methodologies to limit hepatitis transmission by AHF concentrate.

Beginning in 1982, NHLBI did support several studies aimed at evaluating the potential transmission of the etiologic agent of AIDS through blood and blood products. These efforts

included an interagency agreement with the CDC to evaluate immunologic abnormalities in recipients of blood and blood products, initiated in November 1982, and investigation of the possible transmission of the etiologic agent of AIDS to chimpanzees, in May 1983. In July 1983, a request for applications was released by the NHLBI for the development of tests (so-called surrogate markers) to identify individuals who might act as carriers of the AIDS agent. Seven grants, totaling $1.5 million, were awarded for the purpose in April 1984; their utility was eclipsed, however, by the discovery of HIV at about the same time, and the money was devoted to studies of more specific test methods. In October 1984, the NHLBI issued a request for proposals for the development of HIV inactivation methods for plasma derivatives. Although the NIH and NHLBI might have been expected to take similar action with respect to viral inactivation methods focused on hepatitis, there is no evidence that the agency devoted any substantial effort to this end.

Specific Viral Inactivation Methods

By February 1983, all the major plasma fractionators had results from their research on the development of a heat-treated AHF concentrate. The major, if not exclusive, goal of these inactivation methods was the elimination of hepatitis viruses in AHF concentrate. Each plasma fractionation company subjected the AHF concentrate to varying temperatures and conditions for different durations.

Each company used stabilizers to protect the Factor VIII against the heat, but there was uncertainty whether the stabilizers also provided protection for pathogens as well. Using stabilizers such as sucrose resulted in a less than 20 percent loss of potency (Hwang 1982). Each of the manufacturers also initiated chimpanzee studies to determine if the hepatitis virus had been inactivated. Alpha Therapeutics reported that they had also looked for evidence of neoantigenicity but found none after heat treatment (McAuley 1994).

Testing for the Effectiveness of the Inactivation Process

As stated above, the major rationale for developing a viral inactivation procedure for AHF concentrate was to eliminate the hepatitis viruses. Proof that hepatitis had been inactivated, however, required inoculating the treated AHF concentrate into chimpanzees, a time-consuming, expensive, and resource-intensive effort. From 1981 through 1984 each of the plasma fractionators initiated chimpanzee studies to determine whether their viral inactivation processes inactivated HBV and NANB hepatitis virus. The results of initial studies conducted by Armour Pharmaceutical indicated that HBV was not completely inactivated by their heat treatment process, but that NANB was (Feldman pers. com. 1994). Armour Pharmaceutical was licensed for a process in January 1984 that was proven to inactivate NANB hepatitis in chimpanzee studies; but the company was unable to successfully inactivate HBV with their initial heat treatment process (Leahy pers. com. 1995; Rodell interview).

FDA Approval and Licensing of Treated Factor VIII

Table 4.1 summarizes the dates of license application and the FDA's approval of each plasma fractionator's heat-treated Factor VIII concentrate.

Table 4.1 Chronology of Fractionator License Applications and Approvals for Heat-Treated Factor VIII Concentrate

Plasma Fractionator and Method	Date Applied for FDA Licensing	Date License Granted by FDA
Baxter Healthcare (dry heat 60°C for 72-74 hours)	June 1982	March 1983
Miles Inc., (formerly Cutter Biological) (liquid pasteurization 60°C for 10 hours)	August 1983	January 1984
(dry heat 68°C for 72 hours)	November 1983	February 1984
Alpha Therapeutic (wet heat 60°C for 20 hours)	December 1982	February 1984
Armour Pharmaceutical (dry heat 60°C for 30 hours)	December 1982	January 1984

(Persky 1995; Rodell 1982; Petricciani 1983; Hammes 1995; Mozen 1995; McAuley 1995; Feldman 1994)

Baxter's licensing was accomplished in only eight months and licensing for the other fractionators took about 12 months from initial application. All plasma fractionators were licensed for sale of Factor VIII concentrate by February, 1984. Upon licensure of the change in processing of the AHF concentrate products, the plasma fractionators immediately began producing a proportion of their production output using the added heat treatment step (Leahy pers. com. 1995; McAuley pers. com. 1995; Hammes pers. com. 1995; Persky pers. com. 1995). The four relevant plasma fractionators claim to have begun processing and distributing heat-treated AHF concentrate immediately after obtaining FDA licensure. However, none of the companies had entirely converted their manufacturing processes to produce only heat-treated products at the time they were licensed by the FDA to produce heat-treated AHF concentrate.

ANALYSIS AND CONCLUSIONS

As with other areas of scientific investigation, technical advances to improve the safety of blood and blood products relies on the imagination and abilities of individual researchers, the availability of sufficient financial resources to encourage and support new research directions, and the encouragement or pressure applied by regulatory agencies or consumer advocates. Progress in improving the safety of AHF concentrate could have potentially been encouraged by a variety of sources including the plasma fractionation industry, the NIH, the FDA, and the National Hemophilia Foundation. In evaluating the adequacy of the response of each of these groups, the Committee reviewed the sources of technical innovation and research funding for viral inactivation technologies for the hepatitis viruses and HIV. Furthermore, as scientific progress can be greatly facilitated by the open exchange of research findings, the Committee attempted to analyze the communication that took place among these different groups about their efforts to develop effective viral inactivation methods. After reviewing the data on the development of viral inactivation, the Committee concluded that although viral inactivation methods had begun in the late 1970s to eliminate hepatitis, they were not given a high priority for several reasons.

First, most individuals with hemophilia had already been exposed to HBV, which led to the perception that these individuals did not need to be protected through viral inactivation of the AHF concentrate (see Chapter 7) and that initial exposure to the hepatitis virus caused the development of protective antibodies in the majority of individuals with hemophilia (Dietrich, Aledort, Levine interviews). Also, the anticipated availability of a vaccine against HBV led to the expectation that uninfected individuals and infants would be protected against it. This protection, provided by the vaccine, would be accomplished without resorting to methods to improve the safety of AHF concentrate (Pindyck interview). It was not known until sometime between 1976 and 1978, after introduction of the third generation screening test for hepatitis B in 1976 and continued observation of transfusion-associated hepatitis, that the majority of these transfusion-associated hepatitis cases were due to other agents, especially the virus subsequently identified as HCV. This fact, together with the lack of knowledge of the virulence of NANB hepatitis at that time, further contributed to the limited impetus for and the slow pace of the development of viral inactivation technology. In addition, plasma fractionators, government, the medical community, and society as a whole, did not seem to realize that new serious pathogens, or latent agents (e.g. Creuzfeldt-Jacob disease), might also be present in the untreated concentrate. Hepatitis was viewed to be an acceptable risk for individuals with hemophilia because it was considered a medically manageable complication of a very effective treatment for hemophilia (See Chapter 7).

According to the record, all of the product treatment methods that were ultimately proven to be effective in inactivating the hepatitis B and C viruses, and HIV, were developed within the laboratories of the plasma fractionators or by individuals closely associated with these industries. With the exception of Behringwerke, A.G., in Germany, each of the major plasma fractionators developed their inactivation methods at approximately the same time and entirely independently of each other. Dr. Edward Shanbrom, once employed by Hyland Laboratories (Baxter Healthcare), advocated a detergent method for viral inactivation after leaving the company.

Without adequate support for the development or testing of this method, however, it did not gain widespread attention or acceptance. The record thus clearly indicates that, regardless of potential input or support from other sources, the impelling motive and decision to develop viral inactivation methods depended almost entirely on the plasma fractionation industry.

Given the FDA's role in licensing and ensuring the safety and efficacy of AHF and other plasma-derived materials, it would be natural to expect the agency to have had an interest in fostering, supporting, and possibly even conducting research on ways of inactivating hepatitis viruses and other infectious agents present in these preparations. However, review of the FDA's activities in this area uncovered only limited evidence of proactive effort to encourage industry to develop viral inactivation methods to limit hepatitis transmission by AHF. The FDA had essentially no significant internal research activities in this area. The FDA did convene a BPAC meeting in December 1982 to review the approval process for viral inactivation methods, with a particular focus on the details of the requisite chimpanzee challenge experiments. Several BPAC sessions in 1983 were devoted to viral inactivation and marker viruses (Fratantoni 1995) however, this type of activity primarily served to facilitate, rather than actively encourage, the implementation of viral inactivation technologies.

The Committee identified several apparent reasons for the limited level of activity by the FDA, but their relative importance is difficult to determine. In discussions with FDA officials, certain useful perspectives emerged (Aronson, Donohue interviews). First, like most other persons with knowledge of this area, officials at the FDA appear to have been complacent about the risk of hepatitis transmission from AHF concentrate. Thus, although viral inactivation was considered a laudable goal, there seems to have been no sense of urgency in encouraging its development. Second, FDA officials believed that the appropriate expertise for developing viral inactivation methods resided in industry and that innovations would eventually emerge. Only a very limited number of personnel were available for the regulatory oversight of coagulation products in the early 1980s, and much of their time and effort was devoted to the emerging methods for thrombolytic therapy for myocardial infarctions. In addition, the FDA had only very modest internal facilities and support for research on viral inactivation technologies.

Given these factors, it is perhaps not surprising that the FDA looked to industry to provide the specific direction for progress in viral inactivation. However, the factors that influenced the pace of viral inactivation technologies developed by industry included interest in gaining competitive advantage and concerns over yield and cost. While these concerns are understandable from the perspective of a manufacturer, in the absence of active encouragement by the FDA these concerns probably inhibited expeditious progress in inactivation technologies. Further, with the primary responsibility for the development of viral inactivation methods left to industry, inherent limitations were placed on the free exchange of scientific and technical information that might expedite product development efforts. Operating in a competitive market, manufacturers are not inclined to share the details of their research efforts; and the FDA is legally barred from sharing a company's research findings among competitors. Companies interacting among each other could be in violation of antitrust laws and face potential criminal charges, fines and sanctions. Furthermore, the very nature of the competitive world of business is one that normally would cause a company to preserve manufacturing processes and research results for its own benefit, to enable the marketing of products at a competitive advantage.

The Committee found that the plasma fractionators did not seriously consider alternative inactivation processes (e.g., the detergent process) because they placed a low priority on developing inactivation procedures for AHF concentrate and because heat inactivation had been successful for other blood products. Further, inactivation of pooled source plasma before fractionation would have required individual relicensure of all plasma products (Bacich, Hammes, Shanbrom interviews). In addition, inactivation methods used on plasma products could cause neoantigenicity, a problem that would negate the clinical effectiveness of AHF concentrate and possibly render the patient untreatable with these concentrates. The difficulty of testing the efficacy of inactivation procedures was due to the lack of correlation between antigen testing and infectiousness, and the absolute need for (and scarcity of) chimpanzees, which slowed progress in developing inactivation methods (Shanbrom pers. com. 1995; Epstein and Fricke 1990).

Once the initial inactivation methods were developed and shown to be effective in limiting the transmission of hepatitis B and NANB infection in experimentally inoculated chimpanzees, there was a relatively short interval between the product licensing application submission to the FDA and the licensure of the heat-inactivated products. The fact that the plasma fractionation industry was able to produce an inactivated product for license consideration concurrent with, and shortly, after the first reports of AIDS in individuals with hemophilia suggests that hepatitis infection (rather than AIDS) provided the major motivation for the ultimate development of viral inactivation methods.

SUMMARY

Overall, the record of the plasma fractionators and the FDA with respect to the development and implementation of heat treatment is mixed. The Committee's analysis focused on whether scientific information and technology was available earlier for the development of viral inactivation methods for AHF concentrate, and whether industry had appropriate incentives (from the FDA, the NIH, the NHF, or others) to develop these processes. In the Committee's judgment, heat treatment processes to prevent the transmission of hepatitis could have been developed before 1980, an advance that would have prevented many cases of AIDS in individuals with hemophilia. Treaters of hemophilia and Public Health Service agencies did not, for a variety of reasons, encourage the companies to develop heat treatment measures earlier. Strong incentives to maintain the status quo and a weak countervailing force concerned with blood product safety, combined to inhibit rapid development of heat-treated products by plasma fractionation companies.

Once inactivation methods were developed, the plasma fractionators and the FDA moved expeditiously to license them. Following licensure of the first heat-treated AHF concentrate, however, many treating physicians and the National Hemophilia Foundation were slow to encourage their patients to use the new product (See Chapter 6).

AFTERWORD

Subsequent Events

In 1988, the CDC reported the results of a study of 75 HIV infected recipients of Factor VIII. Among this group 75, they identified 18 sole recipients of a batch of Factor VIII from a single manufacturer which had been heat treated at 60°C for 30 hours. Subsequently, the manufacturer withdrew the product from the market and the lyophilized Factor VIII treated for 30 hours or less was no longer produced by any of the manufacturers. Armour Pharmaceutical modified their heating process by heating at 68°C for 72 hours (Feldman pers. com. 1994).

In 1992, investigators in France and Holland reported the development of a high incidence of inhibitor formation in hemophilia patients treated with a specific European manufacturer's preparation of AHF concentrate (Rosendaal, et al. 1993). This event alerted the medical community worldwide to the possibility of inhibitor formation following treatment with virally inactivated products, which had been extensively discussed previously but had not been reported. Although the development of inhibitors to AHF concentrate (heat-treated and non-heat-treated) had been seen in the first few years of treatment of a hemophilia patient, it was rarely observed in multitransfused patients (Rosendaal, et al. 1993).

Current Procedures and Challenges

Since the mid-1980s, each of the plasma fractionators has revised their manufacturing and viral inactivation procedures for Factor VIII and IX. Current procedures used in the United States for viral inactivation include (a) heating in solution (pasteurization), and (b) use of an organic solvent such as N-Butyl phosphate with a detergent such as Triton X-100 or polysorbate 80. Current techniques for purifying the Factor VIII proteins to reduce the amount of virus in the product, include monoclonal antibody affinity chromatography and processes of intensified ultrafiltration. In addition, individual units of plasma are currently screened with the following tests before pooling: HBsAg, anti-HIV 1 and 2, ALT, anti-HCV 2.0, and syphilis (McAuley pers. com. 1995; Mozen pers. com. 1995; Leahy pers. com. 1995; Persky pers. com. 1995).

The production of AHF using genetic engineering techniques is a major advance in blood product safety. Recombinant Factor VIII has been available since 1993 and recombinant Factor IX is currently in clinical trial (Mozen pers. com. 1995). Recombinant factor is produced by synthesizing a glycoprotein from a genetically engineered Chinese hamster ovary cell line, which secretes recombinant antihemophilic factor (rAHF) into a cell culture medium. The rAHF is extracted from the culture medium by immobilizing the monoclonal antibody in a series of chromatography columns to selectively isolate the rAHF in the medium (Persky pers. com. 1995). DNA research in factor proteins had begun at the start of the 1980s and Miles, Inc. cloned the factor VIII gene in 1984 (Mozen pers. com. 1995).

In March 1995, two pharmaceutical companies initiated precautionary voluntary withdrawals of immune globulin products manufactured before December 1994 for possible hepatitis C transmission. The FDA's Center for Biologics Evaluation and Research acknowledged that

"there is no epidemiologic evidence of hepatitis C transmission by intramuscular immune globulins" but evidence exists for transmission of HCV by non-virally-inactivated intravenous immune globulin manufactured after the institution of the anti-HCV testing (Council of Community Blood Centers 1995). According to the Council of Community Blood Centers (1995), the FDA began testing samples of immune globulins lots not subjected to a viral inactivation step in December 1994. This testing program follows a May 1993 recommendation to immune globulin manufacturers to develop viral inactivation procedures for all their products. The FDA recommends positive or untested lots be used only if lots known to be negative are not available (Council of Community Blood Centers 1995).

Finally, the Committee examined recent modifications instituted by several European countries to improve blood supply safety. It was found that blood supply safety measures adopted internationally included implementation of two-stage viral inactivation processes. Other measures included: decreased reliance on blood products imported from other countries; increased centralized oversight, control authorities and processes; regulation of epidemiological surveillance systems; expert advisory panels for research, testing, and quality control; and establishment of a computerized tracking system for monitoring treatment.

REFERENCES

Bacich, John, Baxter Healthcare. Personal communication to the Institute of Medicine; November 16, 1994.

Barker, Lewellys F., Dodd, Roger Y. "Viral Hepatitis, Acquired Immunodeficiency Syndrome, and Other Infections Transmitted by Transfusion," from Petz, Lawrence D., Swisher, Scott N. Clinical Practice of Transfusion Medicine (second edition) Churchill Livingsone, Inc., New York, NY; 1989.

Council on Community Blood Centers. Newsletter; March 10, 1995.

Epstein, Jay S., M.D., Fricke, William A., M.D., "Current Safety of Clotting Factor Concentrates," *Archives of Pathology and Laboratory Medicine*, Vol. 114; March 1990.

Favero, Martin S., Assistant Director for Laboratory Science Centers for Disease Control. Letter to Dr. Edward Shanbrom; September 8, 1982.

Federal Minister of Health. *Report by the Federal Minister of Health to the Committee on Health of the German Parliment;* 1992.

Feldman, Frederick, Armour Pharmaceutical. Personal communication to the Institute of Medicine; November 18, 1994.

Foege, William H., M.D., Assistant Surgeon General and Director Centers for Disease Control. Memorandum to Assistant Secretary for Health; August 6, 1982.

Frantantoni, Joseph C., M.D. Letter to the Institute of Medicine; 1995.

Gerety, Robert J., Barker, Lewellys F. "Viral Antigens and Antibodies in Hemophiliacs" proceedings from Unsolved Therapeutic Problems in Hemophilia Conference sponsored by the Bureau of Biologics, FDA Division of Blood Diseases and Resources, NHLBI, and the National Hemophilia Foundation; 1976.

Hammes, William J., Associate Counsel, Miles, Inc. Letter to Institute of Medicine; February 13, 1995.

Hwang, D. "Hepatitis-Free AHF," Alpha Therapeutics, interoffice memorandum to Dr. C. Heldebrant; September 17, 1982.

Leahy, Beth, Director Public Affairs, Armour Pharmaceutical. Letter to IOM; March 17, 1995.

McAuley, Clyde, M.D., Medical Director, Alpha Therapeutic. Letter to Institute of Medicine; February 8, 1995.

McAuley, Clyde, M.D. Medical Director, Alpha Therapeutic. "Alpha Information Re: AIDS," submission to the Institute of Medicine; September 8, 1994.

Mozen, Milton, Ph.D., Scientific Affairs, Miles, Inc. Personal communication to the Institute of Medicine; January 20, 1995.

Persky, Marla, Associate General Counsel, Biotech Group Baxter Healthcare. Letter to the Institute of Medicine; February 24, 1995.

Rosendaal, et al. "A Sudden Increase in Factor VIII Inhibitor Development in Multitransfused Hemophilia A Patients in the Netherlands." Blood; April 15, 1983.

Seeff, Leonard B. Transfusion Associated Hepatitis: Past and Present. Transfusion Medicine Reviews, Vol 2.; December, 1988.

Shanbrom, Edward. Personal communication to the Institute of Medicine; January 19, 1995.

Trepo, C., et al. "Different Fates of Hepatitis B Virus Markers during Plasma Fractionation," Vox Sang, vol. 35; 1978.

Weidmann, Ernst, M.D. and Hoechst AG. U.S. District Court Northern District of Illinois Eastern Division, Gruca v. Alpha Therapeutic, Co.; November 8, 1993.

Donor Screening and Deferral

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Donor Screening and Deferral

INTRODUCTION

The purpose of donor screening and deferral procedures is to minimize the possibility of transmitting an infectious agent from a unit of donated blood to the recipient of that unit, as well as insuring the welfare of the donor himself. Donor screening and deferral includes measures taken prior to and during the collection of blood or plasma. Specifically, donor screening includes the identification of suitable donors; the exclusion of high-risk groups (for example, prisoners); use of questionnaires, interviews, and medical exams at the time of donation; and providing donors with the opportunity to self-defer by privately coding the unit label as "do not transfuse" or "not for transfusion" (self-deferral is discussed in detail at the end of this chapter). Donor screening also includes laboratory tests performed on the unit of blood collected for the presence of markers of infectious disease. Two types of tests can be used to detect an infectious agent, a surrogate test (such as antibody to hepatitis B core) or a direct test for the virus (anti-HIV using the ELISA test as of March 1985; See Chapter 3). These tests are performed because donors may be unaware that they are asymptomatic carriers of an infectious agent or may be unwilling to identify themselves as a member of a high-risk group. Donor deferral is the temporary or permanent rejection of a donor, based on the results of the screening measures listed above.

By January 1983, the CDC had accumulated enough epidemiological evidence to suggest that the agent causing AIDS was being transmitted through blood and blood products, and also through sexual contact. The evidence also demonstrated that there were several groups in the United States with an increased risk for developing AIDS. The highest incidence of the disease was reported in male homosexuals, who were donating blood frequently in some geographic regions. In the early 1980s, the increased evidence of infections in IV drug users suggested that AIDS was an infectious disease similar to hepatitis B in modes of transmission. As a result, debates began regarding the possibility of increasing the safety of the blood supply through the exclusion of high-risk groups as blood and plasma donors. This chapter describes donor screening and deferral measures before the test for HIV (ELISA) became available in 1985 and addresses whether the actions taken were reasonable given the information available at the time.

Critical Events

Donor screening issues arose in mid to late 1982, when the first cases of AIDS in hemophiliacs were reported and the first possible case of transfusion-associated AIDS was reported in an infant (CDC, MMWR, July 16, 1982; CDC, MMWR, December 10, 1982). As a result, the blood bank community began discussing the costs and benefits of several types of donor screening measures in late 1982 and early 1983. Between December 1982 and December 1983, there were two critical events that presented opportunities for the blood services community to enact new donor screening and deferral policies to reduce the threat of HIV transmission through blood and blood products.

Critical Event 1

On January 4, 1983, the Public Health Service (PHS) held a meeting convened by the CDC in Atlanta on opportunistic infections in hemophiliacs. At the meeting, the blood services community first heard preliminary data on the possibility of a transmissible agent within the blood supply. Scientists from the CDC recommended that blood banks implement specific donor screening measures such as questioning donors about their risk behaviors and running blood donations through a series of tests, among which the most important was for the hepatitis B core antibody insofar as it occurred in most individuals who had AIDS (Foege, Curran, Evatt, McAuley, Rodell, Pindyck interviews; Foege January 4, 1983). There was broad resistance to the implementation of specific donor screening measures, and the meeting ended with no consensus on the validity of such measures for the exclusion of high-risk donors.

Critical Event 2

On December 15–16, 1983, the Blood Products Advisory Committee (BPAC) of the FDA met to discuss, in detail, all possible options of surrogate marker tests for HIV (See also Chapter 3). This meeting is notable for being a second attempt to address the need to implement surrogate tests as a means to increase the safety of the blood supply, and a second occasion when testing was proposed but not recommended.

Explanatory Hypotheses

The Committee identified three hypotheses to guide its analysis of the issues of donor screening and deferral:

1. There was a lack of consensus about the costs and benefits of implementing various donor screening procedures as a means to reduce the risk of transmission of HIV through the blood supply, which resulted in limited responses among organizations to the issues of donor safety.

2. Information available at the time might have been sufficient to convince blood and plasma collectors of the need to directly question donors about their risk behaviors (e.g., sexual preference, drug use) or to use anti-HBc testing as a means to exclude high-risk donors, but other constraints in the environment in which they operated prevented the collectors from implementing a specific policy in the early 1980s.
3. Inappropriate incentives inhibited reasonable decision making by the responsible parties.

Testing these hypotheses against the documentary and personal evidence, the Committee concluded that they were able to support the first and second hypotheses, but unable to support the third. Before turning to a detailed examination of these conclusions, we present a brief history of donor screening practices.

DONOR SCREENING PRACTICES

Hepatitis

Cases of post-transfusion hepatitis were described as early as 1943 (Bensen 1943) and syphilis screening tests were introduced in 1946. In 1965, identification of the virus causing "serum hepatitis" led to a direct test for the presence of an antigenic component of the virus. Prior to 1970, the incidence of posttransfusion hepatitis was 8–17 percent among transfusion recipients (Seeff 1988). During the period from 1970–1972, all blood and plasma collection agencies implemented the test for the presence of hepatitis B virus. Subsequently, hepatitis cases continued to appear in approximately 5-18 percent of transfusion recipients (Office of Technology 1985), strong evidence that viruses in the blood supply other than hepatitis B caused hepatitis (non-A, non-B hepatitis).

Donor Pools

In the late 1970s and early 1980s, blood donor pools included many groups at high risk for AIDS. The homosexual population volunteered to donate blood frequently during this time frame, in efforts to help develop a hepatitis B vaccine and to gain a social acceptance (Evatt, Curran, Perkins, McAuley interviews). In addition to homosexuals, other populations who were at a high risk for infectious diseases, such as prison inmates and persons in other institutional settings (e.g., mental hospitals), served as blood or plasma donors (McAuley, Rodell, Perkins, Shanbrom interviews). People in these groups constituted a large proportion of the paid donors in the United States. Thus, both the paid and volunteer donor pool included many individuals from the high-risk populations.

Early Donor Screening Practices

Efforts to have "safe" donors started in the early 1950s. The aim was to eliminate persons who carried the two known blood-borne infectious agents, those causing syphilis and hepatitis. Blood bank personnel obtained every donor's medical history and deferred any donors who had a history of hepatitis. Blood from volunteer donors was known to be safer than blood from paid commercial donors (Allen, et al. 1959; Eckert 1986). In July 1973, the Secretary of Health, Education, and Welfare called for a transition to an all-volunteer blood donation system (for whole blood) as part of a national blood policy. In November 1975, the FDA required that all blood units collected be labeled as from either a paid or a volunteer donor (U.S. Comptroller General 1975). At this time (and currently), paid donors were the principal source of plasma for fractionation into blood products such as AHF concentrates.

In 1982 the American Association of Blood Banks (AABB) standards required that each donor meet the following criteria: the donor had to appear in good health, the skin at the venipuncture site had to be lesion-free, the donor should not have received blood or blood components (known to be a possible source of hepatitis) in the preceding six months, and the donor's arms had to pass inspection for repeated sites of venipuncture prior to donation. In addition, the standards required permanent deferral of a donor if the donor had a history of viral hepatitis, a history of reactive tests for hepatitis B surface antigen, or had donated the only unit of blood or blood components transfused to a patient who developed posttransfusion hepatitis within the six months following transfusion. Recent travel to areas considered endemic to malaria led to deferral for six months after return, and donors with clinically active hepatitis were unacceptable (AABB 1982). These standards applied to American Red Cross collection centers and to all other community blood banks that were members of the AABB.

In 1982, the AABB required that all its member blood collection sites perform the following tests on each unit collected: determination of ABO type, determination of Rh type, tests for "unexpected antibodies" prior to cross-match, tests for hepatitis B surface antigen, and a confirmatory test on blood type and Rh type after labeling the unit to discover any labeling errors (AABB 1982).

ANALYSIS AND FINDINGS

January 4, 1983, CDC Meeting

As a follow-up to meetings in July 1982 (see Chapter 3), the meeting in Atlanta on January 4, 1983 was convened to consider opportunities to prevent AIDS transmission, both person-to-person, and through blood and blood products. This meeting was widely publicized, and over 200 people attended, including representatives of the CDC, the FDA, NIH, the National Hemophilia Foundation, the National Gay Task Force, blood banks, and the plasma fractionation industry. While there was a consensus among most plasma and blood collection organizations and PHS agencies that steps should be taken to reduce the risk of AIDS transmission through the blood supply, members of the scientific and medical community disagreed on measures for detecting high-risk donors.

William Foege, director of the CDC, opened the meeting, which was chaired by Jeffrey Koplan, assistant director for public health practice at the CDC. James Curran and Bruce Evatt of the CDC presented data they had collected on AIDS in hemophiliacs and transfused patients. They concluded that AIDS was transmitted by sexual contact and through blood (Curran, Evatt, Foege interviews). They also stated that this infectious agent might have entered the blood supply through donations from infected people, particularly male homosexuals. By January 1983 more than 700 cases of AIDS had been reported, of which approximately 70 percent were in homosexual men. The CDC officials suggested changing the donor screening process to identify homosexual donors with multiple sexual partners by asking male donors whether they had ever had sex with a man (Foege January 4, 1983).

At the meeting, CDC scientists also recommended performing a surrogate test for AIDS (to detect antibodies against hepatitis B core antigen) on all blood units. Surrogate testing is "the use of nonspecific laboratory markers" to detect infectious agents that show a correlation with HIV infection. The CDC predicted that implementing the anti-core test for hepatitis B would detect 90 percent of donors with AIDS. There was no agreement that the test would be effective, and there was no consensus to use it.

Outcomes of the Meeting

A series of responses followed the meeting. On January 6, 1983, Donald Francis, assistant director for medical science of the Virology Division at the CDC, wrote a memo to Dr. Koplan, stating that the CDC should proceed to promulgate its recommendations in the hope that the FDA would agree. One of the CDC recommendations was deferral of all blood and plasma donors who

- are IV drug users (already in place);
- are sexually (heterosexually or homosexually) promiscuous (more than an average of two different people per month for the previous two years);
- have had sexual (heterosexual or homosexual) contact with someone who is sexually promiscuous or an IV drug user in the past two years;
- have lived in Haiti in the past five years; and
- have a serologic test positive for anti-HBc.

Francis estimated that this deferral process would eliminate over 75 percent of AIDS-infected donors (Francis 1983).

The blood banks (American Association of Blood Banks, American Red Cross, and Council of Community Blood Centers) issued a joint statement entitled "Acquired Immune Deficiency Syndrome Related to Transfusion" on January 13, 1983. They recommended that donor screening include specific questions to detect early symptoms of AIDS or exposure to patients with AIDS, but they did not recommend asking about high-risk sexual practices. The joint statement addressed the question of whether it was appropriate to limit voluntary blood donation from groups at high-risk for AIDS, and pointed out that this question involved many medical, ethical, and legal issues that were not easily resolved. The recommendations held that despite

pressure on the blood banks to restrict blood donation by gay male donors, "direct or indirect questions about a donor's sexual preference are inappropriate." The joint statement also encouraged the use of autologous donations, especially in elective surgery, and called upon blood banks to prepare to handle increased requests for cryoprecipitate (AABB, et al. 1983).

During the early months of 1983, prior to any PHS recommendations, many blood banks added to their donor questionnaires inquiries about symptoms associated with AIDS, such as presence of enlarged lymph nodes, night sweats, and weight loss. On January 14, 1983, the Medical and Scientific Advisory Council (MASAC) of the National Hemophilia Foundation recommended that the plasma product industry take steps to eliminate high-risk donors (e.g., IV drug users, homosexuals) from plasma donation. The plasma fractionators began questioning donors and excluding high-risk donors in the first months of 1983, but did not implement surrogate testing (National Hemophilia Foundation 1983).

The American Blood Resources Association (ABRA), a trade organization for the manufacturers of blood products, issued its recommendations on donor deferral on January 28, 1983. One of the three focal areas of ABRA's recommendations was surrogate laboratory testing. At the time, ABRA recommended against large scale surrogate testing pending an assessment of the issues underlying the implementation of surrogate testing, specifically determining "the adequate availability of testing reagents and equipment of any of the several possible tests under consideration, their economic and logistical impact upon the plasma supply network, the efficacy of the test to exclude high risk individuals, and other potential consequences to plasma products resulting from the imposition of additional testing requirements" (ABRA 1983).

The PHS promulgated its first official recommendations on the prevention of HIV on March 4, 1983. Individuals at high risk for AIDS were required to refrain from donating plasma and/or blood. Persons at increased risk of AIDS included the following:

- persons with symptoms and signs suggestive of AIDS;
- sexual partners of AIDS patients;
- sexually active homosexual or bisexual men with multiple partners;
- Haitian entrants to the United States;
- present or past abusers of IV drugs;
- patients with hemophilia; and
- sexual partners of individuals at increased risk for AIDS.

Prior to the issuance of these recommendations, donor selection policies [AABB 1982 Standards for Transfusion Services] for both the collection of whole blood and plasma already sought to identify people in the following high-risk groups as being at increased risk of infectious diseases: drug abusers, persons with residence in or recent travel to Haiti, and those with a history of recent treatment with blood products. The PHS made the following new recommendations for preventing transmission of AIDS through blood and blood products:

- Sexual contact should be avoided with persons known to have or suspected of having AIDS.

- Members of groups at increased risk for AIDS should not donate blood and/or plasma; centers collecting plasma or blood should notify donors of this recommendation.
- Studies should be conducted to evaluate screening procedures, including lab tests and physical examinations, for their effectiveness in identifying and excluding plasma and blood with a high probability of transmitting AIDS.
- Physicians should adhere strictly to medical indications for transfusions and encourage autologous donations.
- Work should continue toward development of safer blood products for use by hemophilia patients.

The PHS did not recommend directly questioning donors about high-risk sexual behavior nor did it recommend surrogate testing of donated blood (CDC, MMWR, March 4, 1983).

Later in March 1983, the FDA notified all establishments collecting source plasma and whole blood for transfusion, and manufacturers of plasma derivatives, of the steps needed to decrease the risk of blood or plasma donation by persons who might be at increased risk of transmitting AIDS. The FDA advised the blood and plasma facilities to train personnel who screen donors to recognize the early signs of AIDS and to establish educational programs to inform persons at increased risk for AIDS that they should stop donating. The FDA issued three letters on the reduction of the risk of transmission of HIV through blood and blood products (see appendix D for the text of these letters, and chapter 6 for further discussion). The letters recommended the following steps for whole blood and plasma collection centers:

(a) Educational programs should be instituted to inform persons at risk of AIDS that until the AIDS problem was resolved or a definitive test for AIDS became available, they should refrain from donating blood;
(b) Personnel responsible for donor screening should be retrained to recognize signs and symptoms of AIDS; and
(c) The standard operating procedure should include the quarantine and disposal of any products collected from a donor that was known to have AIDS or was suspected of having AIDS (Petricciani 1983a,b);

The following additional steps applied only to plasma collection centers:

(d) If plasma was collected from a donor belonging to a high-risk group, label each unit to identify it for restricted use only;
(e) Examine donors for lymphadenopathy; and
(f) Keep an accurate record of each donor's weight and monitor for significant weight loss (Petricciani 1983c).

These advisories constituted an interim measure to protect recipients of blood and blood products until specific laboratory tests became available.

The FDA recommendations for plasma fractionators stated that "extensive discussions among licensed manufacturers, the Office of Biologics and concerned groups such as the NHF, have led to a consensus concerning an appropriate approach to decreasing the potential risk of

transmitting AIDS by certain plasma derivatives." The recommendations included (a) do not fractionate plasma collected from donors at increased risk of AIDS into derivatives already known to have a high risk of disease transmission; (b) use plasma from donors in high-risk groups only for the manufacture of albumin, plasma protein fraction (PPF), globulin or in vitro diagnostic products; and (c) all establishments must label products containing plasma proteins from high-risk donors with "caution, for use in . . ." (Petricciani 1983c). The memo made the restrictions effective immediately. Although the FDA did not call the recommendations in these letters regulations, blood and plasma collection organizations promptly implemented them (Perkins, Bove, Sandler, Petricciani interviews).

Donor Questioning and Opposition to It

A representative from Alpha Therapeutics, a commercial manufacturer of AHF concentrate, announced at the January 4, 1983, meeting that the company had instituted direct donor questioning designed to exclude high-risk individuals from plasma donation. On December 17, 1982, Alpha Therapeutics had required the exclusion of all donors who had been in Haiti, used IV drugs, or, if male, had had sexual contact with another man. The announcement of this action met with a great deal of opposition from many groups, including the volunteer blood banks and the gay community. These groups took the position that donor sexual preference was a private matter and that the questionnaire was an invasion of privacy. Additionally, Alpha Therapeutics took the position at the January 4, 1983, meeting that AIDS should be a reportable disease, in order to assist in donor screening (Alpha Therapeutics 1994).

Representatives from other plasma fractionation companies also present at the January 4, 1983 meeting discussed the potential threat to the safety of plasma and their manufactured products. One representative from the Pharmaceutical Manufacturers Association stated: "The fractionation industry voluntarily led the way several months ago in designing and implementing donor-processing programs that were aimed at minimizing participation in plasma collection by members of AIDS high-risk groups. By the early part of 1983, each of the companies . . . had in place donor education and questioning programs specifically requesting members of high risk groups to identify themselves and refrain from donating plasma (FDA, BPAC, July 1983)." One explanation for the plasma fractionators' aggressive approach to donor screening may have been the profit motive that drives one company to distinguish itself from its competitors. Executives at Alpha Therapeutics and other companies may have acted upon their belief, or strong suspicion, that AIDS was caused by a blood-borne infectious agent, and as a result implemented screening policies to protect both their company from product liability and the recipients of their products from harm. In addition, Alpha's insistence on the exclusion of high-risk donors in late 1982 may have led other companies, which did not want their products to appear less safe than Alpha's, to implement donor screening policies in 1983.

Some nonprofit blood centers initiated projects directed towards excluding donors or removing infected blood from the available supply. For example, by February 1983, the Greater New York Blood Program was providing donors with information about AIDS, high-risk groups and the possibility of transmitting AIDS through blood. They asked donors either not to give blood or to give it for research purposes if they identified themselves as a member of a high-risk

group (self-deferral). Medical screening resulted in the deferral of an additional two percent of donors, and a confidential questionnaire resulted in self-deferral by 1.4 percent of the donors (Pindyck 1985). The prevalence of anti-HBc in the group who indicated their blood was for research only was approximately 12 percent, compared to 6 percent among those donations marked for transfusion. These gains were weighed against the estimated cost of the anti-HBc test ($3.00 per test) and the cost of discarding a unit and replacing a donor (FDA, BPAC, December 15-16, 1983; Pindyck 1985). As a result, the New York program relied on "confidential unit exclusion" as a safety measure, rather than implementation of a routine anti-HBc surrogate test. (Confidential unit exclusion involves use of a bar code sticker to label a unit "do not transfuse" or "not for transfusion." See Afterword below.)

Although blood banks did not implement direct questioning of donors about their sexual preferences at the same time plasma collectors did, they did comply with the FDA's recommendations issued on March 4, 1983. These recommendations included the following steps: to expand medical screening of donors, to provide written educational materials to donors about those groups at increased risk of AIDS and the necessity of refraining from donation if identified as a member of the high-risk groups, as well as allowing for individual methods (e.g., confidential unit exclusion) for confidential self-deferral (OTA 1985).

Some people viewed direct questioning about sexual behavior and drug use as a violation of an individual's right to privacy. Public health officials countered by saying that the individuals' rights were less important than the collective public health. Many in the gay community objected to direct questioning and donor deferral procedures as discriminatory and persecutory. Many in the blood bank community questioned the appropriateness of asking direct or indirect questions about a donor's sexual preference (Curran, Evatt, Foege, Sandler, Bove interviews). Other individuals and organizations were concerned about providing the public with information about AIDS that might scare them away from donating blood (Curran, Evatt, Foege interviews). The National Hemophilia Foundation, physicians, and hemophilia treatment centers were concerned about AHF concentrate shortages and favored conveying a "let's not panic" attitude to the public (Curran interview).

The blood banks began with the view that a volunteer blood donor is an altruistic person who, despite the inconvenience, takes the time to donate blood. The idea of confronting such a donor with a prying and personal question about his sexual behavior seemed reprehensible and potentially very damaging to donor motivation (Bove, Sandler interviews). In addition, the blood banks perceived that the gay community might not cooperate if gay donors were rejected on the basis of sexual orientation, and furthermore, that they might donate on purpose or out of spite (Evatt, Silvergleid interviews). Because of their fear of blood shortages, the blood banks strongly opposed implementation of direct questioning. It appears that they decided that informal, "out of the spotlight," negotiations with the gay community were more likely to reduce the number of high-risk donors then implementing direct questioning of donors (Curran, Evatt, Bove, Sandler interviews). As one blood banker representative expressed it, "direct questioning will be counterproductive in most ARC regions, given the public nature of the blood donation process. How many men . . . are going to step forward, out of their closet, in front of their

peers and admit they are 'queers'? Or even call in later to have their donation discarded (Cumming 1983)."

With respect to hepatitis, donor selection practices had changed in late 1982 and early 1983 to restrict donations by some populations with a prevalence of hepatitis B greater than the general population (e.g., prison inmates). Although there was recognition that the male homosexual population had a prevalence rate of infection with hepatitis B that exceeded the prevalence rate in the prison population, homosexual men were not included in the exclusionary criteria (Dodd 1982). No one articulated a convincing rationale for failing to exclude the donor group with the highest prevalence of hepatitis (i.e., male homosexuals) while acting swiftly to exclude other groups (Haitians) whose prevalence was lower.

Prior to the January 4 meeting, the CDC had worked with gay groups to enlist their support for deferring from blood donations (Curran, Evatt interviews). By early 1983, the male homosexual population had established groups that defended their interests in the political arena. Spokespersons for some of these groups were present at the Atlanta meeting and appeared to express concerns that any restriction on blood donations by male homosexuals would be a form of discrimination. Although some representatives of gay groups characterized male homosexuals as willing to undergo testing of donated blood (but not questioning of donors about sexual preference), some expressed doubts that homosexual males would answer direct questions about sexual activities truthfully, in light of the stigma attached to homosexuality (Foege 1983). Representatives of the National Gay Task Force opposed the suggestion to defer homosexual men. The CDC took the position that donor screening procedures were the only way to minimize the risks of infection at the time (Evatt interview).

In sum, the plasma fractionators favored donor questioning as a way to protect their products, and the users of their products from harm and, possibly, to protect themselves from product liability. The gay community saw donor questioning as an infringement of their rights. The CDC viewed it as the sole means of protecting the public health at the time. The blood banks saw donor questioning as damaging to donor motivation and possibly counterproductive to risk reduction. Generally, decision makers who did not insist upon direct questioning of donors had several reasons: they were unsure of the propriety of asking donors about sexual activities; they did not believe that direct questions would obtain reliable answers from donors about a sensitive issue such as sexual behavior; and they were concerned about the legal and political ramifications of direct questioning (see for example, ARC, memo Dr. Cumming to Mr. de Beaufort; February 5, 1983 enclosed in Appendix D).

Surrogate Testing and Opposition to It

At the January 4, 1983, Atlanta meeting, CDC scientists also recommended testing all blood units with an anti-HBc test, predicting that the anti-core test for hepatitis B would detect 90 percent of donors with AIDS.

Published data on the accuracy of surrogate marker testing varied in the reported proportion of AIDS patients who had positive tests for anti-HBc. Unpublished data presented by the CDC showed a high prevalence of anti-HBc in AIDS patients, based on data from a cohort of homosexual men with AIDS who attended a sexually transmitted disease (STD) clinic (Foege

1983). Data from several studies based on different groups resulted in findings dissimilar from those reported by the CDC. These studies estimated that the implementation of anti-HBc would detect only between 25 percent and 40 percent of blood donors with AIDS (Foege 1983; Bove, Pindyck interviews). These studies suggest that there may have been variations between groups from different geographic areas. The Irwin Memorial Blood Bank conducted a pilot test on anti-HBc, and found a higher correlation between ethnicity and prevalence of hepatitis B than between homosexuals and hepatitis B. The significance of such data did not clearly illustrate the benefit of using the test as a means to identify donors at high risk of transmitting AIDS (Perkins, Pindyck interviews; FDA, BPAC, December 1983).

A careful reading of the evidence shows why people could not agree about the frequency of anti-HBc in people who could transmit AIDS. The CDC claimed that 90% of AIDS patients had anti-HBc. This statement appeared in public statements and letters, but the Committee was unable to find any 1982-84 account that described the clinical characteristics and size of their AIDS study population, the methods for measuring anti-HBc, or a table of results. In other words, the standard basis for evaluating a scientific claim, a published report, was missing.

Because those that claimed a much lower impact on anti-HBc published their work, it is possible to evaluate its relevance to preventing the transmission of AIDS by excluding donors who had anti-HBc. These investigators described the frequency of anti-HBc in various high risk groups (homosexuals, donors who designated their blood for research rather than transfusion, and residents of San Francisco census tracts that had a high proportion of homosexual men). Of course, only a fraction of these populations were infected with HIV. Therefore, the prevalence of anti-HBc in these high risk populations would be much lower than in a population of people infected with HIV.

In early 1985, the CDC did publish a well-designed study that showed that 62% of donors to whom the CDC had traced a transfusion-related AIDS case had anti-HBc (McDougal 1985). The ELISA test and the Western blot would be available within a few months (the 1985 article contained the results of using the ELISA and Western blot to test their study subject's serum for HIV), and a surrogate test for HIV infection was no longer needed. When it was important to know the effect of surrogate testing on AIDS transmission, however, the evidence was inadequate or unpublished. Apparently, no one examined the evidence from all these studies and did what is commonplace in the mid-1990s: to dismiss conclusions based on inadequate evidence and call for well-designed studies. Those who used inadequate or unpublished evidence to support their position were not called to account, and disputants could not agree on a policy for surrogate testing.

Discussions among the CDC's AIDS Working group in early 1984 concluded that instituting anti-HBc tests would lead to exclusion of far more donors than would be expected to (or actually) have AIDS. If the test were implemented, its primary benefit would have been to allay patient's and physician's fear of AIDS, not to significantly reduce exposure to AIDS (OTA 1985). Thus, during the early debates surrounding the issue of whether or not to use the test for anti-HBc as a means to reduce AIDS transmission, knowledge about the usefulness of the test was inconsistent and the value of the test was highly uncertain. The Committee found no evidence that an evaluation was ever undertaken to systematically examine these differences and to determine the utility of the test. In the Committee's view, evidence suggested there were

differences geographically that may have made the test more useful in some areas of the U.S. than in others.

The disagreements about the benefits of surrogate testing resulted in the rejection of the recommendation to implement surrogate testing. There were several reasons behind this decision, including

- the cost of the test
- the availability of the surrogate test
- uncertainty as to the usefulness of the anti-HBc test as a screening measure for donors at risk of having AIDS
- the fact that the test was not an AIDS test, and that, as the cause and treatment of AIDS was not yet known, the notification of deferred donors as to why they were deferred would be difficult (Perkins, Bove interviews; FDA, BPAC, December 1983).

The blood bank community believed that implementing surrogate testing while there was no specific test for AIDS would appear discriminatory and would result in discarding much noninfectious blood. Blood bank physicians raised doubts about the usefulness of the anti-core test for hepatitis B for three reasons. They questioned the validity of the CDC data on the correlation of anti-HBc to AIDS cases among a cohort of homosexuals who attended an STD clinic. They were concerned about donor attrition, which they estimated at over 5 percent among volunteer donors and up to 20 percent among commercial donors, which in turn could lead to serious blood shortages. Finally, some raised the concern that eliminating donors with the protective antibody for hepatitis B could endanger the blood supply, especially for plasma derivatives like gamma globulin (Perkins, Sandler, Rodell interviews). In addition, many believed that blood banks that performed surrogate testing (e.g., Stanford University in 1983) for HIV would attract high-risk donors who wanted to be tested to see if they were infected (Perkins, Evatt, Curran, Francis, Silvergleid interviews), which would decrease the safety of the blood supply (Bove, Sandler interviews; Doll, et al. 1991). At the time, there thus appeared to be within the blood bank community both many who feared for the safety of the blood supply if surrogate testing were implemented, and some who did not view the possibility of an infectious agent in the blood supply as great enough to warrant such testing. The FDA did not mandate screening for hepatitis B core antibody until the late 1980s as a surrogate test for non-A, non-B hepatitis (CCBC 1994; Evatt, Perkins interviews).

Criticism of the CDC's Data and Motives

Participants in the Atlanta meeting and others in key decision-making roles expressed reservations about the validity of the CDC data, as they did not believe the CDC to be a credible source of information regarding AIDS (Gallo, Donohue interviews). Some perceived the CDC's urgency regarding AIDS as a self-serving strategy to ensure its (CDC's) survival. A January 26, 1983, interoffice memo of the American Red Cross stated:

> CDC is likely to continue to play up AIDS—it has long been noted that CDC increasingly needs a major epidemic to justify its existence. . . especially in light of Federal funding cuts . . . AIDS probably played some positive role in CDC's successful battle with OMB to fund a new $15,000,000 virology lab. This CDC perspective is also obvious from the general "marketing nature" of the January 4, 1983 . . . meeting. . . . We can *not* depend on CDC to provide scientific, objective, unbiased leadership on the topic. . . . Because CDC will continue to push for more action from the blood banking community, the public will believe there is a scientific basis and means for eliminating gays . . . To the extent the industry (ARC/CCBC/AABB) sticks together against CDC, it will appear to some segments of the public at least that we have a self interest which is in conflict with the public interest, unless we can clearly demonstrate that CDC is wrong [Cumming 1983].

In particular, as stated earlier, blood bank physicians questioned the validity of the CDC data on the correlation of anti-HBc to AIDS cases among a cohort of homosexual who attended an STD clinic.

Risk Assessment

Erroneous assumptions about the incubation period and the mortality rate for AIDS led to widely differing, inaccurate projections of the outcome of more vigorous donor screening. Some of the key decision makers relied upon their knowledge of the epidemiology of other viral diseases to guide them in developing prevention and control measures. For example, it was believed that the incubation period for AIDS was one year, and at the maximum, two to three years (FDA, BPAC, February 1983). A minority of persons proposed that AIDS was caused by a disease agent that had a much longer incubation period. In August 1982 *Medical World News* published a theory that AIDS was caused by a retrovirus; in 1982 Edgar Engleman, M.D., also proposed that AIDS was caused by a retrovirus (Gallo, Engleman interviews). The U.S. surveillance systems were ill-equipped to identify diseases with a long incubation period such as AIDS. Although 90 percent of AIDS cases were identified, it was difficult to identify those who were HIV infected but did not have AIDS (Francis interview).

The assumption by many decision makers that AIDS was similar to other viral agents in being caused by an agent with a short incubation period led to confusion regarding the incidence of AIDS in transfusion recipients or hemophiliacs, given the large number of blood units and blood products transfused annually (FDA, BPAC, February 1983). At the time, there was insufficient information to state the mortality rate of AIDS; many believed it was approximately 40 percent or higher (FDA, BPAC, February 1983). Decision makers did not know the high case fatality rate of AIDS and tended to deny the possibility of an infectious disease agent that could cause a devastating disease that would be fatal to most (if not all) of its victims. This information deficit, combined with incorrect assumptions regarding the natural history of AIDS, led to inaccurate analyses of targeted interventions for donor selection and donor blood testing. Thus, the known costs associated with donor screening interventions seemed to outweigh their benefits, which were unknown but depended on what were still incomplete scientific data.

If decision makers had known that AIDS had a long asymptomatic period during which people were infectious, they would have had to admit that the risk of AIDS transmission by transfusion was much higher than "one case per million patients transfused" (estimate of the

American Association of Blood Banks, the American Red Cross, and the Council of Community Blood Centers, June 22, 1983; see Chapter 3). In addition, if they had known AIDS was virtually always fatal, decision makers might have been more aggressive about donor screening policies.

Lack of Leadership

The January 4, 1983, meeting in Atlanta was an opportunity for someone to take charge, but the meeting ended in disarray. The CDC had expected to leave the meeting with a consensus to draft recommendations to question donors, exclude all homosexuals, and implement surrogate testing (based on work done in their laboratories). The CDC had chosen Jeffrey Koplan, its assistant director for public health practice, to chair the meeting because he was believed to be a neutral figure in the AIDS effort (Curran, Evatt, Foege interviews). Whereas the CDC had hoped to pass the lead role over to FDA (Evatt interview), Dr. Bruce Evatt said he was stunned that the CDC "hit a brick wall" with the FDA. The CDC had been looking for overall agreement, but the crowded and raucous atmosphere made it impossible to achieve consensus (Evatt, Curran interviews).

The American Red Cross representative, Dr. Gerald Sandler, recalled that everyone at the meeting was "very frustrated" that the meeting did not reach a consensus on actions needed. He also noted that not one of Donald Francis' superiors had supported a recommendation to implement hepatitis B core testing. As a result, few in attendance accepted Francis' suggestions, as they assumed he did not have the support of CDC Director William Foege (Sandler interview). The FDA's role in implementing surrogate testing was not clear, as the FDA representatives believed that more research was needed before the FDA could issue a recommendation (Parkman interview). The lack of good interagency communication was a problem, and some participants believed that someone should have established an interagency, national task force (Sandler interview).

After the meeting, the sentiment at CDC was one of frustration that they had failed to convince others that the evidence supported their hypothesis that the disease was transmitted through blood and blood products (Curran, Foege interviews). Several CDC scientists recall that it was difficult to convince others of the potential for blood-borne transmission and to motivate them to respond (Curran, Evatt interviews).

In his summary report of the meeting, Dr. Foege recommended that each Public Health Service Agency provide candidate sets of recommendations for the prevention of AIDS in patients with hemophilia and for other recipients of blood and blood products to Dr. Koplan, Assistant Director for Public Health Practice, CDC and, the three agencies (CDC, NIH, FDA) should then develop a uniform set of recommendations on AIDS. In addition, Dr. Foege expressed his belief that the meeting had been successful in presenting the most recent data on AIDS and had served as a "forum" for different views to be expressed (Foege 1983).

Conclusions

Blood banks, government agencies, and manufacturers were unable to reach a consensus on how extensively to screen for high-risk donors in order to substantially reduce the risk of HIV transmission through the blood supply. There was no consensus at the January 4, 1983, meeting, and it appears that no individual or organization took the lead to develop a consensus in the months that followed. Lack of agreement on the interpretation of scientific data, pressure by special interest groups, organizational inertia, and the unwillingness of the regulatory agencies to take a lead role in the crisis resulted in a delay of more than one year in implementing strategies to screen donors for risk factors associated with AIDS.

December 1983 BPAC Meeting

Interim Local Efforts to Screen Aggressively

In early to mid 1983, studies had shown that AIDS patients had a low ratio of CD4 lymphocytes to CD8 lymphocytes when compared with healthy individuals (Evatt, Engleman interviews; Goedert 1989). On July 1, 1983, Stanford University Blood Bank became the first in the United States to screen donated blood with a surrogate test, which identified reversed T-cell ratios, to reduce transmission of AIDS. Between July 1983 and June 1985 at Stanford, a total of 33,831 blood donations were screened for CD4/CD8 ratios. Of those donations, 586 had CD4/CD8 ratios less than or equal to 0.85 and were discarded. However, serum samples from these donors were retained and later tested for HIV when the test became available. Dr. Edgar Engleman found that 1.9 percent of the 586 discarded donations were later found to be HIV positive (Galel, et al. 1995). The 1.9 percent of 586 donations translates to approximately 11 infected donations that were discarded. Each donation is usually divided into three components (red cells, platelets, and plasma), each of which is typically transfused into a different patient. Therefore, the removal of 11 infected units of blood may have protected 33 patients from acquiring HIV (Engleman interview; Galel, et al. 1995).

The test was relatively easy to implement at Stanford because the Stanford University Blood Bank was conducting immunological research at the time. Others interviewed stated that the CD4/CD8 ratio test would have been difficult to implement on a nationwide scale because the equipment required was costly and the test had to be performed manually (Perkins, Sandler, Osborn, Gompert interviews). It was believed that large-scale use of the CD4/CD8 ratio test required a flow cytometer, which was available only in research laboratory settings (Gompert interview).

In July 1983, NIH's National Heart, Lung, and Blood Institute released a request for application to develop tests to identify the AIDS carrier states and to measure the sensitivity of the tests. Shortly thereafter, Irwin Memorial Blood Bank in San Francisco, directed by Dr. Herbert Perkins, evaluated the anti-HBc test as a surrogate marker for HIV. The study took approximately three months, and the results were difficult to interpret, as the correlation between a positive anti-core test and selected areas of residence in San Francisco was more prominent by ethnic origin than sexual preference. Overall, 6 percent of donors tested positive for anti-HBc. The frequency of anti-HBc was higher in males than females, and the difference in frequency was larger between people of differing ethnic origins than between homosexuals and

heterosexuals. The author concluded that implementing the test would not be of clear benefit and that the subsequent exclusion of 6 percent of donors could lead to blood shortages. In general, anti-core testing showed a 6 percent positive rate in blood donors, a 12 percent positive rate in blood donors who self-excluded, a 70 percent positive rate in gay men, and a 95 percent rate in AIDS patients in STD clinics (Pindyck interview). Irwin Memorial Blood Bank did implement the test in May 1984 to ease recipients' fears of receiving blood (Perkins interview).

Reliability of Surrogate Tests

On December 15-16, 1983, the FDA's Blood Products Advisory Committee (BPAC) held a two-day meeting to discuss the possible implementation of surrogate tests on blood donations to exclude high-risk donors. The objective of the BPAC meeting was to "review the results of research to define tests which could be applied to blood, plasma, or donors that would indicate an increased risk of the transmission of AIDS (FDA, BPAC, December 1983)."

Dr. Dennis Donohue, director of the FDA's Division of Blood and Blood Products, had recommended that hepatitis B anti-core testing be incorporated for routine plasma screening (in addition to current requirements) since it would identify 90 percent of all potentially infectious (or high risk) donors (FDA, BPAC, December 1983). In his opinion, the implementation of anti-core testing would add a further measure of confidence in product safety at a relatively low cost (Donohue interview; Ojala 1983). He stated, "Anti-core testing lends itself to the plasma situation," with only five to six central testing laboratories and one site responsible for product safety within each laboratory (CCBC 1983).

At the December BPAC meeting, industry representatives proposed creation of a task force to deliberate the details of the recommendation and provide further information in three months (FDA, BPAC, December 1983). According to CDC and FDA documents, industry proposed the task force in order to delay the implementation of surrogate testing (Donohue interview; Ojala 1983). An internal memorandum of one participant, Cutter Biological, stated that the proposal to convene a task force "was one that had been agreed upon by all the fractionators the previous evening" and that "the general thrust of the task force [was] to provide a delaying tactic for the implementation of further testing" (Ojala 1983). Although Dr. Donohue was not completely satisfied with the task force approach, he agreed to it; and thus the BPAC created an industry task force to consider the logistics of anti-HBc (core antibody) as an additional screening test.

Task Force Report on Surrogate Testing

The task force created at the December 15-16 1983, BPAC meeting reported their findings on March 6, 1984. The members were divided as to "whether routine testing of potential blood and/or plasma donors for the presence of anti-HBc was an appropriate means of identifying members of high risk groups associated with AIDS" (Rodell 1984). The report contained a

majority position paper opposing the implementation of anti-HBc and a minority report favoring its implementation.

The task force reviewed several pilot tests performed at blood banks in high-risk areas. The pilot tests comprised four studies on anti-HBc; two studies on B2-microglobulins; and one each on Cytomegalovirus (CMV) and Epstein-Barr virus (EBV), immune complexes, Neopterin, T-cell ratio measurement, Thymosinal, and Alpha interferon. The discussion focused on the anti-HBc test.

Data showed that 5 percent to 18 percent of blood and plasma donors had a positive test for anti-core. The CDC data showed that 84 percent of homosexual males tested positive for anti-HBc and that 96 percent of IV drug users had a positive test for anti-core. The test itself was highly sensitive (98%) but not specific (70%).

The discussion at the December BPAC meeting had stipulated that "cost-benefit analysis and disease prevalence must be considered in the decision regarding whether or not to use the test" (FDA, BPAC, December 1983). However, the task force could not agree upon the true cost of the test, with estimates as low as $2.50 per test for plasma collectors and as high as $12.00 per donation for whole blood collections (Rodell 1984). Additional costs were the blood that would be discarded and the recruitment and replacement of donors. The task force could not agree on the costs and the benefits of using the anti-core test as a surrogate for high-risk donors.

A contemporaneous internal Cutter memorandum indicated that industry believed core testing would eventually become a requirement. At that time, Cutter executives recommended that the company implement core testing as quickly as possible to "obtain a competitive advantage in the market place" and that they "[make] no mention of [their] plans to others" (Ojala 1983).

Support for the Implementation of Anti-HBc. The minority who favored implementation of the anti-HBc test presented the following arguments: 60–80 percent of homosexuals tested positive for anti-HBc; the test would reduce the need for recall of blood products (i.e., AHF concentrate); the test could help reduce the incidence of non-A, non-B hepatitis in recipients of blood products; and blood and plasma collectors had an obligation to do all that was possible to increase the safety of the blood supply.

Opposition to Surrogate Testing. The majority against using the test believed that the anti-HBc test was insufficiently specific for AIDS and would exclude excessive numbers of donors. In addition, some speculated that there would be a reduction in the availability of donations from groups such as Mexican, African, and Asian Americans, who have a higher prevalence of core antibody but whose rare blood types are needed in the blood supply to service that very population. Finally, the high proportion of positive sera from known homosexuals suggested that the test was not distinguishing homosexuals with multiple partners who may have been carriers of AIDS from homosexuals who were not at increased risk of having AIDS (FDA, BPAC, December 1983; CCBC 1983). They argued that wide-scale implementation of core testing of donated blood would eliminate approximately 15 percent of plasma donors and 6–7 percent of whole blood donors (FDA, BPAC, December 1983). Additional arguments were that the epidemic seemed somewhat contained within defined risk groups; the test would cause blood banks to incur high cost; and there would be a loss of the protective antibodies to hepatitis B in the blood supply.

Comment on the Blood Products Advisory Committee

The BPAC served in this instance as a forum through which the blood banks and plasma industry could, and did, influence the FDA to adopt policies that favored their interests at the expense of the public interest. The membership of BPAC included blood and plasma organization representatives, scientists, and physicians (FDA, BPAC, December 1983). The group was not a monolith. Its members differed on the role of government agencies and actions to take regarding blood safety. There is also evidence from internal, nonpublic correspondence that some BPAC members deemphasized the risk to the blood supply in their public remarks but were very concerned in private. At a BPAC meeting in Washington in December 1982, Joseph Bove, M.D., committee chairman (and also chair of the American Association of Blood Bank's Committee on Transfusion Transmitted Diseases), said that there was not enough evidence that the blood supply could transmit AIDS to restrict donations from male homosexuals. However, in a contemporaneous report of the American Association of Blood Banks, Dr. Bove acknowledged the likelihood that AIDS was transmitted by blood. "I believe the most we can do is buy time," he stated, adding, "there is little doubt in my mind that additional transfusion-related cases and additional cases in patients with hemophilia will surface" (Bove 1983).

Informing the Public

The blood industry was concerned about providing information on AIDS to the public lest donors take fright and stop donating blood (Curran interview). In January 1983, Dr. Bove reported on behalf of the AABB's Committee on Transfusion Transmitted Disease that "we do not want anything we do now to be interpreted by society (or by legal authorities) as agreeing with the concept—as yet unproven—that AIDS can be spread by blood" (Bove 1983).

AIDS Politics

Although many groups within the U.S. population had a stake in blood donations and blood transfusion, male homosexuals were well represented at the table where policymaking occurred, while other affected groups had minimal representation (e.g., patients with hemophilia were represented by the National Hemophilia Foundation) or no representation (e.g., future recipients of blood or blood products). The influence of special interest groups was reflected in the inconsistent recommendations about donor screening in the early 1980s. For example, as discussed earlier, prisoners could not donate blood even though their rate of hepatitis B infection was lower than the rate reported in male homosexuals. Haitians and tourists who had visited Haiti within the past three years could not donate (Katz 1983). There were no restrictions on donation, however, by the group with the highest prevalence of AIDS and hepatitis had no restrictions on donation (homosexuals). Representatives of the homosexual groups demanded protection of gay rights to privacy or confidentiality. Morever, there was a concern that

homosexuals might lie about their sexual orientation and donate blood if blood banks implemented direct questions about sexual orientation (Evatt, Silvergleid interviews). Given the scientific uncertainties and lack of representation by other consumer groups, the demands of the gay groups exerted considerable force in the debates regarding donor screening (Rodell interview).

CONCLUSIONS

This review of the issues and central events concerning donor screening and deferral before the test for HIV (ELISA) became available in 1985 leads to several conclusions, the first of which follows:

- When confronted with a range of options for using donor screening and deferral to reduce the probability of spreading HIV through the blood supply, blood bank officials and federal authorities consistently chose the least aggressive option that was justifiable.

In adopting this limited approach, responsible officials rejected options that may have slowed the spread of HIV to individuals with hemophilia and other recipients of blood and blood products. Among these options were asking male donors about sexual activity with other men and screening donated blood for the anti-HBc antibody. The Committee believes that both of these activities were reasonable to require in January 1983. The question is, given that these options were reasonable and justifiable, why did public health authorities reject them?

Having reviewed the available documentary evidence and having interviewed many of the key participants, the Committee believes that two of its three hypotheses were powerful influences on decision making about donor screening and deferral during 1983. The first hypothesis stated that lack of consensus about costs and benefits of screening and deferral resulted in decisions that took a limited approach to issues of donor safety. The second hypothesis stated that other constraints in the environment—which we categorize below as political, organizational, and historical—prevented decision makers from implementing screening for high-risk sexual practices and for anti-HBc. Though both of these hypotheses are supported by the facts, the first hypothesis explains rather different outcomes and events than the second. Their policy relevance differs widely as well.

Hypothesis One

There is little question that lack of consensus about the method of HIV transmission, the natural history of HIV-related disease, and the consequences of alternative modes of intervention to prevent its transmission was an important factor in decision making on donor screening and deferral. There was, for example, uncertainty about the sensitivity and specificity of anti-HBc antibody screening as a method for identifying high-risk donors, and about the consequences of such screening for the safety of the blood supply. Some observers believed that the test was insensitive and would reduce the availability of naturally occurring antibody against hepatitis B

infection. Others believed that the test was comparatively sensitive and that the benefits of its use would outweigh any possible costs. Lack of consensus also affected decision making about using a history of homosexual encounters as a screening question. Though some observers, including most at the CDC, had concluded that HIV was spread in a manner analogous to hepatitis B (by exchange of bodily fluids, including blood) other reputable scientists continued to dispute this point of view or to argue that the probability of blood-borne transmission was very slight—a matter of one in a million, and therefore not a threat to those dependent on blood and blood products.

The absence of consensus on these basic matters of epidemiology led to second-order disagreements about the costs and benefits of alternative actions. These cost-benefit calculations were often hidden and unspoken. Indeed, the Committee suspects that many of those arguing alternative views would have been surprised and uncomfortable if told they were actually engaged in a dispute over cost-benefit calculations. However, as they projected the scenarios about what would happen if they undertook one strategy or another (e.g., the implementation of a screening test, the deferral of a high-risk group) and drew conclusions about the desirability of those scenarios, they were, in effect, tallying advantages and disadvantages of alternative courses of actions and reaching sums and totals that diverged from those advocating other approaches.

Uncertainty of this type is common in public decision making, and it would be a mistake to relieve public health authorities of responsibility for their actions every time such legitimate disagreement occurred. When present, however, it has important implications for how decisions are made. Thus, when present, the forces postulated in the first hypothesis heighten the impact of the forces postulated in the second.

Hypothesis Two

It is worth dwelling at some length on the nature and manifestations of environmental influences on decisions concerning donor screening and deferral, for the working of these influences reveals the clearest opportunity for improving decision making with respect to the safety of the blood supply. The environmental forces working on the process of deciding about donor screening and deferral fit the following general categories: political, ideological, organizational, and historical.

Political Factors

The political circumstances influencing the outcome of decisions on HIV/AIDS took at least two general forms. First, interest group politics were at work in the efforts by homosexual groups to prevent the PHS from recognizing homosexuality as a risk factor in donor screening and deferral. The strong opposition of gay organizations undoubtedly had a major impact in heightening the sensitivity of FDA and CDC personnel to the potential negatives of taking a public health action—avoiding donation by men with a history of sex with other men—that would otherwise have made considerable sense. Interest group politics were also at work in the

opposition of the blood products industry to screening for anti-HBc antibody. For the blood banks and plasma fractionators, this was a matter of dollars and cents, and they used their access to FDA and to the BPAC to make their case.

- Gay groups, plasma fractionators and blood banks had more freedom to make their self-interested cases because the scientific information that would have clarified the nature of the calamity facing the United States was still in dispute.

Political influences took a second form as well in this debate, expressed in the general lack of sensitivity that the executive branch of government showed toward HIV and AIDS during the 1980s. The precise reason for this insensitivity is unclear, but it is clear that the administration was generally reluctant during the first half of the 1980s to treat AIDS as an urgent and serious public health threat. Thus, there was little potential political reward, and some political cost, associated with taking a leadership position in AIDS prevention, especially one that attracted political opposition from vocal and powerful groups that could argue that proposed actions were not required by scientific information.

Ideological Factors

An important ideological consideration at work during the period under review was a general antagonism or the part of the administration toward regulation. Even if AIDS had not been a topic of distaste for the Reagan administration, the issue of regulation itself made controlling the blood supply to prevent AIDS—in the absence of incontrovertible evidence of a public health crisis—an uphill battle.

- The ideological position of the executive branch with respect to regulation put the burden of proof on agencies that wanted to take leadership in regulatory affairs. This consideration occasions the Committee's fourth conclusion about donor screening and deferral.

Organizational Factors

Interagency squabbling, lack of coordination, and miscommunication are part of the bureaucratic landscape in any governmental setting whether one is talking of towns, cities, states, or national governments, in this country or abroad. Such forces were clearly at work in the case of decision making with regard to donor screening and deferral during the period under review. The Committee concluded:

- By far the most important organizational factor at work in explaining the cautious choices of public health authorities with regard to donor screening and deferral was mistrust and rivalry between the CDC and the FDA.

The Committee was particularly struck by comments made by FDA officials indicating a lack of confidence in the scientific capabilities of some of the CDC personnel. This lack of confidence seems to have reduced the credibility of CDC's early warnings and led FDA regulators, blood banks and plasma fractionators to discount warnings presented at the January 4, 1983, meeting. The history of the CDC's handling of the swine flu episode less than a decade earlier (during 1976–1977) might have colored FDA perceptions, but the startling fact remains that key personnel in the agency primarily responsible for preventing epidemic transmission through the blood supply (namely, the FDA) harbored significant doubts regarding the competence of the primary U.S. agency responsible for warning of the threat of such an epidemic. It is hard to imagine an instance in which such interagency disagreement could have contributed to a more unfortunate outcome.

The Committee drew another conclusion about organizational influences:

- The structure and process of the FDA's Blood Products Advisory Committee (BPAC) lacked dimensions required to address nontechnical aspects of the controversy.

Because of the highly technical nature of many of its decisions, and the uncertainty that often accompanies them, the FDA has a history of relying on outside advisory groups to provide direction for many of its potentially controversial decisions. The area of blood policy and regulation was no exception. However, in this instance, the advisory system may have failed the FDA because the agency itself failed to understand the extent to which nontechnical issues, that is, issues of how to compare risks (such as the risk of HIV transmission versus the risk of further stigmatizing homosexuals), were actually at stake. The BPAC did not have the social, ethical, political, and economic expertise necessary to understand fully the ramifications of the decisions it was making. Furthermore, given how much authority FDA in effect has ceded to this advisory group, it did not sufficiently represent all potentially affected groups. In hindsight, such representation would have assured that all pertinent points of view would be considered during committee deliberations.

Historical Factors

Throughout the Committee's review of events concerning donor screening and deferral in the early 1980s, we were struck by how one historical event influenced the way in which individuals and organizations conducted themselves and interpreted the evidence they were presented regarding the HIV epidemic. This episode, already mentioned above, was the federal government's experience with the swine flu epidemic. In early 1976, at the urging of officials of the Centers for Disease Control (CDC), the federal government, with the visible participation of President Ford, engaged in a crash program to immunize every American against a disease that never materialized. Millions were vaccinated, however, and some died of complications that they attributed to the vaccine (Neustadt and Fineberg 1978).

- The swine flu episode seems simultaneously to have reduced the self-confidence of the agency and increased the skepticism with which its warnings have been regarded by other public health service groups.

It may be that CDC officials did not take a more forceful stand in urging their views out of fear of jeopardizing the CDC's remaining credibility. To what extent the lessons of the swine flu experience have positively influenced the behavior of the CDC, for example, by increasing the care with which it assesses the scientific evidence before issuing a warning of a new or threatening epidemic may never be known. However, the HIV case constitutes one clear example in which the experience and its lessons, however they were applied, led to disastrous results because of concern that being wrong on AIDS and the blood supply could destroy what remained of CDC's ability to see its warnings lead to public policy.

Although participants at the January 4, 1983, CDC meeting did not come to an agreement on actions regarding donor screening, there were several plasma fractionators and blood centers that initiated donor selection and screening interventions that surpassed the recommendations of the blood bank community and federal agencies. The decision makers could have defended wide-scale execution of these strategies in two ways: by obtaining information from a broader base of constituents, and by obtaining more information about possible consequences of action or nonaction from representatives of different theoretical premises regarding the epidemiology of AIDS. Instead, swine flu was used as a model by decision makers to illustrate the consequences of imprudent action. An important difference between swine flu and AIDS, however, was that swine flu was a threat that did not materialize, whereas AIDS cases were real, not theoretical, and were growing exponentially. Given the serious nature and devastating consequences of AIDS, all parties vested with the protection of the public health or the safety of the blood supply would have been justified in initiating both direct donor questioning and blood testing.

The Committee has not documented that any actions taken by decision makers were inconsistent with their responsibilities, but does believe that decision makers chose the least risky course (to them) throughout the events as they unfolded. A good example of this is that blood and plasma collection organizations failed to undertake anti-HBc testing, and failed to recommend direct screening of homosexuals in 1983.

More stringent donor screening activities were not implemented in 1983 because of the limited scientific information related to AIDS and the influence of political, economic and regulatory forces with different agendas. The lack of adequate scientific knowledge prevented the key actors from making an accurate (or reasonable) risk/benefit analysis of proposals to change the blood donor selection process. As a result of these uncertainties and pressures from the blood industry and special interest groups, options that would have reduced HIV infection were not chosen, and policies that resulted in minimal change to the blood donor selection process were implemented. These policies not only provided a minimum of political risk to the blood banks and regulatory agencies in 1983, they also provided a minimum of protection from HIV for recipients of blood or blood products.

AFTERWORD

Donor Screening 1985–1995

With the implementation of HIV testing in 1985, the extent of the problem of the HIV infectious agent in the blood supply was quickly understood. The perception of the safety of the blood supply changed both in the public's view and among the blood bank professionals. The era of HIV shifted the field of blood banking from one dominated by serology to one in which infectious disease transmission, donor concerns, and the quest for total safety have become paramount (Bove 1990). Several changes were introduced concerning donor screening, mainly the introduction of new laboratory tests.

Since 1985, donor screening has involved "lookback." Lookback is the tracing of a blood donor found to have anti-HIV, (and who had donated in the past), to all recipients of the previous donation(s), who in turn are tested for HIV. Donor deferral lists had been used in the blood banks since the 1970s regarding donors positive for hepatitis B surface antigen (HBsAg) as well as donors linked with posttransfusion hepatitis. These lists have been extended to include donors found to be HIV positive and donors positive for other disease markers. Every donation is checked for previous donation by that donor to see if any unit from the donor has been rejected in the past.

The measures taken up to 1985 are still in effect: avoiding high-risk individuals, questions regarding HIV-associated symptoms, and confidential self-exclusion. Questions regarding foreign travel have been added in order to defer donors visiting areas endemic for malaria or those visiting central Africa, which has a high HIV prevalence. Questions regarding previous treatment with growth hormone have been added to defer previously treated donors because of the fear of transmission of Creutzfeldt-Jakob disease (CJD).

Additional screening tests for donated blood have been considered and were added after 1985, both for HIV and for hepatitis.

HIV

The anti-HIV test implemented in 1985 (ELISA) became more sensitive and specific following the first available kits. In spite of the improvement, a few post-transfusion HIV infections from donations in the "window" period (the time period between infection with the virus, but prior to a detectable antibody response in blood or plasma) continued to occur. In order to evaluate the effect of adding the p24 antigen test (a viral antigen that can be present in the window period), 500,000 donors in 10 different areas in the United States were tested for p24 (Alter, et al. 1990). As no cases of p24 positive blood donors were found, the test was not implemented on a wide-scale basis.

HIV-2 is a retrovirus that is distantly related to HIV-1 (HIV) that also causes AIDS in humans. Although it is prevalent in areas of West Africa and other parts of the world, it is only very rarely found in the United States. Despite its rarity in the United States, the FDA required that all blood donations be screened for HIV-2 in April 1992. A new variant, known as HIV

subtype 0, has also been described and may also be included in the routine screening in the future.

Hepatitis

Post transfusion non-A, non-B hepatitis cases continued to be reported. Without any evidence that the causative agent would soon be elucidated, surrogate tests were suggested. Based on previous studies and new evidence, the surrogate testing for non-A, non-B hepatitis was instituted during 1986–1987 by using both the ALT and Anti-HBc tests. In 1989, the genomic structure of a putative NANB virus (Hepatitis C virus) was discovered. As a result, a test for antibodies to the HCV virus was licensed and implemented as a screening test for HCV in 1990.

In an NIH consensus conference held in January 1995 (there was no other consensus conference held earlier by the NIH), it was recommended that the ALT surrogate test be discontinued. However, anti-HBc was retained, not as a non-A, non-B surrogate marker, but as a second hepatitis B screening test for cases with low HBsAg titer.

HTLV-I and HTLV-II

In 1988 (Williams, et al. 1988) six positive HTLV I cases were reported among 40,000 donors. In November 1988, a screening test for HTLV I (virus that causes leukemia and myelopathy) was instituted for all blood units. HTLV I has been found in the United States, but HTLV II has been seen more frequently. Not all blood donors with HTLV-II infection are effectively identified using the HTLV I antibody tests; instances of transmission of HTLV II by blood screened negative for HTLV I have been reported.

Current Donor Screening Procedures

Currently, donor screening provides a potential donor with four opportunities to self-defer. Prior to donating blood, each donor is asked to read an introductory pamphlet about donating blood and about infections transmitted by blood, especially HIV. Those who think they are at risk are asked not to donate. This is the first opportunity to self-defer. A trained health professional then conducts a confidential interview with each donor, taking a health history and asking direct questions about high-risk behaviors, including drug use, sexual relations with drug users, and, for men, if they have had sexual relations with another man since 1977. Answering yes to one or more of these questions results in a temporary or indefinite deferral, in accordance with FDA recommendations and requirements. At this time the donor is asked to sign a release statement confirming that he or she has no risk for infection with HIV. This is the second opportunity to self-defer.

Donors are tested for anemia and checked for physical signs of intravenous drug use. Donors receive a "confidential unit exclusion" form and a call-back card. High-risk donors who may not wish to publicly acknowledge their risk behaviors may confidentially exclude their unit

of blood by peeling a bar code sticker off the unit exclusion form and placing it on their donation record. A computer reads the bar code as "transfuse" or "do not transfuse" depending upon which sticker is used. This is the third opportunity to self-defer. The call-back card gives donors a telephone number to call within 24 hours and a special identification code to use if for any reason after leaving the donation site they decide their blood should not be used. This is the fourth opportunity to self-defer.

Any unit of blood found positive for any of the tests is destroyed and the donor is permanently deferred by being placed in a computer database (American Red Cross Blood Services 1994).

Current Infectious Risk Through Blood Transfusion

The current estimated risk (Dodd 1992; Dodd 1994; Lackritz, et al. 1995; Busch 1995) of becoming infected by the viruses being tested for is:

HIV (AIDS)	1:420,000
HCV (hepatitis C)	1:2,000 to 1:6,000
HBV (hepatitis B)	1:200,000
HTLV (leukemia and myelopathy)	1:50,000 to 1:70,000

Other infectious agents that are a possible hazards are an additional hepatitis agent (non A,B,C), Chagas disease, Creutzfeldt-Jakob disease, Babbeiosis, new zoonotic infections, and new unknown agents. The problems associated with bacterial infection in blood units and especially in platelet concentrates have also not been completely resolved. Other issues concerning the safety of blood transfusion involve the long-term effects of lymphocytes transfused along with red blood cells, as well as with platelet transfusions.

REFERENCES

Allen, J. Garrott, et al. Blood Transfusion and Serum Hepatitis. Annals of Surgery, vol. 150; 1959.

Alpha Therapeutics. Statement submitted to Institute of Medicine; September 9, 1994.

Alter, Harvey, et al. Prevalence of HIV Type 1 p24 Antigen in U.S. Blood Donors—An Assessment of the Efficacy of Testing in Donor Screening. New England Journal of Medicine, vol. 323; 1990.

American Association of Blood Banks, American Red. Cross and Council of Community Blood Centers. Joint Statement on AIDS Related to Transfusion. January 13, 1983.

American Association of Blood Banks. Standards for Blood Banks and Transfusion Services, Tenth Edition, Washington, D.C.; 1982.

American Blood Resources Association, Recommendations on AIDS and Plasma Donor Deferral. January 28, 1983.

American Red Cross Blood Services, Documents submitted to the Institute of Medicine; September 1, 1994.

Bensen, Paul B. Jaundice Occurring One to Four Months After Transfusion of Blood or Plasma. Journal of the American Medical Association, vol. 121: 1943.

Bove, Joseph, Chairman, Committee on Transfusion Transmitted Disease. *Report to the Board,* American Association of Blood Banks; January 24, 1983.

Bove, Joseph. Testing in the Years Ahead. Transfusion, Vol. 30; 1990.

Busch, Risk of Human Immunodeficiency Virus transmission by blood transfusions before the implementation of HIV-1 anti-body screening. Transfusion; 1991.

Busch, et al. Paper presented at the NIH Consensus Development Conference; January 1995.

Centers for Disease Control, *Morbidity and Mortality Weekly Report*, July 16, 1982

Centers for Disease Control, *Morbidity and Mortality Weekly Report*, December 10, 1982

Centers for Disease Control, *Morbidity and Mortality Weekly Report*, Prevention of Acquired Immune Deficiency Syndrome (AIDS): Report of Inter-Agency Recommendations; March 4, 1983.

Council of Community Blood Centers. Blood Products Advisory Committee Recommends Fractionators Use Anti-Core Screening Test. Council of Community Blood Centers Newsletter; December 23, 1983.

Council of Community Blood Centers. Submission to the Institute of Medicine; 1994.

Cumming, American Red Cross. Memorandum to Mr. de Beaufort, American Red Cross National Headquarters; February 5, 1983.

Dodd, Roger, American Red Cross. Memorandum to Katz, Executive Director, Blood Services; July 9, 1982.

Dodd, Roger. "Adverse Consequences of Blood Transfusion: Quantitative Risk Estimates." in Blood Supply: Risks, Perceptions, and Prospects for the Future. American Association of Blood Banks; 1994.

Dodd, Roger. The Risk of Transfusion-Transmitted Infections. New England Journal of Medicine, vol. 327; 1992.

Doll, et al. Human Immunodeficiency Virus type 1 Infected Blood Donors: Behavioral Characteristics and Reasons for Donation. Transfusion; May 1991.

Eckert, R. AIDS and the Blood Bankers. Regulation; September 1986.

Food and Drug Administration. Blood Products Advisory Committee, July 19, 1983.

Food and Drug Administration. Blood Products Advisory Committee, February 7, 1983.

Food and Drug Administration. Blood Products Advisory Committee, December 15-16, 1983.

Foege, William. *Summary Report of Workgroup to Identify Opportunities for Prevention of Acquired Immune Deficiency Syndrome (AIDS);* January 4, 1983.

Francis, Donald, CDC. Memorandum to Koplan, Jeffrey; January 6, 1983.

Galel, et al. Prevention of AIDS Transmission Through Screening of the Blood Supply. Annual Reviews of Immunology, Vol. 13; 1995.

Goedert, A Prospective Study of HIV Type 1 Infections and the Development of AIDS in Subjects with Hemophilia. New England Journal of Medicine, 1989.

Katz, American Red Cross. Information to Blood Service Regions, BSL 83-12; January 26, 1983.

Lackritz, et al. Paper presented at NIH Consensus Development Conference; January 1995.

McDougal, J.S., Martin, L.W., Cort, S.P., Mozen, M., Heldebrant, C.M., Evatt, B.L., "Thermal Inactivation of the Acquired Immunodeficiency Syndrome Virus, Human T Lymphotrophic Virus-III/Lymphadenopathy-associated Virus, with Special Reference to Antihemophilic Factor," *The Journal of Clinical Investigation*, Vol. 76; August 1985.

National Hemophilia Foundation. Recommendations to Prevent AIDS in Patients with Hemophilia. January 14, 1983.

Neustadt, R. and Fineberg, H. The Swine Flu Affair: Decision-Making on a Slippery Disease. U.S. Department of Health, Education, and Welfare; 1978

Ojala, S., Cutter. Memorandum to those listed; December 19, 1983.

Office of Technology Assessment. *Blood Policy and Technology*. U.S. Government Printing Office, Washington, D.C; January 1985.

Petricciani, John, M.D., Food and Drug Administration, Office of Biologics. Letter to All establishments collecting human blood for transfusion. March 21, 1983a.

Petricciani, John, M.D., Food and Drug Administration, Office of Biologics. Letter to All establishments collecting source plasma. March 24, 1983b.

Petricciani, John, M.D. Food and Drug Administration, Office of Biologics. Letter to All licensed manufacturers of plasma derivatives. March 24, 1983c.

Pindyck J, et al. Measures to Decrease the Risk of Acquired Immune Deficiency Transmission by Blood Transfusion. Evidence of Volunteer Blood Donor Cooperation. Transfusion, vol. 25; 1985 .

Rodell, Michael. Hepatitis B Core Antibody Testing Study Group. Plasma Quarterly; Fall 1984.

Seeff, Leonard. Transfusion Associated Hepatitis: Past and Present. Transfusion Medicine Reviews; December 1988.

U.S. Comptroller General. Report to the Congress, *Problems Carrying Out the National Blood Policy;* 1975.

Williams, Alan E., et al. Seroprevalence and Epidemiological Correlates of HTLV-1 Infection in U.S. Blood Donors. Science, vol. 240; 1988.

Regulations and Recall

CONTENTS

Conclusions and Recommendations

The HIV epidemic has taught scientists, clinicians, public health officials, and the public that new infectious agents can still emerge. The nation must be prepared to deal with a fatal illness whose cause is initially unknown but whose epidemiology suggests it is an infectious disease. The AIDS epidemic has also taught us another powerful and tragic lesson: that the nation's blood supply—because it is derived from humans—is highly vulnerable to contamination with an infectious agent. A nation's blood supply is a unique, essential, life-giving resource. Whole blood and many blood products are lifesaving for many people. As a whole, our nation's system works effectively to supply the nation with necessary blood and blood products and its quality control mechanisms check most human safety threats. The events of the early 1980s, however, revealed an important weakness in the system—in its ability to deal with a new threat that was characterized by substantial uncertainty. The potential for recurring threats to the blood supply led this Committee to reappraise the processes, policies, and resources through which our society attempts to preserve its supply of safe blood and blood products.

GENERAL CONCLUSIONS

The events and decisions that the Committee has analyzed underscore the difficulty of decision making when the stakes are high, when decision makers may have personal or institutional biases, and when knowledge is imprecise and incomplete. The Committee attempted to understand the complexities of the decision-making process during the period analyzed in this report and develop lessons to protect the blood supply in the future. In retrospect, the system was not dealing well with contemporaneous blood safety issues such as hepatitis, and was not prepared to deal with the far greater challenge of AIDS.

By January 1983, the CDC had accumulated enough epidemiological evidence to conclude that the agent causing AIDS was almost certainly transmitted through blood and blood products and could be sexually transmitted to sexual partners.. The conclusion that the AIDS agent was

blood-borne rested on two findings. First, AIDS was occurring in transfusion recipients and individuals with hemophilia who had received AHF concentrate; these AIDS patients did not belong to any other known high-risk group for contracting AIDS. Second, the epidemiologic pattern of AIDS was similar to hepatitis B, another blood-borne disease. However, the magnitude and consequences of the risk for transfusion and blood product recipients was not known at this time. Furthermore, the epidemiological pattern of the new disease was difficult to interpret because, unlike most infectious diseases, there seemed to be several years between exposure leading to infection and the development of symptoms. As a result, physicians and public health officials underestimated the large number of infectious people who had no symptoms of AIDS but could transmit the disease to others and therefore substantially understated the risk of infection.

Compared to the pace of many regulatory and public health decision processes, the federal government responded relatively swiftly to the early warnings that AIDS might be transmitted through blood and blood products. Public and private sector officials considered a range of clinical and public health interventions for reducing the risk of AIDS transmission through blood and blood products. This period, however, was characterized by a great deal of scientific uncertainty about the risks of HIV infection through blood and blood products and about the costs and benefits of the available options. The result, the Committee found, was a pattern of responses which, while not in conflict with the available scientific information, was very cautious and exposed the decision makers and their organizations to a minimum of criticism. This limited response can be seen in the refusal of blood banks in 1983 and 1984 to screen for and defer homosexuals or use surrogate tests (Chapter 5), in the FDA's cautious and inadequate regulatory approach to the recall of potentially contaminated AHF concentrate (Chapter 6), and in the failure of physicians and the National Hemophilia Foundation to disclose completely the risks of using AHF concentrate and the alternatives to its use (Chapter 7).

Blood safety is a shared responsibility of many diverse organizations. They include U.S. Public Health Service agencies such as the CDC, the FDA, and the NIH, and private-sector organizations such as community blood banks and the American Red Cross, blood and plasma collection agencies, blood product manufacturers, groups such as the National Hemophilia Foundation, and others. The problems the Committee found were inadequate leadership and inadequate institutional decision making processes in 1983 and 1984. No person or agency was able to coordinate all of the organizations sharing the public health responsibility for achieving a safe blood supply.

Decision Making Under Uncertainty

The management of a public health risk requires an evolving process of decision making under uncertainty. It includes interpretive judgment in the presence of scientific uncertainty and disagreement about values. Public health officials must characterize and estimate the magnitude of the risk, which involves considering both the likelihood that infection might occur in various circumstances, and the costs and benefits associated with each of the possible uncertain outcomes. They must also develop and test public health and clinical care strategies, and communicate with the public about the risk and strategies for reducing it. When confronted with

a poorly understood and anomalous public health threat, inertia often influences decisions. It is often easier to maintain the status quo than to make a change. In fact, regulatory policymakers, health scientists, and medical experts often require substantial scientific evidence before informing the public and adopting remedial action. Lack of scientific consensus becomes a kind of amplifier for the usual discord and conflict that can be expected whenever an important science-based public policy decision—one profoundly affecting lives and economic interests—must be made. First, uncertainty creates opportunities for advocates of self-interested and ideological viewpoints to advance plausible arguments that favor their desired outcome. Second, uncertainty intensifies bureaucrat cautiousness.

In the course of its investigations, the Committee learned several lessons about decision making under uncertainty. These are set out here both as general lessons and to provide a framework for the recommendations that follow.

Risk Perception

Risk perception is shaped by social tensions, and cultural, political, and economic biases (Douglas 1985). It is important to understand the different contexts in which risk is perceived and the complex system of beliefs, values, and ideals that shape risk perception (Nelkin 1989). There are several other factors that influence risk perception, including locus of control, the type of risk posed by the threat, and the time interval involved in evaluating the risk. For example, people tend to underestimate risks that they perceive to be under their control, risks associated with a familiar situation, and low probability events (Douglas 1985). People have difficulty accepting estimates of a risk that is involuntary, uncertain, unfamiliar, and potentially catastrophic. (Fischoff 1987). The epidemic caused by HIV in the blood supply illustrates these patterns of perception and behavior with respect to risk.

Risk Assessment Versus Risk Management

A central precept of risk management is to separate the assessment of risk from the management of its consequences (National Research Council 1983). Otherwise, risk managers tend to bias their estimates of the magnitude of the risk in favor of their preconceived notions about appropriate or desirable policy choices. The events that the Committee studied provide examples of what can happen when this precept is not followed. When there is uncertainty, it may be necessary to assess risk by making subjective estimates rather than by obtaining objective measures. Such was the case in 1983 when, as part of implicit risk/benefit calculations about donor screening and deferral, blood banks and blood product manufacturers had to make judgments about the risk that their products could transmit AIDS (see Chapter 5). Anticipating the consequences of taking action, which is in the domain of risk management, may bias risk estimates toward values that support risk-averse action. When blood bank officials estimated the risk of transmitting AIDS as "one per million" transfusions, they chose a rate that was low enough to justify their reluctance to take further action. Despite mounting evidence that the risk was much higher, they maintained their original estimate throughout 1983. If the CDC had

made numeric estimates of the risk, and the blood banks, blood product manufacturers, or the FDA had used these estimates in a formal analysis of the decision problem, they might have reached different conclusions about, for example, surrogate testing for AIDS.

Consider the Full Range of Possibilities

When there is uncertainty about the facts that will determine the consequences of a decision, a systematic approach is usually best (National Research Council 1994). One important principle is to consider the full range of assumptions and alternative actions, not only worst case scenarios. In the events studied by the Committee, systematic denial of worst case scenarios was a recurring theme, as can be seen in the way that the NHF and the FDA discussed the CDC's warnings in 1982 and early 1983. The plasma fractionators introduced a worst case scenario of their own at the July 1983 BPAC meeting, when they estimated that three or four suspect donors and an automatic recall policy could lead to recall of all of the nation's supply of AHF concentrate (Chapter 6). A closely related principle is to scrutinize the evidence to ascertain what is based on fact, what is a "best guess" estimate, and what is simply untested conventional wisdom.

One approach to such an analysis would be to use a formal group process to systematically sample expert opinion on relevant factors such as the probability of infection and the economic and non-economic costs and benefits of each of the possible outcomes. Often these officials should use decision analysis, which takes into account the likelihood of events and the magnitude of their outcomes, as a tool to compare the expected value of the outcome of the policy alternatives under consideration. Two somewhat analogous models to consider include those used in Institute of Medicine studies to establish priorities for the development of new vaccines (Institute of Medicine 1985) and to evaluate the artificial heart program of the National Heart, Lung, and Blood Institute (Institute of Medicine 1991). The book *Acceptable Risk* (Fischoff, et al. 1981) also offers sensible approaches to dealing with this kind of situation.

Risk Reduction Versus Zero Risk

Decision makers tend to seek zero-risk solutions even when they are unattainable or unrealistically costly (National Research Council 1994). In doing so, they may run the risk of failing to implement solutions that are less effective but are certain to reduce illness. The failure to adopt risk reduction strategies can be seen in the resistance of blood banks to screening for homosexual activity or using surrogate tests for AIDS (Chapter 5) and in FDA's limited approach to product recall decisions (Chapter 6). Chapter 7 also points out that many risk reduction strategies for individuals with hemophilia were available but not fully disclosed or recommended. The perfect should not be the enemy of the good.

Risk Communication

Risk communication is a sensitive area because of its influence on the perceptions and behaviors of health professionals and consumers, regulatory policies, and public decision making (Nelkin 1989). Many public health officials and physicians wish to appear in command and infallible. When uncertain, they remain silent rather than disclose their ambivalence (National Research Council 1989). In the Committee's view, however, the greater the uncertainty, the greater the need for communication. The Committee's analysis of physician-patient communications at the beginning of the AIDS era illustrates the tragedies that can accompany silence about risks (Chapter 7). Risk communication skills are equally important when presenting information to the general public. The blood banks' reluctance to acknowledge the risk of transfusion-associated AIDS (Chapter 5) seems to have been due in part to the difficulties that they foresaw in presenting this information to potential donors and recipients.

Other important principles of risk communication are that the source of the information must be credible, the process should be open and two-way, and the message should be balanced and accurate (National Research Council 1989). When there was no other sources of information for physicians treating people with hemophilia and for their patients, the NHF and its MASAC took on an important risk communication role—providing what would now be called "clinical practice guidelines." The NHF's credibility in this area was eventually seriously compromised by its financial connections to the plasma fractionation industry.

Bureaucratic Management of Potential Crises

Federal agencies had the primary responsibility for dealing with the national emergency posed by the AIDS epidemic. The Committee scrutinized bureaucratic function closely, and came to the following conclusions about the management of potential crises.

Coordination and Leadership

A crisis calls for extraordinary leadership. Legal and competitive concerns may inhibit effective action by agencies of the federal government. Similarly, when policymaking occurs against a backdrop of a great deal of scientific uncertainty, bureaucratic standard operating procedures designed for routine circumstances seem to take over unless there is a clear-cut decision-making hierarchy. An effective leader will insist upon coordinated planning and execution. Focusing efforts and responsibilities, setting timetables and agendas, and assuming accountability for expeditious action cannot be left to ordinary standard operating procedures. These actions are the responsibilities of the highest levels of the public health establishment.

The Public Health Service failed to bring these leadership functions to bear when CDC scientists raised concerns about the blood supply at the January 4, 1983 meeting but received no public support from the director of the CDC or the Office of the Assistant Secretary for Health. Similarly, the record does not indicate that the highest levels of the FDA or the PHS were involved in responding to advice from the BPAC regarding donor deferral or product

recall. Part of this leadership problem may stem from major changes in the PHS leadership that took place during this period: the leadership of the FDA, the CDC, and the NIH, and the person serving as the Assistant Secretary for Health all changed between 1982 and 1984.

Advisory Mechanisms

In the early 1980s the FDA and other agencies did not have a systematic approach to conducting advisory committee proceedings. Such an approach requires that agencies tell their advisory committees what is expected of them, keep attention focused on high priority topics, and independently evaluate the advice offered. No regulatory process should have its information base effectively controlled by an advisory panel. Public agencies must be able to generate and analyze the information that they need to assure that decisions serve the needs of the public. The FDA failed to observe this principle when it allowed statements and recommendations of the BPAC to go unchallenged, apparently because it could not independently analyze the information (Chapter 6).

Because mistakes will always be made and opportunities sometimes missed, regulatory structures must be organized and managed to assure both the reality and the continuous appearance of propriety. The prominence of representatives from blood banks and blood product manufacturers on the BPAC, with no balancing influence from consumers and no process within the FDA to evaluate its recommendations (Chapter 6), is a failure of advisory committee management. Perhaps advisory committees should contain fewer topical experts and more members with expertise in principles of good decision making and the evaluation of evidence. A committee so constituted might run a reduced risk of standing accused of having conflicts of interest.

Analytic Capability and Long-Range Vision

Leadership passes to the organization that has access to information and the ability to analyze it. Federal agencies should avoid exclusive reliance upon the entities which they regulate for analysis of data and modeling of decision problems. The FDA should have had some independent capacity to analyze the information presented at the July 1983 BPAC meeting that suggested that with only three or four suspect donors, an automatic recall policy would completely deplete the nation's supply of AHF concentrate (Chapter 6). In addition, there did not seem to be any focus within the Public Health Service prepared to, or charged to, analyze the options, costs, and benefits of the options for protecting the blood supply that were discussed at the January 4, 1983 meeting convened by CDC.

In addition, agencies need to monitor more systematically the long-term outcomes of blood transfusion and blood product infusion and to think far ahead to anticipate both new technologies and new threats to the safety of the blood supply. Because new pathogens can enter the blood supply and be propagated very rapidly through it, a low level of suspicion about a threat should trigger high-level consideration of how to manage and monitor the problem.

Through its fact-finding interviews and through written documents, the Committee found little evidence that the PHS agency heads and the Assistant Secretary for Health were involved

in making decisions about protecting the blood supply in 1983 and 1984 when HIV was becoming increasingly apparent as a threat. Most decisions and interagency communication seems to have occurred several levels below the top.

Presumptive Regulatory and Public Health Triggers

The Committee believes that the Public Health Service should prepare for future threats to the blood supply by specifying in advance the types of actions that should occur once the level of concern passes a threshold. In the face of scientific uncertainty, the PHS needs a series of criteria or triggers for taking regulatory or other public health actions to protect the safety of blood and blood products. The Committee favors a series of triggers in which the response is proportional to the magnitude of the risk and the quality of the information on which the risk estimate is based. Not all triggers should lead to drastic or irrevocable actions; some merely require careful consideration of the options or developing new information. This general principle is detailed by examples in each of the Committee's four areas of inquiry. Table 8.1 summarizes these triggers and corresponding actions.

Table 8.1 Triggers for Taking Actions in Response to Uncertain Risks

Trigger	Action
Product Treatment	
Proposal to increase safety	Public sector to assume responsibility for thorough analysis and development
Initiation of risk/benefit or cost/benefit analysis	Ensure that the analysis takes into account possible secondary and other benefits
Donor Screening	
Identification of a high-risk population	Self-deferral and segregation of lots
Plasma fractionators' action to increase screening	All companies consider why they should not follow suit and set in motion a consensus development mechanism
Availability of a surrogate test or other partially effective interventions that have minimal risks	Use the test/intervention unless it is certain to be redundant prior to realizing its benefits
Recall	
Implementation of a new test or treatment process	Recall untested or untreated products as expeditiously as possible
Beginning of a recall action	Provide clear guidance and monitoring
Communication of Risk	
New information relevant to a public health agency's actions	Tell affected communities what they need to know to make an informed choice among listed options: the facts, the gaps in knowledge, and the implications thereof