
PART IV

International Responses to the Risk of HIV in the Blood Supply

Introduction

Among the matters I was asked to review and report on are “the structures and experiences of other countries, especially those with comparable federal systems.” Accordingly, I have examined the structures of blood transfusion services in Australia, France, Germany, Japan, the Netherlands, the United Kingdom, and the United States. In this Part, I describe those structures and some of the measures taken in those nations to safeguard the blood supply from HIV or AIDS during the period 1981 to 1987.

The selection of nations to be reviewed was, of necessity, arbitrary. The purpose of the review was to understand the AIDS pandemic as the context in which the events surrounding the contamination of the Canadian blood system, and the efforts made to deal with it, occurred. I chose to confine the review to developed nations. The health care systems of developed countries share many common values and traditions; they perform similar functions; and they have resources on which to draw when confronted by a threat to public health. Their blood transfusion systems are highly developed and have comparable levels of expertise. Persons working in public health and in the blood system of developed countries during the 1980s had access to much of the medical and scientific knowledge about HIV or AIDS that was published in professional journals and presented at international meetings.

The words “especially those with comparable federal systems” in the Commission presented a problem. The differences in the constitutional distribution of legislative powers among the federal nations of the world are such that it is difficult to say that there are truly comparable federal systems. Australia and the United States are the closest in the developed world to such a description, and they are on the list of nations chosen. Of the others, Germany is also a federal state.

The national systems selected for study represent different types of blood systems. In three of the countries – Australia, Japan, and the Netherlands – the blood system is operated exclusively by the national Red Cross societies; in France and the United Kingdom, it is operated by state monopolies; and in Germany and the United States, both not-for-profit and commercial organizations are involved in collecting, manufacturing, and distributing blood and blood products.

I sought assistance from a variety of sources. In late 1993, I wrote to a number of persons who might be expected to have information about how their country addressed the problem of HIV or AIDS and the blood supply. These persons included ministers of health, persons working in blood transfusion services, government officials, and representatives of hemophilia organizations. I also wrote to officials working in international organizations to learn about measures their organizations might have taken to promote blood safety during the early 1980s. From other persons, I received personal accounts of events, government documents, legislation, government reports, and court records. These documents were extremely helpful, and I am greatly indebted to my correspondents for making them available. Research was then undertaken to supplement the primary sources with articles from medical and scientific journals, books, and periodicals. Except for discussions with the few persons who testified about events in other countries, or who participated in round table discussions, no interviews were conducted, and no visits were made to foreign countries. A select bibliography at the end of each chapter lists the most useful references I consulted.

Because of the nature of the sources relied on, the study necessarily has limitations. It is not a commentary on the performance of the seven nations in minimizing the spread of HIV or AIDS through blood and blood products; neither is it an exhaustive chronicle of events. It is simply a summary of events in the nations selected. Although efforts have been made to obtain all the relevant information that is publicly available and to present a balanced and accurate summary of events based on this information, it may fall short of that description. It is important to point out that many of the documents relied on were translations into English of the language of the country of origin. It is possible that nuances in meaning found in the original text have been lost in translation and may not be reflected in the description of events.

Among the countries studied, HIV or AIDS first appeared in the United States, so that country is reviewed first, in Chapter 27, and then the review of the other six countries follows in alphabetical order, in Chapters 28 through 33. Much of what was learned in the United States about the disease was relevant to and influenced events in other countries. Each of the chapters is similar in format. First, the structure of the blood system during the 1980s is briefly outlined. Second, the number of persons infected with HIV or AIDS from the use of blood and blood products is given. Third, the time of the emergence of HIV or AIDS and the response of public health authorities are set out. Among the themes discussed are the efforts made to exclude donations of blood from persons who might be at risk of contracting HIV or AIDS; the dates when blood manufacturers began to use methods to inactivate viruses in factor concentrates; whether regulatory authorities or blood transfusion services recalled factor concentrates that had not been virally inactivated; and the dates when blood transfusion services began testing blood

donations for HIV or AIDS. Other sections set out what hemophiliacs were told about the risks of HIV or AIDS, and the documented efforts that were made to discover persons who had received blood or blood products and to inform them of the need to be tested for the virus. Where applicable, summaries are given of the evaluations made by government inquiries or the courts of the measures taken in a particular country to safeguard the blood supply. Finally, the issue of financial assistance for persons infected and affected is addressed. I will not attempt to summarize these events here; reference tables have been placed at the end of Part IV for that purpose.

Canada is by no means alone in wanting to understand the events surrounding the contamination of the blood supply. In the early 1990s, governments in many countries created special commissions or committees to examine why so many persons became infected with HIV or AIDS through the use of blood and blood products. Among the countries studied, four have done so – Germany, Japan, the Netherlands, and the United States. In two countries, France, and more recently in Japan, persons involved in the decision making during the early 1980s have been charged with criminal offences. Multi-party or class actions have been brought against blood transfusion services, blood product manufacturers, and governments in Australia, Japan, the United Kingdom, and the United States. With the exception of the United States, the governments have granted financial assistance to persons infected or affected. The Japanese government made a formal and public apology to persons infected.

In many of the countries studied, committees investigating past events have made recommendations to improve the safety of the blood system, and they have often reached similar conclusions about perceived weaknesses in the system. The recommendations that were made, and the changes to the blood transfusion systems that were implemented in response to these recommendations, reflect a widespread recognition of the need to centralize decision making. They also emphasize the need for national standards that are clearly explained in legislation, and for a strong regulator to ensure compliance with those standards. Finally, they acknowledge the importance of consumer representation in decision making.

International Milestones: HIV and AIDS 1981-8

Year	Medical and Scientific Knowledge	U.S. Events	International Events	Canadian Events
1981	<p>June 1981 First report of AIDS in American homosexual men — <i>MMWR</i></p> <p>December 1981 Report of AIDS in heterosexual intravenous drug users — <i>NEJM</i></p>	<p>July 1981 CDC creates a task force on Kaposi's sarcoma and opportunistic infections</p>	<p>February 1981 Behringwerke is licensed to distribute heat-treated factor concentrate in Germany</p> <p>August 1981 Report of AIDS in a homosexual man in France</p> <p>Sept.-Dec. 1981 Reports of AIDS in homosexual men in the Netherlands and the U.K.</p>	
1982		<p>March 1982 CDC conference on Kaposi's sarcoma and opportunistic infections</p>	<p>Spring 1982 French epidemiologists establish a national AIDS surveillance system</p>	<p>March 1982 First published report of AIDS in a homosexual man — <i>CDWR</i></p>

Year	Medical and Scientific Knowledge	U.S. Events	International Events	Canadian Events
1982	<p>June 1982 CDC formulates the first definition of AIDS — <i>MMWR</i></p> <p>Evidence that AIDS may be sexually transmitted — <i>MMWR</i></p> <p>July 1982 Report of AIDS among Haitians living in the U.S. — <i>MMWR</i></p> <p>Report of AIDS in three American hemophiliacs treated with factor VIII concentrate — <i>MMWR</i></p> <p>December 1982 Report of infant with transfusion-related AIDS. Report of four additional cases of AIDS in hemophiliacs — <i>MMWR</i></p>	<p>July 1982 CDC creates a working group to study AIDS in hemophiliacs. PHS holds meeting to discuss hemophilia cases</p> <p>December 1982 FDA asks blood product manufacturers not to use plasma from high-risk areas</p> <p>NHF makes treatment recommendations</p> <p>Alpha begins asking donors if they are at risk for AIDS</p>	<p>November 1982 Report of AIDS in German homosexual men</p>	<p>August 1982 Eight cases of AIDS are reported to the LCDC</p>

Year	Medical and Scientific Knowledge	U.S. Events	International Events	Canadian Events
1983		<p>January 1983 CDC holds a public meeting to identify ways to prevent the transmission of AIDS through blood and blood products</p> <p>Blood banks announce donor-screening measures</p> <p>NHF makes recommendations to physicians, manufacturers, and blood banks about reducing the risk of AIDS</p> <p>March 1983 PHS makes recommendations to prevent transmission of AIDS. FDA requests that blood and plasma centres screen out donors at high risk for AIDS</p> <p>Hyland-Travenol receives FDA approval to distribute dry heat-treated factor VIII concentrate</p> <p>All blood and plasma centres give prospective donors information about AIDS</p>	<p>January 1983 Netherlands Red Cross meeting to discuss donor screening</p> <p>April 1983 Report of AIDS in two German hemophiliacs</p>	<p>March 1983 CRCS issues press release asking persons at high risk of AIDS not to donate</p>

Year	Medical and Scientific Knowledge	U.S. Events	International Events	Canadian Events
1983	<p>May 1983 Montagnier isolates LAV, a new retrovirus that might cause AIDS — <i>Science</i></p>		<p>June 1983 Council of Europe recommends that member countries begin excluding donors at high risk for AIDS</p> <p>Blood banks in Australia, France, Germany, and the Netherlands begin to exclude donors at risk for AIDS</p> <p>August 1983 Report of AIDS in a hemophiliac in the U.K.</p> <p>September 1983 Blood banks in the U.K. begin to exclude donors at risk for AIDS</p> <p>November 1983 German health authorities hold public meeting to discuss ways to reduce the risk of AIDS transmission through factor concentrates</p>	<p>May 1983 First meeting of the National Task Force on AIDS</p> <p>June 1983 First published report of a Canadian hemophiliac with AIDS — <i>CDWR</i></p> <p>July 1983 CRCS issues second press release asking persons at high risk of AIDS not to donate</p> <p>September 1983 CRCS becomes aware of report of pediatric transfusion-associated AIDS</p> <p>November 1983 Heat-treated factor concentrates licensed in Canada</p>

Year	Medical and Scientific Knowledge	U.S. Events	International Events	Canadian Events
1984	<p>January 1984 Report of 18 U.S. cases of transfusion-associated AIDS — <i>NEJM</i></p> <p>Report of AIDS in the spouse of a hemophiliac — <i>Ann. Int. Med.</i></p> <p>April 1984 Gallo isolates the AIDS virus, HTLV-III</p> <p>May 1984 Gallo publishes study showing that HTLV-III may cause AIDS — <i>Science</i></p>	<p>Jan.–Feb. 1984 Three blood product manufacturers — Cutter, Armour, and Alpha — are licensed by the FDA to distribute heat-treated factor concentrates</p> <p>April 1984 Announcement by HHS that the AIDS virus has been isolated and that a test to detect it will be made available in six months.</p> <p>April–July 1984 Five blood banks in the San Francisco area and one blood product manufacturer, Cutter, implement hepatitis B core testing as a surrogate test for AIDS</p>	<p>July 1984 Report of transfusion-related AIDS in Australia</p> <p>Blood bank in London introduces confidential unit exclusion</p>	<p>May 1984 CRCS issues its first pamphlet to donors about AIDS</p>

Year	Medical and Scientific Knowledge	U.S. Events	International Events	Canadian Events
1984	<p>September 1984 Levy et al. show that heat inactivates retroviruses — <i>The Lancet</i></p> <p>October 1984 CDC reports that there are 52 cases of AIDS in hemophiliacs — <i>MMWR</i></p> <p>December 1984 Editorial in <i>The Lancet</i> recommends use of heat-treated factor concentrates</p>	<p>December 1984 FDA recommends use of confidential unit exclusion</p>	<p>October 1984 Blood bank in New South Wales, Australia, implements hepatitis B core testing</p> <p>November 1984 Three infants die of transfusion-related AIDS in Australia</p>	<p>August 1984 LCDC announces it will test blood samples for HIV</p> <p>September 1984 LCDC receives report of transfusion-associated AIDS in an adult</p> <p>November 1984 BoB directs the CRCS to replace non-heat-treated factor concentrates with heat-treated factor concentrates</p> <p>December 1984 Consensus conference on heat-treated factor concentrates</p>
1985	<p>January 1985 HTLV-III and LAV are shown to be related viruses</p> <p>February 1985 Study shows that use of heat-treated factor concentrates prevents HIV infection in hemophiliacs — <i>The Lancet</i></p>		<p>January 1985 Donors in Australia are required to sign a declaration that they are not at risk for AIDS</p>	

Year	Medical and Scientific Knowledge	U.S. Events	International Events	Canadian Events
1985		<p>March 1985 FDA grants Abbott Laboratories a licence to distribute HIV test kits</p> <p>May 1985 HIV-antibody testing begins</p> <p>July 1985 FDA recommends that blood and plasma centres establish a look-back policy for blood products that may be contaminated</p>	<p>March 1985 Report of AIDS in two Japanese hemophiliacs</p> <p>April 1985 Blood transfusion service in the U.K. begins heat treating factor VIII concentrate</p> <p>May 1985 French health authorities learn that factor VIII concentrate produced in Paris may be contaminated</p> <p>Blood banks in Australia implement HIV testing</p> <p>June 1985 Netherlands Red Cross produces heat-treated factor VIII concentrate and begins testing donations for HIV</p> <p>August 1985 HIV testing introduced in France</p>	<p>April 1985 First published report of transfusion-related AIDS in an adult — <i>Medical Post</i></p> <p>July 1985 Only heat-treated factor concentrates are distributed in Canada</p>

Year	Medical and Scientific Knowledge	U.S. Events	International Events	Canadian Events
1985			<p>September 1985 Council of Europe recommends donations be tested for HIV</p> <p>October 1985 France and Germany distribute only heat-treated factor VIII concentrate</p> <p>HIV testing is implemented in Germany and the U.K.</p> <p>December 1985 Netherlands Red Cross produces heat-treated cryoprecipitate</p>	<p>November 1985 CRCS completes implementation of HIV-antibody testing</p>
1986	<p>April 1986 Reports of HIV infection among hemophiliacs using dry heat-treated factor concentrates — <i>The Lancet</i></p>		<p>March 1986 HIV testing is implemented in Japan</p>	

Year	Medical and Scientific Knowledge	U.S. Events	International Events	Canadian Events
1986		<p>June 1986 Blood banks announce that recipients of blood or blood products made from donations by donors who have tested positive for HIV should be located</p>	<p>October 1986 U.K. government recalls Armour's heat-treated factor VIII concentrate</p>	
1987		<p>March 1987 Blood banks endorse CDC's recommendation that patients transfused between 1978 and the spring of 1985 be tested</p>		<p>Fall 1987 CRCS establishes a look-back policy</p> <p>October 1987 Reports of HIV infection in hemophiliacs using Armour's heat-treated factor VIII concentrate</p> <p>December 1987 BoB announces recall of Armour products and directs that only wet heat-treated factor concentrates be used</p>

Year	Medical and Scientific Knowledge	U.S. Events	International Events	Canadian Events
1988			February 1988 Dutch government recalls Armour's heat-treated factor VIII concentrate	February 1988 Consensus conference on wet heat-treated concentrates July 1988 Full conversion to use of wet heat-treated factor concentrates

Abbreviations:

<i>Ann. Int. Med.</i>	<i>Annals of Internal Medicine</i>
BoB	Bureau of Biologics
CDC	Centers for Disease Control
CDWR	<i>Canada Diseases Weekly Report</i>
CRCS	Canadian Red Cross Society
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
LCDC	Laboratory Centre for Disease Control
MMWR	<i>Morbidity and Mortality Weekly Report</i>
NEJM	<i>New England Journal of Medicine</i>
NHF	National Hemophilia Foundation
PHS	Public Health Service

The United States

The blood system in the 1980s

The blood system in the United States is made up of two main sectors: the voluntary, not-for-profit sector and the commercial sector. Whole blood is collected from unpaid donors by the American Red Cross, which collects almost half the nation's blood supply, and by community blood banks and hospital blood banks, which collect the rest. Plasma, on the other hand, is collected from remunerated donors at plasmapheresis centres, many owned and operated by manufacturers of blood products, where donors are paid between \$15 and \$20 per donation. Plasma collected from these centres is then sent to manufacturers' facilities for fractionation into such blood products as immune globulin, albumin, and factor concentrates.

The voluntary sector

The American Red Cross (Red Cross) is a not-for-profit congressionally chartered corporation that is financially self-supporting through donations and the recovery of costs. The purpose of its blood service is to provide "the safest, most reliable, most cost-effective blood." The Red Cross's national office is in Washington, DC. It operates forty-four blood banks throughout the United States and nine testing centres. Like the Canadian Red Cross Society, the Red Cross collects blood exclusively from unpaid donors.

Community blood banks are independent not-for-profit organizations, governed by volunteer boards, with the single function of providing the community's blood supply. Local interests, rather than any master plan, have influenced their development, and they vary in the role they play. Some centres provide all the blood needed by hospitals in their communities; some are also able to supply blood to hospitals outside their communities; others fall short of demand, and hospitals in their areas must obtain blood elsewhere.

Some large hospitals collect blood for their own use. Very few, if any, collect enough to meet all their needs, and most, if not all, must buy additional blood from blood centres. These hospitals collect approximately 12 per cent of the nation's supply.

Most community and hospital blood banks are members of one and sometimes two blood-banking associations. These associations are the American Association of Blood Banks and the Council of Community Blood Centers (known as America's Blood Centers since October 1996).

The American Association of Blood Banks, established in 1947, is a non-profit organization for persons and institutions involved in blood and tissue banking and in transfusion and transplantation medicine. It has approximately 2,400 institutional members, including blood centres, hospital blood banks, and hospital transfusion services, and 9,500 individual members. It operates a voluntary accreditation and inspection system that helps blood banks and transfusion services evaluate their own operations against established standards. All institutional members must be accredited. In addition to inspection and accreditation, the association sets standards, maintains a file of rare donors, certifies technologists in blood banking, operates educational programs, provides legislative and regulatory advice to its members, and participates in the National Marrow Donor Program, the National Blood Foundation (which funds research), and the National Blood Exchange (which facilitates the movement of blood among centres).

The Council of Community Blood Centers, established in 1962, represents the common interests of more than sixty independent (that is, non-Red Cross) not-for-profit community blood banks. It is governed by a board consisting of one representative from each member institution. Services are managed by volunteers and include the group purchase of supplies and liability insurance, professional development, promotion of both volunteer blood donation and research, attempts to influence federal and state regulations and policies, and production of a weekly newsletter.

The commercial sector

The high demand for blood products has made the collection of plasma a commercial enterprise. Persons who undergo plasmapheresis receive a modest sum of money to compensate them for the lengthy and often uncomfortable procedure they must endure.

There are more than 400 licensed plasma collection centres in the United States that perform approximately thirteen million plasmapheresis collection procedures per year and provide 60 per cent of the world's needs for plasma. The collected plasma is sent to fractionation plants, owned by large pharmaceutical manufacturers, to be made into blood products.

In the United States during the 1980s, four major pharmaceutical manufacturers fractionated plasma into blood products. These were Alpha Therapeutic Corporation (Alpha), Armour Pharmaceutical Company (Armour), the Hyland Therapeutics Division (Hyland) of Travenol Laboratories Inc. (Travenol), later Baxter Healthcare Corporation (Baxter), and the Cutter Biological Division (Cutter) of Miles Laboratories Inc. (Miles) (later Bayer Corp.) (Bayer). Alpha, owned by the Japanese pharmaceutical company Green Cross, is one

of the major producers of blood products in the world. In 1981, it sold more than U.S.\$10 million of blood products in the United States; by 1988, this figure had increased to U.S.\$38 million. Armour, owned by the French conglomerate Rhône-Poulenc Rorer Inc., has a fractionation plant located in Kankakee, Illinois, that produces a wide variety of blood products. In 1982, Armour's domestic plasma sales were approximately U.S.\$51 million; they increased to U.S.\$125 million by 1988. Baxter processes and markets various therapeutic biologic proteins, including factor concentrates, and was the first manufacturer to receive Food and Drug Administration approval for heat-treated factor VIII concentrate (Hemofil-T). Hyland's domestic sales of fractionated blood products totalled almost U.S.\$60 million in 1982 and U.S.\$98 million by 1988. Bayer, and its predecessor Miles, has had plants in San Diego and Berkeley, California, and in Clayton, North Carolina. It also has a long-standing agreement to fractionate plasma collected by the Red Cross. In 1982, it had plasma fraction sales of almost U.S.\$69 million, and approximately U.S.\$123 million by 1988.

Commercial plasmapheresis centres and the corporations that manufacture plasma-based products belong to the American Blood Resources Association, a trade association founded in 1971. It develops manufacturing standards and guidelines for the industry and certifies both premises and staff. Membership worldwide includes a majority of the manufacturers of blood products.

The federal government

The U.S. Public Health Service, a division of the Department of Health and Human Services, is the federal governmental authority responsible for public health management. Three agencies within the Public Health Service – the Centers for Disease Control and Prevention, the Food and Drug Administration, and the National Institutes of Health – are involved in efforts to promote the safety of blood and blood products.

The Centers for Disease Control and Prevention (CDC) is the agency that provides leadership and direction in the prevention and control of infectious and vector-borne diseases. As part of this mandate, the CDC collects, analyses, and disseminates national and international data to public health officials and health care organizations. Its publication, the *Morbidity and Mortality Weekly Report*, which is circulated and read worldwide, is an important tool in disseminating such information. The CDC has the expertise and the responsibility for surveillance, detection, and warning of potential public health risks associated with blood and blood products. It uses its nationwide surveillance system to identify and monitor blood-borne diseases, and informs appropriate government officials when known diseases or new disease-causing organisms (pathogens) are identified as potential threats to the safety of the blood supply. Its responsibility for blood safety extends

to epidemiological surveillance, investigations of disease outbreaks related to blood and blood products, studies to assess the risk of direct and secondary transmission of specific infectious agents, and the development of preventive measures to address new threats to the blood supply. Although the CDC plays an important role in promoting blood safety, it is the Food and Drug Administration that exercises regulatory authority over blood and blood products.

The Food and Drug Administration is the regulatory arm of the Public Health Service. Its goal, among other things, is to help ensure the safety of the nation's blood supply by minimizing such risks as the transmission of infectious diseases and, at the same time, the maintenance of an adequate supply. Accordingly, it "oversees all phases of blood preparation and manufacture, from donor selection and testing to factor concentrates collection, processing, labelling and storage."

Within the Food and Drug Administration, the Center for Biologics Evaluation and Research (formerly the Office of Biologics Research and Review) regulates the blood and plasma industry. Its broad scope of activities involves the development of standards, the licensing and inspection of blood centres and blood product manufacturers, and the approval of biological products. It inspects and licenses blood establishments that ship blood products in interstate commerce, and inspects more than 2,500 intrastate blood establishments that collect or process blood throughout the United States. In the event of violations, it has authority to issue warning letters and to suspend or revoke licences. It also approves test kits and biological products under the provisions of the *Public Health Services Act* and the *Federal Food, Drug, and Cosmetic Act*. In compliance with this legislation, the center issues and enforces standards for safety, efficacy, and labelling and has the power to recall blood and blood products from the market. Finally, its officials conduct extensive research into new and existing blood products in order to develop a scientific basis for standards, addressing such issues as the preparation, preservation, and safety of blood and blood products. In addition to its responsibilities for blood and blood products, the center has been a focus for AIDS research and has participated in the development of diagnostic test kits.

For independent advice on technical issues, the Center for Biologics Evaluation and Research relies on several advisory committees, including one devoted exclusively to blood and blood products – the blood products advisory committee. This committee has the task of evaluating data related to the safety, effectiveness, and labelling of blood components and blood products. During the 1980s, the committee was composed of experts drawn from the blood-banking and fractionation industries and a variety of other relevant disciplines, including public health, laboratory medicine, infectious diseases, virology, hematology, and oncology.

The National Institutes of Health is the federal government's principal agency for biomedical research. In addition to other health-related issues, it is engaged in continuing research to improve blood-banking operations and blood safety, a task undertaken by its National Heart, Lung, and Blood Institute. In the past, the National Heart, Lung, and Blood Institute has supported research to evaluate the efficacy of various direct and surrogate tests, to determine the prevalence of specific viruses in donor populations, and to develop techniques for inactivating viruses and for making blood substitutes. It has convened a number of interagency workshops and conferences to discuss these and other current issues. The National Cancer Institute, also part of the National Institutes of Health, was instrumental in identifying the AIDS virus.

The National Hemophilia Foundation

The National Hemophilia Foundation is a non-profit national advocacy organization devoted to serving the needs of persons with bleeding disorders. It is made up of forty-six self-governing chapters and a national board of directors that serves as the policy-making body. This board elects the officers for the foundation, and, with respect to the chapters, grants and terminates charters, determines their territorial jurisdictions, and establishes and enforces uniform rules. Decisions are made for the foundation by the president, four vice-presidents, the chairman of the board, the executive director, and the chair of the medical and scientific advisory council. During the 1980s, this council was responsible for giving advice to the National Hemophilia Foundation board of directors about medical and scientific issues of relevance to persons with hemophilia and for making appropriate recommendations to members. Physicians from regional hemophilia treatment centres sat as members of the council.

Prevalence of blood-related HIV or AIDS

According to a study published in 1995 by the Institute of Medicine, a private non-profit organization that gives health policy advice to the National Academy of Sciences, more than half of the 16,000 hemophiliacs in the United States became infected with HIV during the 1980s. In the same period, more than 12,000 blood transfusion patients were infected with HIV. Some of them unknowingly transmitted the virus to their spouses, partners, or newborn children. As for the prevalence of blood-related AIDS cases, according to data compiled by the CDC, by the end of December 1996, 4,674 hemophiliacs and 8,261 recipients of blood transfusions had contracted AIDS.

Protecting the blood supply from HIV or AIDS

Study by the Institute of Medicine

In July 1993, the Secretary of Health and Human Services asked the Institute of Medicine to review the events of the early 1980s relating to the transmission of HIV through the blood supply. It was not asked to assess the current safety of the nation's blood supply.

The Institute of Medicine appointed a special committee, the Committee to Study HIV Transmission through Blood and Blood Products (Institute of Medicine committee), composed of experts in various disciplines throughout the country, to undertake the study. After two years of investigation, the committee published a report on 13 July 1995 in which it examined events relating to donor screening, communicating information about risk to both physicians and patients, inactivating viruses in blood products, recalls, surrogate testing, and informing transfusion recipients of contaminated blood and blood products. No thorough examination of these events had previously been undertaken by government, although a number of issues related to the safety of the blood supply and the adequacy of Food and Drug Administration regulations were canvassed during the hearings of the Presidential Commission on the Human Immunodeficiency Virus Epidemic, held in 1987–8, and the hearings of the Subcommittee on Oversight and Investigations, held in 1990. In this chapter, great reliance has been placed on the report of the Institute of Medicine committee.

[The sections entitled “The emergence of HIV or AIDS” and “Response to the emergence of HIV or AIDS” contain information discussed earlier in the Report. A more detailed account of these events is given in Chapter 9, “The Recognition of AIDS as a Blood-Borne Disease.”]

The emergence of HIV or AIDS

In late 1980 and early 1981, the Centers for Disease Control (CDC) in Atlanta, Georgia, began to receive reports of male homosexuals suffering from Kaposi's sarcoma, a rare form of skin cancer that until then had been seen only in elderly men, and *Pneumocystis carinii* pneumonia, which until that time had been found only in patients with severely weakened immune systems. During this period there was a marked increase in requests for pentamidine, a drug used in the treatment of *Pneumocystis carinii* pneumonia that could be obtained only from the CDC.

On 5 June 1981, the CDC's *Morbidity and Mortality Weekly Report* included a report of five cases of *Pneumocystis carinii* pneumonia that were strikingly similar. All five patients were homosexual men who had used inhalant drugs and had cytomegalovirus infection and candidiasis. Cytomegalovirus and candida are microorganisms commonly found in humans. They cause opportunistic infections in persons with weakened immune systems, but do not usually cause disease in other persons. Four of the patients showed evidence

of past hepatitis B infection, and three had abnormal cellular immune function. These findings were said to suggest “the possibility of a cellular-immune dysfunction related to a common exposure that predisposes individuals to opportunistic infections.” A month later, the CDC reported that twenty-six cases of Kaposi’s sarcoma and ten more cases of *Pneumocystis carinii* pneumonia had been diagnosed among homosexual men in New York City and California during the previous thirty months. In August 1981, it reported seventy more cases of Kaposi’s sarcoma or *Pneumocystis carinii* pneumonia, the vast majority among homosexual or bisexual men. In that report, the clustering of both diseases among homosexual men was seen to suggest a common underlying factor. The new disease was provisionally named Gay Related Immunodeficiency Disease, or GRID.

By the end of 1981, the CDC was investigating 160 cases of GRID, and five to six new cases were being diagnosed every week. The authors of an article published in the *New England Journal of Medicine* of December 1981 warned that a “nation-wide epidemic of immunodeficiency among male homosexuals” was taking place. There was also evidence that the epidemic was beginning to affect new risk groups. Intravenous drug users and Haitians were now also suffering from these opportunistic infections. Another study published in the *New England Journal of Medicine* in December 1981 found that of eleven new cases of *Pneumocystis carinii* pneumonia, six were homosexual men and seven were drug users, and by the summer of 1982, the CDC had also received thirty-four reports of cases of opportunistic infections among Haitians who had recently arrived in the United States.

Blood-related AIDS cases began to appear in the summer of 1982. In late June 1982, Dr James Curran, coordinator of the internal task force on Kaposi’s sarcoma and opportunistic infections, reported that the CDC was investigating reports of *Pneumocystis carinii* pneumonia among hemophilia patients. Three cases had been identified, one in Florida, one in Colorado, and one in Ohio, sites that were scattered and distant from the centres in which the disease had until then been concentrated – New York, San Francisco, and Los Angeles. A report of the three cases of *Pneumocystis carinii* pneumonia in hemophiliacs appeared in the *Morbidity and Mortality Weekly Report* of 16 July 1982. The investigators concluded that, since the patients lived in different states and had not received common lots of factor concentrate, “[a]lthough the cause of the severe immune suppression is unknown, the occurrence among the three hemophiliac cases suggests the possible transmission of an agent through blood products.”

The *Morbidity and Mortality Weekly Report* of 10 December 1982 stated that four more cases of opportunistic infections in hemophiliacs and one suspected case that did not meet the strict criteria for AIDS had been reported, and that the three hemophiliac AIDS patients whose cases had been reported in July had since died. These newly diagnosed patients, like the three original

hemophiliacs who were diagnosed with AIDS, lived in disparate geographical regions and had been treated with different lots of factor VIII concentrate. The CDC said that the number of hemophiliacs with AIDS was continuing to increase, and that patients with hemophilia might be at significant risk of contracting AIDS.

The *Morbidity and Mortality Weekly Report* of 10 December 1982 also included the first published report of transfusion-associated AIDS. A twenty-month-old infant in San Francisco had died after receiving a transfusion of blood from a donor who subsequently developed AIDS. This case was significant for several reasons. Both the donor and the recipient had AIDS. The incubation period from receipt of the blood until the onset of AIDS could be established, and was approximately a year and a half. The donor had no symptoms of AIDS at the time of donation. These circumstances lent strong support to the theory that AIDS might be caused by an infectious agent transmitted through exposure to blood and blood products.

Throughout 1983, evidence that AIDS could be transmitted by both blood and blood products continued to accumulate, and in January 1984 the *New England Journal of Medicine* published a summary of eighteen cases of AIDS, none of which involved any risk factors other than receipt of blood components within five years of the onset of the illness. Based on these investigations, the authors concluded that “exposure to as little as one unit” might result in transmission of AIDS. Many persons involved in transfusion medicine were aware of this article before its publication and were persuaded by the evidence. As Dr Thomas Zuck, a former director of the division of blood and blood products in the Food and Drug Administration, said in his testimony, the article “put the whole medical community and perhaps the world on notice that AIDS is transmitted by blood transfusions,” and that, by January 1984, “the debate [was] over.”

Response to the emergence of HIV or AIDS

To ensure that new cases of opportunistic infections were properly monitored and investigated, in July 1981 the CDC created an internal task force led by Dr Curran, the chief of its venereal disease control division, to study Kaposi’s sarcoma and opportunistic infections. The task force undertook passive surveillance (obtaining data from telephone reports, requests for pentamidine, and reports from state health departments, physicians, and gay community networks), active surveillance in eighteen major cities (communicating with the heads of the infectious disease, dermatology, oncology, and pathology departments of all major hospitals), interviews with patients to identify the syndrome’s characteristics and factors, and a national case control study to search for clues to the cause of the disease.

In March 1982, the CDC convened its first interagency meeting in an effort to recruit the assistance of the Food and Drug Administration and the National Institutes of Health in laboratory research and in investigating the history

and cause of the disease. In June 1982, the CDC formulated the first definition of what came to be known as AIDS. The CDC's definition, which was adopted in other countries, was modified over time to reflect the current knowledge about AIDS. It defined a case as "illness in a person who 1) has either biopsy-proven KS or biopsy- or culture-proven life-threatening opportunistic infection, 2) is under the age of 60, and 3) has no history of either immunosuppressive underlying illness or immunosuppressive therapy."

In July 1982, on learning of the possible link among the three hemophilia cases, the CDC decided to convene a small ad hoc expert advisory committee, composed of representatives from the CDC, the Food and Drug Administration, the National Institutes of Health, and the private sector to identify the implications of this latest report for blood products and to make recommendations within thirty days to the assistant secretary for health. On 9 July, the director of the CDC, Dr William Foege, reported the three cases to state and territorial health officers, blood-banking organizations, the Food and Drug Administration, the National Institutes of Health, and regional offices of the CDC. He told them that the reported immune dysfunction among the three hemophiliacs might be caused by a transmissible agent and that "concern about possible transmission through blood products has been raised." He said the CDC would be conducting surveillance, and asked hemophilia treatment centres to report cases of opportunistic infections or suspected immune deficiency to the CDC immediately through state health departments.

On 14 July 1982, the National Hemophilia Foundation told hemophilia patients and treating physicians about the three cases. It said that the CDC believed that the immune deficiency might be caused by a virus transmitted through blood or blood products, as was hepatitis, but that the risk of contracting this immunosuppressive agent was minimal.

On 16 July 1982, officials of the Office of Biologics Research and Review met with representatives of the CDC, the National Institutes of Health, the National Hemophilia Foundation, and various blood-banking organizations to determine whether any common factor could be identified in the three cases reported among hemophiliacs and the earlier cases known among homosexuals and drug users. At this meeting, a committee on opportunistic infections in patients with hemophilia was established to exchange information about the cases and to conduct surveillance.

That committee met in Washington, DC, on 27 July 1982. It was attended by representatives of the key federal agencies (the CDC, the Food and Drug Administration, and the National Institutes of Health), a number of national organizations involved in the blood system (the American Association of Blood Banks, the American Red Cross, the American Blood Resources Association, the Council of Community Blood Centers), the National Hemophilia Foundation, the Pharmaceutical Manufacturers Association, and the National

Gay Task Force (the largest gay civil rights organization in the United States). The meeting had two issues before it. They were whether the cause of immunodeficiency in hemophiliacs was the same as the cause of immunodeficiency in members of other high-risk groups, and whether certain blood products placed recipients at risk of contracting this form of immunodeficiency.

There was agreement that the disease was caused by an infectious agent and that those at risk of developing the disease included intravenous drug users and Haitians, in addition to homosexual men. The task force accordingly decided that the disease should be renamed the "Acquired Immune Deficiency Syndrome," or AIDS, and recommended that a surveillance study of hemophiliacs be carried out, that laboratory studies be undertaken of hemophiliacs with no symptoms of opportunistic infections, and that techniques be developed immediately to reduce or eliminate the risk of infection from factor VIII concentrate. The surveillance study, conducted by the National Hemophilia Foundation and the CDC, began in late October and early November.

At a meeting of the Food and Drug Administration's blood products advisory committee in September 1982, the matter of AIDS in hemophiliacs was discussed, but the minutes record that the committee concluded that "there are insufficient data to suggest that any immediate action [be taken] with licensed blood products."

In October 1982, the National Hemophilia Foundation recommended that homosexual men, intravenous drug users, and Haitians be excluded from donating blood or plasma in circumstances in which the plasma from the donations could be used to manufacture factor VIII or factor IX concentrates.

In December 1982, Dr Bruce Evatt of the CDC reported to the blood products advisory committee that the epidemic was growing at an almost exponential rate, doubling every six months, and expressed a concern that transfusion cases "may follow the same increasing pattern seen with hemophilia patients." The committee discussed immediate steps that could be taken to reduce the risk of AIDS transmission in blood and blood products. These measures included relying on cryoprecipitate (a clotting product that is derived from the plasma of only a few donors) in treating hemophilia rather than factor concentrates (blood products that are derived from a pool of thousands of donors, with increasingly greater risk of contamination); developing methods of processing that would reduce the likelihood of infection in blood products; excluding donors at high risk for the disease; and carrying out additional routine tests to screen for markers of infection in donated blood and plasma. The committee made no recommendations, pending further investigation and study.

In December 1982, in response to reports of HIV or AIDS among patients who had been transfused, officials from the CDC, the Food and Drug Administration, and the National Institutes of Health decided to establish an

ad hoc advisory group on AIDS, to report to the assistant secretary for health, recommending methods of reducing the risk of AIDS transmission through blood and blood products.

A meeting of the advisory group was held on 4 January 1983. More than 200 persons were present at that meeting, including employees of the CDC, the Food and Drug Administration, and the National Institutes of Health, representatives of the blood and plasma centres, the plasma sector, the four large U.S. blood product manufacturers, the gay community, and the National Hemophilia Foundation, as well as some treating physicians.

At the meeting, Dr Evatt presented evidence suggesting that AIDS could be transmitted by blood. He discussed the cases of AIDS seen in hemophiliacs, described the case of an infant in California who had received a transfusion at birth, and said that five unconfirmed cases of transfusion-associated AIDS were under investigation.

Several measures were suggested to reduce the risk of transmission. Dr Donald Francis, the assistant director for medical science in the CDC's division of virology, advocated direct questioning of blood donors about behaviour that would have placed them at risk of contracting AIDS. He also recommended that donations be tested for the presence of antibody to the hepatitis B core antigen, in the belief that persons who had been exposed to hepatitis B would also be at greater than normal risk of contracting AIDS. Representatives of the gay community objected to his first proposal because it would be discriminatory, and representatives of the blood banks and plasma industry objected to the second, primarily because it would be too expensive. Dr Oscar Ratnoff, a physician at Case Western Reserve University who treated hemophiliacs, recommended that hemophiliacs use cryoprecipitate instead of factor concentrates. Ultimately, the meeting endorsed none of these measures. Although the participants reached a general consensus that "it would be desirable to exclude high-risk donors to reduce the risk of AIDS transmission," there was no agreement about a method of accomplishing that goal. There was also no consensus on the question of whether AIDS was caused by a transmissible agent, on the risk of AIDS from blood donations, or on the desirability of introducing new methods of donor screening or testing to reduce the risk of transmission. Instead, the CDC, the Food and Drug Administration, and the National Institutes of Health were each asked to submit a set of recommendations after the meeting for the prevention of AIDS in patients with hemophilia and for other recipients of blood and blood products, so that a uniform set of recommendations might be developed.

The Public Health Service recommendations were announced by the Department of Health and Human Services on 4 March 1983. Although they were not binding on blood banks, their principles were endorsed three days later in a joint statement by the American Red Cross, the American Association of Blood Banks, and the Council of Community Blood Centers. Members of

groups at high risk of contracting AIDS were to be urged to refrain from donating blood or selling plasma, in part by information given at the collecting site. High-risk groups were identified as persons with AIDS, sexual partners of persons with AIDS, persons with symptoms and signs suggestive of AIDS, sexually active homosexual or bisexual men with multiple partners, Haitian entrants to the United States, present or past users of intravenous drugs, and sexual partners of individuals at high risk of contracting AIDS.

In May 1983, the Department of Health and Human Services announced that the Conference of State and Territorial Epidemiologists had passed a resolution that AIDS should become a notifiable disease. Physicians and health care institutions were urged to report cases to their state health departments.

Excluding persons at risk: Donor screening

If the transmission of AIDS in the United States was to be kept to a minimum, it was essential to refrain from accepting donations from persons at risk of contracting AIDS. Ironically, in the early 1980s, persons belonging to high-risk groups were among those who were most frequently recruited by the blood and plasma industry as donors. As the Institute of Medicine committee observed:

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. In addition to homosexuals, other populations who were at high risk for infectious disease, such as prison inmates and persons in other institutional settings (e.g., mental hospitals), served as blood or plasma donors. 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.

Measures to exclude donors who were at risk of contracting AIDS were accordingly at the forefront of efforts to control the spread of AIDS. They included two types of screening. The first was passive exclusion, commonly known as “voluntary self-exclusion” or “self-deferral,” in which prospective donors were given pamphlets and brochures designed to identify those at greatest risk of contracting AIDS and to ask them to exclude themselves from the donor pool voluntarily. The second was active exclusion, in which staff at blood and plasma centres asked prospective donors whether they had any signs and symptoms of AIDS or whether they might have been in contact with persons at high risk of contracting AIDS (often referred to as “exposure to persons with AIDS”). In addition, the centres conducted physical examinations of donors to detect symptoms of AIDS; required donors to sign statements that they had read the educational materials provided and were not members of a risk group (donor declarations); halted collection in areas with a high incidence of AIDS; provided a method by which

donors could indicate that their donation should not be used for transfusion (confidential unit exclusion); and questioned donors orally about their membership in a risk group (direct questioning). These measures were not introduced simultaneously by the various blood-banking organizations.

Responses by the voluntary and the commercial sectors

The first recommendation to exclude high-risk donors such as homosexual men, intravenous drug users, and recent Haitian immigrants was made at a meeting of the National Hemophilia Foundation's medical and scientific advisory council on 2 October 1982. The issue of screening out high-risk donors was also raised at the Food and Drug Administration's blood products advisory committee meeting of 3–4 December 1982, but no recommendation was made, despite the fact that it was known that the CDC had received eight reports of AIDS among hemophilia patients and five reports of transfusion-related cases. Dr Dennis Donohue of the Food and Drug Administration expressed the view that the screening of donors was "not subject to responsible regulatory action" and that "voluntary blood banking organizations must look at the question, remembering their responsibility for the blood supply and their basic social responsibility." Not until the following month was there any substantive discussion about the implementation of national screening guidelines for donors.

On 4 January 1983, the CDC held a public meeting in Atlanta to draft recommendations for preventing the spread of AIDS. Among those attending were representatives from the voluntary and the commercial blood sectors, the Food and Drug Administration, the National Institutes of Health, the National Hemophilia Foundation, and the National Gay Task Force. Although there was agreement that it was desirable to exclude high-risk donors, there was no agreement about the means of doing so. As the Institute of Medicine committee noted in its report, "[t]here was broad resistance to the implementation of specific donor screening measures, and the meeting ended with no consensus on the validity of such measures." Among the measures discussed was the self-deferral of donors within high-risk groups, which participants agreed was both inexpensive and relatively easy to initiate; direct questioning of donors about their membership in a risk group; and physical examination of donors for symptoms of AIDS. At the close of the meeting Dr Foege, the director of the CDC, recommended that the Public Health Service use these discussions and subsequent communications from participants as a basis for developing a uniform set of recommendations.

By January 1983 only one manufacturer, Alpha, had implemented donor screening for AIDS in its commercial plasmapheresis centres. In the previous month, Alpha had told all its plasma collection centres to exclude intravenous drug users, homosexual men, and persons who had resided in Haiti. Donors were asked directly if they were members of the risk groups, and a

statement was obtained from every male donor confirming that he had never had sex with a man. Using this method, Alpha excluded 308 donors in just three weeks (from the last week of December to mid-January).

Motivated by concerns raised at the meeting of 4 January 1983 and by the manufacturers' desire to remain competitive within the marketplace, blood banks decided to follow Alpha's example. They would attempt to exclude donors most at risk of contracting AIDS, but by considerably less intrusive methods.

At a meeting held on 6 January 1983, the members of the voluntary blood sector – the American Association of Blood Banks, the Red Cross, and the Council of Community Blood Centers – agreed on a number of measures to reduce the risk of transmitting AIDS. From that time, they announced in a statement issued on 13 January 1983, medical histories should include specific questions designed to detect symptoms of, or exposure to, AIDS. Prospective donors would be asked whether they had a history of night sweats, unexplained fevers, unexpected weight loss, or were suffering from lymphadenopathy or Kaposi's sarcoma. They would not, however, be asked about their sexual practices or orientation – an omission that was applauded by members of the gay community.

Within the voluntary sector, then, donor screening for AIDS was initiated as early as mid-January 1983. The Red Cross, for example, told its employees to expand health history interviews to include specific questions to detect symptoms of AIDS and exposure to AIDS. In areas with a high incidence of AIDS, screening was in place by early February. On 8 February 1983, the Irwin Memorial Blood Bank in San Francisco announced that it would be introducing a revised questionnaire to exclude donors with symptoms of AIDS and donors "who may have been in contact with persons at high risk for AIDS," including intravenous drug users, Haitian immigrants, and homosexually active men. The same type of screening was initiated by the Greater New York Blood Program. By 14 February 1983, a donor's medical history was to be revised to include questions about the presence of swollen glands, prolonged fever, and recent unexplained weight loss.

The commercial sector made similar efforts to modify its donor-screening process. At a meeting of the National Hemophilia Foundation's medical and scientific advisory council and representatives from the plasma industry on 14 January 1983, three manufacturers – Armour, Cutter, and Hyland – stated that they would introduce active methods of donor screening within the next two weeks. By the end of the month, it was clear that all manufacturers would be following suit. On 28 January 1983 the American Blood Resources Association, a group representing blood product manufacturers, issued a statement recommending that member firms distribute pamphlets designed to discourage high-risk donors, that donors be questioned about symptoms of AIDS, and that donors be required to sign a declaration acknowledging that they were not at high risk of contracting AIDS.

In the early months of 1983, the voluntary and commercial sectors also tried to minimize recruiting donors in high-risk groups, although it is unclear to what extent these efforts were successful. In their joint statement of 13 January 1983, the American Association of Blood Banks, the Red Cross, and the Council of Community Blood Centers had announced that persons responsible for recruiting donors should no longer focus on groups that might have a high incidence of AIDS. In a meeting with plasma industry representatives on 6 January, the National Hemophilia Foundation asked the manufacturers to adopt a similar position, recommending that they stop using plasma obtained from centres located in "hot spots," or areas with a significant incidence of AIDS, such as New York, San Francisco, the Hollywood area of Los Angeles, and prisons. Alpha had already ceased collecting in these places, and Armour, Cutter, and Hyland ceased soon thereafter. There is evidence, however, that the voluntary sector refused to stop collecting in high-risk areas, though its blood donor recruiting officials no longer targeted high-risk individuals, and that the commercial sector also continued to operate in such areas. There is also evidence that the Red Cross and the Council of Community Blood Centers objected to exclusion based on geographical location, because it might erode local support.

Finally, in late February 1983, the Greater New York Blood Program introduced a method enabling donors to request that their donations not be used for transfusion. All donors were given a questionnaire listing high-risk groups and asking members of these groups to direct that their blood be used for laboratory studies only. This measure, referred to as "confidential unit exclusion," produced a deferral rate of 1.4 per cent.

To summarize, by February 1983 both voluntary blood centres and commercial plasma centres were asking donors whether they had symptoms of AIDS and were making efforts to avoid recruitment in areas where the population was at high risk of contracting AIDS. Plasma centres were recommending the use of pamphlets and donor declarations; one plasma centre had implemented direct questioning; and one blood bank had introduced confidential unit exclusion.

Recommendations of the Public Health Service and the Food and Drug Administration

On 4 March 1983, federal Public Health Service officials issued a press release announcing interim recommendations to prevent the transmission of AIDS. One recommendation was that, as a temporary measure, members of groups at increased risk of contracting AIDS should refrain from donating plasma or blood, and that blood and plasma centres should inform potential donors of this recommendation. Groups at risk included persons with AIDS, sexual partners of persons with AIDS, persons with symptoms and signs suggestive of AIDS, sexually active homosexual or bisexual men with multiple partners,

Haitian entrants to the United States, present or past abusers of intravenous drugs, and sexual partners of individuals at high risk of contracting AIDS. These recommendations were published in the *Morbidity and Mortality Weekly Report* the same day and were set out in a joint statement on 7 March 1983 by the American Association of Blood Banks, the Red Cross, and the Council of Community Blood Centers.

In response, the Red Cross announced that its blood centres would immediately begin to give potential donors information about AIDS and to ask high-risk donors to refrain from donating. The American Association of Blood Banks announced that, like the plasma sector, its members would give donors educational materials about AIDS, ask them to sign an acknowledgement card stating that they had read the information, and, during the interview, attempt to identify potential donors who had early signs or symptoms of AIDS.

The Public Health Service's interim recommendations were replaced on 24 March 1983 by stricter guidelines issued by the Food and Drug Administration. Blood banks were told to introduce educational programs to inform groups at increased risk of contracting AIDS to self-exclude, and to revise donor medical histories to include specific questions designed to detect possible symptoms of AIDS or exposure to persons with AIDS. There would be standard questions about a history of night sweats, unexplained fevers, unexpected weight loss, or signs of lymphadenopathy or Kaposi's sarcoma. Plasma centres were told not only to give donors information about AIDS and to question patients about symptoms of AIDS but to examine donors physically for lymphadenopathy and weight loss. Standards imposed on plasma centres were considerably more stringent than those imposed on the voluntary sector because officials thought that voluntary donors posed less risk than paid donors. Finally, manufacturers were informed that plasma collected from donors suspected of being in a high-risk group might only be used in the production of derivatives not known to transmit infectious diseases. Although these guidelines lacked the force of regulations, they were promptly implemented by the blood and plasma industry. In March 1983, the American Association of Blood Banks, the Red Cross, and the Council of Community Blood Centers issued another joint statement affirming that they would comply with these recommendations. By the end of March 1983, all these organizations had issued donor-screening pamphlets and had begun screening for symptoms of AIDS or exposure to AIDS. In the same month, the American Association of Blood Banks introduced donor declarations. By 25 March 1983, more than 1,100 cases of AIDS had been reported in the United States since June 1981, with more than 400 deaths.

In compliance with these guidelines, plasma centres began to examine donors physically for symptoms of AIDS in March 1983. Some had begun to do so earlier. Cutter, for instance, introduced supplementary physical examinations for male donors in February 1983.

Thus, by the end of March 1983, all blood and plasma organizations had revised medical histories to include questions about symptoms of AIDS, had halted collection in areas with a high incidence of AIDS, and had introduced pamphlets to educate donors about categories of individuals most at risk. Some blood banks were asking donors to sign acknowledgements that they were not at risk, and plasma centres were examining donors for signs and symptoms of AIDS.

Although the Food and Drug Administration's definition of risk groups was reproduced in most of the information materials prepared for donors, some blood banks found it necessary to clarify this definition because the category of "sexually active homosexual or bisexual men with multiple partners" was proving to be a source of confusion. As epidemiological knowledge of the disease evolved, many blood banks took the initiative of revising the definition. On 12 July 1983, the Irwin Memorial Blood Bank, the community blood bank in San Francisco, told its employees to interpret the word "multiple" to mean more than one. Consequently, only gay men who had been monogamous for a period of three years were eligible to donate. In January 1984, the Red Cross revised its donor-screening pamphlet to inform donors that references to multiple sexual partners meant "more than one partner." The Food and Drug Administration published revised guidelines in December 1984 to eliminate any further confusion. The reference to "sexually active homosexual or bisexual men with multiple sexual partners" was deleted and replaced by "males who have had sex with more than one male since 1979 and males whose male partner has had sex with more than one male since 1979."

During the 1980s, the Food and Drug Administration continued to amend its guidelines of March 1983 in light of new epidemiological data. In December 1984, it defined "recent Haitian entrants" as those who had entered the United States after 1977, and added persons with hemophilia as a new risk group. In September 1985, the group at risk was augmented to include "any male who has had sex with another male since 1977," and those who have had "a single homosexual experience and may not regard themselves as being homosexual or bisexual." This change was prompted by the discovery that the majority of donors with positive HIV tests were individuals at high risk of contracting AIDS who did not so identify themselves. In October 1986, the categories of those at risk were again revised to include persons who had been prostitutes in the years since 1977, along with their heterosexual partners within the last six months, and persons emigrating since 1977 from countries where heterosexual activity was thought to play a major role in the transmission of HIV infection. In December 1990, the Food and Drug Administration included among the persons at high risk for AIDS those who, within the past twelve months, had been treated for a sexually transmitted disease, had had sex with a prostitute, or had received a transfusion of blood or blood products.

As noted earlier, in 1983–4 a number of blood-banking organizations had introduced a method by which donors could confirm in writing that they were not at risk of contracting AIDS. In 1986, the Food and Drug Administration endorsed the use of these donor declarations by recommending that consent forms for both blood and plasma donors allow donors to acknowledge that they had read and understood the information about AIDS and to attest in writing that they were not at risk.

Confidential unit exclusion

Some blood banks also found it useful to provide donors with a “second exclusion opportunity.” This method enabled persons under societal or peer pressure to complete their donation, yet discreetly exclude themselves. Two methods were used – confidential unit exclusion and call-back. With the former, donors were given a questionnaire asking them to identify their donation as being for “research” purposes only. With the latter, donors were given a telephone number to call to request that their donation be discarded.

The Greater New York Blood Program had introduced confidential unit exclusion in early 1983. The next year, the Red Cross introduced the less expensive measure, call-back, on a national scale. As of 1 February 1984, persons who were concerned about the blood they had donated could call the blood centre and request that their blood not be used for transfusion. The American Association of Blood Banks and the Council of Community Blood Centers soon endorsed measures to permit donors to inform the centre that their donation should not be used. In a statement made on 3 January 1984 responding to reports of transfusion-associated AIDS, these organizations suggested that in areas with a high incidence of AIDS it might be important to allow donors to indicate that their donations should not be used for transfusion. This self-exclusion method would include the use of a confidential form at the time of donation, or a call to the centre after the donation had been made.

In March 1984, the plasma industry’s study group on hepatitis B core testing reviewed the Greater New York Blood Program’s experience with confidential unit exclusion and recommended that pilot programs be developed in plasma collection centres. By late 1984, the use of confidential exclusion had gained considerable acceptance and, in the ensuing years, continued to garner support. In December 1984, the Food and Drug Administration published a recommendation that all blood banks and manufacturers introduce this method of screening donors. The importance of providing donors with an opportunity to withdraw their blood confidentially was reaffirmed by the Food and Drug Administration in a memorandum issued on 7 May 1985. In July 1986, at a National Institutes of Health consensus conference, it was agreed that since testing was imperfect, blood banks should introduce confidential unit exclusion. In September 1986, the practice also received the endorsement of the Food and Drug Administration’s blood products advisory

committee. In October, the Food and Drug Administration once again issued a recommendation to blood banks in support of confidential unit exclusion, stating that, at a minimum, the procedure should allow for removal of designated units, strict confidentiality of the donor's decision and a confidential environment in which to make the decision, HIV testing of all donated units, notification of donors with positive test results, and assurances to donors that units confidentially excluded would be used for laboratory testing.

Direct questioning

At the meeting of the Public Health Service on 4 January 1983, CDC officials raised the suggestion that donors be questioned directly by staff members at blood centres about their membership in risk groups. On the basis of their experience with hepatitis B, these officials had confidence that homosexual men would answer the questions honestly. Although most of the participants at the meeting agreed that questioning donors about their nationality, sexual orientation, or personal habits was only an extension of the screening history already used in blood banks, it was opposed on the grounds that it was potentially intrusive into personal matters and might stigmatize groups already subject to prejudice. In addition, it might ultimately be ineffective in identifying persons in high-risk groups.

The resistance to direct questioning, however, went far deeper. The gay community regarded it not only as discriminatory but as "persecutory," "reminiscent of miscegenation blood laws that divided black blood from white" and "similar in concept to World War II rounding-up of Japanese-Americans." Both the voluntary and the commercial sectors were opposed to it because it might cause blood shortages. The voluntary blood sector in particular regarded it as a threat to donor recruitment. As the Institute of Medicine committee found, blood banks viewed the idea of confronting donors with prying questions about their sexual behaviour as potentially damaging. It was also suggested that the practice could be counter-productive. Closeted gay men might donate to avoid being identified as gay, and militant gay men might deliberately donate to protest against "discriminatory" behaviour, thereby increasing the risk. Only the CDC and the National Hemophilia Foundation saw direct questioning as a means to reduce the risk of AIDS, and the National Hemophilia Foundation included the implementation of direct questioning of donors among its recommendations to manufacturers in January and October 1983.

Because of these concerns, in their joint statement of 13 January 1983 the blood banks announced that direct or indirect questions about a donor's sexual preference were both inappropriate and ineffective in excluding donors at risk. The Public Health Service eventually concurred with this view. When donor-screening recommendations were made in March 1983, there was no reference to the questioning of donors about high-risk behaviour. Direct questioning was thus not universally adopted by the voluntary and

commercial sectors in the 1980s as a means of excluding donors at risk; only a few blood banks asked potential donors questions about homosexual activities. Nor was its use recommended by the Food and Drug Administration until the end of 1990.

In its review of donor screening, the Institute of Medicine committee found that incorrect 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.” It said that “[i]f 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 far higher than the ‘one case per million’ patients transfused.” Moreover, it concluded, if they had known that AIDS was virtually always fatal, “decision makers might have been more aggressive about donor screening policies.”

In particular, the Institute of Medicine committee was critical of the guidelines issued by the Food and Drug Administration in March 1983 and of its failure to require direct questioning of donors. With respect to the guidelines, the committee stated that blood banks and manufacturers might have been unclear whether implementation of the guidelines was mandatory, or whether they were simply a recognition of good practices. Because the guidelines “did not reveal their own legal status,” their recipients could, and did, respond in quite different ways. By failing to assert its regulatory authority, the Food and Drug Administration failed to ensure maximum efficacy. With respect to direct questioning, the Institute of Medicine committee said that donors should have been questioned about their sexual behaviour as early as January 1983. It therefore regarded the failure to question donors about risk factors as a missed opportunity to protect public health. Similarly, it viewed the Food and Drug Administration’s failure to require direct questioning as evidence that the agency did not adequately use its regulatory authority.

Inactivating viruses in blood products

The need to inactivate viruses in blood products began with hepatitis, not with AIDS. In 1968, a direct test for the presence of hepatitis B (HBsAg, or hepatitis B surface antigen) was developed and used to identify persons with the disease. Studies performed in the late 1970s and early 1980s demonstrated that the prevalence of post-transfusion hepatitis was 7 to 21 per cent in recipients of blood from volunteer donors. Hepatitis, a major risk in the use of blood products made from pooled plasma, led many different persons and organizations to explore ways of inactivating the virus.

During the 1970s, two methods were developed in an attempt to inactivate the hepatitis B virus. The first, developed by Dr Edward Shanbrom, a scientist with Hyland, was a detergent method for treating plasma before it was fractionated into factor concentrates. Unfortunately, other manufacturers

showed little interest in this process. They were already conducting their own research into inactivating viruses, and if Dr Shanbrom's method had been used, manufacturers would have had to apply again to the Food and Drug Administration for licensing of fractionated products. The second method, a pasteurization procedure developed by the German blood product manufacturer Behringwerke AG, involved heating factor concentrates at 60°C for ten hours. This pasteurized factor concentrate was licensed in Germany in February 1981, and an article demonstrating the efficacy of the process was published the same year. Other manufacturers were reluctant to adopt this technique for several reasons. Estimates projected that the process would produce a substantial loss of yield (50 to 90 per cent), a loss that would jeopardize supply; the cost of producing the pasteurized factor concentrates was ten times that of producing unpasteurized concentrates; the effectiveness of these concentrates in inactivating non-A, non-B hepatitis (liver disease that was not caused by the hepatitis A and B viruses) was unknown; and, finally, there were fears that these factor concentrates might cause patients to develop inhibitors, or antibodies to the concentrates themselves, thereby complicating their future treatment.

By the early 1980s, most U.S. manufacturers were beginning to develop their own viral inactivation processes, primarily by using heat to prevent the transmission of hepatitis. For example, Baxter began studies on dry heat methods, which involved heating concentrates in the lyophilized, or freeze-dried, state, and Alpha began to develop a wet heat process, by which concentrates were immersed in a heptane solvent and heated at 60°C for twenty hours. Because of the competitive nature of the business, however, specific details about the effectiveness of these various methods were kept confidential.

Awareness of the need for inactivating viruses in blood products to reduce the risk of AIDS dates from the July 1982 meeting held by the CDC to discuss three cases that had appeared among hemophiliacs. The participants reviewed what had then been learned, and agreed that methods of decreasing the infectious risks from factor VIII concentrate should be identified. That was the main purpose of the Food and Drug Administration blood products advisory committee's meeting in December 1982. The committee discussed experimental methodologies to inactivate the hepatitis B virus and recommended that inactivation methods continue to be developed. The question of viral inactivation was also discussed at the public meeting held on 4 January 1983. Two problems were identified. There was no laboratory model to determine the success of each approach; and a single method of viral inactivation was not suitable for all products. Nevertheless, Food and Drug Administration officials at the meeting estimated that heat-treated factor VIII concentrate would be available within the year. In the same month, the National Hemophilia Foundation recommended that the development of methods to inactivate viruses be expedited.

By early 1983, most manufacturers had conducted experiments on the hepatitis viruses, measuring the level of viral inactivation achieved by heating factor concentrates at varying temperatures for various periods, and had undertaken studies on chimpanzees to determine if the virus had indeed been inactivated. Manufacturers began to seek regulatory approval of their processes in late 1982 and early 1983.

The first manufacturer to receive approval from the Food and Drug Administration was Hyland in the spring of 1983. By early 1984, three other manufacturers had received approval to distribute heat-treated factor concentrates. In January 1984, Cutter was licensed to distribute factor concentrates subjected to a liquid pasteurization process involving heating at 60°C for ten hours, and the following month it was licensed for a dry heat treatment at 68°C for seventy-two hours; Armour was licensed in January 1984 for a dry heat process at 60°C for thirty hours; and, finally, Alpha received approval in February 1984 for factor concentrates subjected to a wet heat treatment process at 60°C for twenty hours. Hyland's licence was granted in a period of eight months, and subsequent applicants received approval from the Food and Drug Administration within approximately one year from the time of application. According to the Institute of Medicine committee report, Hyland, Cutter, Alpha, and Armour claimed to have begun processing and distributing heat-treated factor concentrates immediately after receiving their licences, but none had converted production to heat-treated factor concentrates exclusively.

Although heat treatment had been developed as a means of reducing the risk of hepatitis, it was hoped that it would also inactivate the AIDS virus. Until the discovery of the virus, however, there was no scientific basis for this hope. When the Secretary of Health and Human Services, Margaret Heckler, announced in April 1984 that the causative agent of AIDS had been isolated, however, investigations began into the effectiveness of heat-treatment processes on this retrovirus.

Preliminary research revealed that HIV was susceptible to heat and that the risk of transmission could be substantially reduced by heat treatment. Confirmation of that fact was first reported in *The Lancet* by Dr Jay A. Levy and colleagues in September 1984. Dr Levy added mouse retroviruses (believed to be similar to HIV) to human plasma and found that freeze-dried material had to be heated at 68°C for several hours before substantial quantities of the infectious virus were inactivated. He concluded that adoption of prolonged heating at 68°C in the manufacture of factor VIII concentrate should result in materials "free of these infectious viruses."

In a November 1984 meeting of the blood products advisory committee, the CDC and the Food and Drug Administration reported that they were conducting a study to evaluate the various methods of heat treatment. Although these studies were completed in December 1984 and the preliminary results had been published in the *Morbidity and Mortality Weekly Report*

in October 1984, the final results were not published until August 1985. In these studies conducted by Dr Steven McDougal at the CDC, HIV was added to commercial factor VIII and factor IX concentrates and heated to different temperatures for different durations. Dr McDougal reported that the virus was at least as sensitive, and perhaps more sensitive to heat than the mouse retrovirus studied by Dr Levy and his team. Since data showed no detectable virus in factor concentrates after heating at either 68°C or 60°C, Dr McDougal suggested that heating at 60°C for twenty hours “should provide a large, if not absolute, measure of safety.”

At a conference for treating physicians and CDC officials held in September 1984, there was agreement that physicians treating hemophiliacs should consider changing to heat-treated factor concentrates, even though there was as yet insufficient proof that heat treatment was effective in inactivating the AIDS virus. Most participants thought that hemophilia treatment centres should use discretion in the way they undertook the conversion to heat-treated concentrates, although a very vocal minority advocated the recall of all non-heat-treated factor concentrates. The following month the National Hemophilia Foundation advised treating physicians to consider switching to heat-treated factor concentrates, and the National Heart, Lung, and Blood Institute issued a request for proposals to develop methods to inactivate HIV in plasma derivatives. An editorial in December 1984 in *The Lancet* said that HIV was sensitive to heat, and that heat treatment could be rapidly introduced. The editorial concluded that it was “reasonable to switch to heat-treated factor VIII concentrate,” and “indefensible” to do otherwise.

In December 1984, also, the National Hemophilia Foundation informed its members that Alpha, Cutter, and Hyland had begun to distribute heat-treated factor IX concentrate in late October.

In 1985, several studies demonstrated that heat treatment was effective in substantially reducing the risk of AIDS from factor concentrates. In February, European researchers reported that patients treated with Hyland’s heat-treated factor concentrates exclusively did not seroconvert, or show signs of infection, but that patients using non-heat-treated factor concentrates did. In April, participants at the CDC conference on AIDS in Atlanta heard that heating had been effective in killing the AIDS virus in factor concentrates. In June, Dr Levy and colleagues published a study concluding that, although retroviruses could withstand procedures used to purify factor VIII, “heating lyophilised F[actor] VIII for 72 h[ours] at 68°C or liquid factor concentrates for 10 h[ours] at 60°C will eliminate infectious ARV [HIV] if it is not present in the plasma at more than 10⁶ infectious particles/ml.” In October, Dr John Petricciani, the director of the division of blood and blood products of the Food and Drug Administration, wrote in *The Lancet* that “infectious LAV/HTLV-III [HIV] is unlikely to be present in currently licensed heat-treated factor concentrates, and that the use of such factor concentrates should not result in additional cases of AIDS in persons with hemophilia.”

In its 1995 report, the Institute of Medicine committee concluded that if the technology to inactivate hepatitis had been developed and introduced before 1980, fewer hemophiliacs would have been infected with HIV. Although research into methods to inactivate viruses was undertaken in the late 1970s to reduce the risk of transmitting hepatitis, the work was not given a high priority because physicians, hemophilia patients, and the Public Health Service accepted the risk of infection with hepatitis as a reasonable price to pay for the benefits of factor concentrates. Hepatitis was then regarded simply as “a medically manageable complication of a very effective treatment for hemophilia.” The industry, then, had no incentive to produce safer factor concentrates.

The government’s health officials were equally acquiescent. The Institute of Medicine committee concluded that, “[a]lthough the National Institutes of Health and National Heart, Lung, and Blood Institute 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.” In 1982, the National Institute of Health’s division of blood diseases and resources established a five-year plan in which the development of viral inactivation was made a research priority, but the Institute of Medicine committee was unable to find any evidence of grants awarded in 1982 and 1983 to support this work actively. Similarly, the Food and Drug Administration did little to support viral inactivation research. The Institute of Medicine committee surmised that officials within the Food and Drug Administration relied on the manufacturers because the Food and Drug Administration itself had only modest facilities and limited support for research on viral inactivation technologies, and because they believed that the manufacturers, given their expertise in these areas, would eventually develop processes to inactivate viruses.

The task of developing viral inactivation methods fell to the manufacturers without any pressure from consumers, physicians, or the Food and Drug Administration. The Institute of Medicine committee concluded that such factors as the manufacturers’ interest in obtaining competitive advantage, their inability to share information on research efforts, and their concerns about yield and cost, combined with the lack of encouragement from the Food and Drug Administration, may have adversely affected the development of viral inactivation processes. It found that the manufacturers failed to give serious consideration to other inactivation processes, such as the detergent method, because heat inactivation had been successful for other blood products and because inactivation of pooled source plasma before fractionation would have required the individual relicensing of all plasma factor concentrates. When the processes for inactivating viruses were developed, however, the Food and Drug Administration granted its approval expeditiously.

Removing products from the market

The removal of factor concentrates from the market, known as product withdrawal or recall, is a task undertaken by the manufacturers but overseen by the Food and Drug Administration, which has the authority to seize factor concentrates or to revoke the licence of the manufacturer. The issue whether to recall blood products containing plasma donated by a person with AIDS, or suspected of having AIDS, was first discussed at a meeting of the blood products advisory committee in July 1983. Industry representatives at the meeting pointed out that since a single frequent plasma donor might have his or her plasma in as many as fifty plasma pools in one year, a decision to recall all products made from those pools in that year could result in a recall of 25 to 250 million units of concentrate. A policy of automatic recall could lead to serious shortages of factor concentrates. Faced with striking a balance between the “theoretical” risk of such factor concentrates to recipients and the need for an uninterrupted supply of concentrates, the committee decided that recalls should not be automatic, but should be evaluated on a case-by-case basis. The Food and Drug Administration adopted the committee’s recommendation and, in August, issued a policy directive to that effect. As a consequence, any decision to recall blood products would be based on such factors as the accuracy of the diagnosis, the occurrence of symptoms in relation to the date of donation, and the impact of the recall on the supply of factor concentrates. Manufacturers did in fact recall many lots throughout 1983 and 1984. The National Hemophilia Foundation disagreed with this policy and, at the blood products advisory committee meeting in July and in recommendations issued on 22 October 1983, took the position that every lot containing plasma from a person identified as having AIDS, or characteristics strongly suggestive of AIDS, should be recalled.

At the CDC conference on the treatment of hemophilia in September 1984, participants debated the subject of converting to heat-treated factor concentrates. While a minority of participants strenuously argued in favour of discarding or withdrawing all non-heat-treated factor concentrates, the majority took the view that any replacement of inventory should be a matter for local medical care personnel and treatment centres to determine. By early 1984, all U.S. manufacturers had licences for heat-treated concentrate, and by 1985, when it became known that the process effectively inactivated HIV, most were distributing heat-treated factor concentrates. However, the Food and Drug Administration did not require the recall and destruction of all non-heat-treated units until 1989.

In April 1985, the National Hemophilia Foundation reversed its earlier recommendation for the recall of factor concentrates that may have been derived from a donor with AIDS. Now that heat-treated factor concentrates were available, it recommended against recall because “HTLV-III [HIV] appears to be adequately killed under currently licensed heat treatment procedures.” Only non-heat-treated factor concentrates, it said, should be recalled.

In its assessment, the Institute of Medicine committee found it “puzzling” that recalls were not considered until July 1983. The first opportunity the Food and Drug Administration had to recall blood and blood products arose in March 1983, when it issued donor-screening recommendations to blood banks and manufacturers. These recommendations failed to specify what was to be done about blood and plasma that had been collected from unscreened donors but had not yet been used, and certainly did not suggest that this material be segregated or recalled. Although the Institute of Medicine committee conceded that a recall might have temporarily jeopardized the supply of blood and blood products, it was unable to determine why the Food and Drug Administration had not even considered this option:

[T]he Committee is puzzled why there is not evidence from any of the materials that it reviewed that a careful analysis was made of the availability issue or that thought was given to some form of “staged recall” that would replace unscreened inventories as soon as new screened and segregated products became available in requisite quantities ... Hence it is not possible for the Committee to conclude that the FDA appropriately balanced the two public health concerns, risks of infection and availability of blood products.

The Institute of Medicine committee was also critical of the recall policy developed by the Food and Drug Administration in 1983. With regard to the blood products advisory committee meeting in July 1983, it found that the majority of scientists by then had accepted the conclusion that AIDS was transmissible by blood and blood products; that the “worst-case scenario” put forward by the blood industry about the magnitude of a recall was not supported by any data; that no serious consideration was given to a means of managing collection and pooling to avoid possible contamination; that it was not clear why alternative treatment methods could not have been used as a temporary measure; and that there was no assurance that plasma fractionators would learn about all the donors with AIDS, since at the time there was no established way of tracking the health of blood donors, the disease was not yet notifiable, and the CDC could not distribute its lists of AIDS cases to the manufacturers. The Institute of Medicine committee concluded that the Food and Drug Administration failed to conduct any independent risk-benefit analysis of an automatic recall policy, but based its conclusions solely on the recommendations of the blood products advisory committee. It adopted a poorly conceived “non-policy,” which in the view of the Institute of Medicine committee should have been rejected in favour of a more positive approach:

The Committee believes it is not possible to conclude that the FDA made a decision that was clearly in the interest of public health given available information as of July 19, 1983. A close reading of the data suggests that a policy, not only of automatic recall, but of delicensing AHF [anti-hemophilic

factor] concentrate until further information was available concerning its role in the transmission of AIDS might have been justified on public health grounds. This would have included, of course, a recall of all stocks of AHF then on the market and withdrawal of all AHF concentrate in the inventory of producers.

The sorry story of blood product withdrawals highlighted the weakness of consensus policy making. The Institute of Medicine committee said that “[i]n the absence of scientific consensus, [the] FDA seemed to feel itself bound to craft a middle-of-the-road policy, which was remarkably vague and had unknown efficacy to protect the blood supply.” The decision to adopt recalls on a case-by-case basis suggested that the agency lacked the capacity to structure its advisory process adequately and to analyse independently the recommendations it received.

With respect to the introduction of heat-treated factor concentrates, the Institute of Medicine committee concluded that it would have been difficult for the Food and Drug Administration to insist on a simultaneous recall of all non-heat-treated factor concentrates. First, before October 1984 at the earliest, the Food and Drug Administration was unable to demonstrate that heat-treated factor concentrates were in fact safer; second, there was some resistance among physicians to the use of heat-treated concentrates, partly because of fears that hemophilia patients would become intolerant to factor VIII as a result; and, third, the economic costs to plasma fractionators of rapidly removing non-heat-treated concentrates from the market were unknown. In summary, the Institute of Medicine committee concluded that recalls illustrated the contrast between the Food and Drug Administration’s potent formal powers and its actual informal operation.

Surrogate testing for AIDS

The possibility of using surrogate tests to detect donors with HIV infection was first raised by CDC scientists in January 1983 at a Public Health Service meeting in Atlanta. The potential efficacy of various tests, including the absolute lymphocyte count, the ratio of T-helper cells to T-suppressor cells (the T-cell test), and the test for antibody to the hepatitis B core antigen (the anti-core or anti-HBc test), was discussed, and the anti-core test was considered as the most promising. This test detects not only those who are currently infected with the hepatitis B virus but also those who have previously been exposed to the virus. In his presentation at the meeting, Dr Thomas Spira of the CDC stated that on the basis of data from a cohort of homosexual men with AIDS who attended a sexually transmitted disease clinic, 88 per cent of known definite AIDS cases were also positive for anti-HBc. In contrast, only 5 per cent of the general population of voluntary donors were positive for anti-HBc. Despite these data, the meeting produced no consensus on the use of such tests. There was concern that the test would be expensive, that testing

would increase the cost of processing, and that additional costs would be imposed by the loss of each destroyed unit. The availability of adequate test materials and the necessity for new training were other subjects of concern. Dr Aaron Kellner of the Greater New York Blood Program outlined a proposal for a pilot screening study that would focus on the "AIDS hot spots" of New York, Los Angeles, and San Francisco and that would evaluate both the cost of surrogate tests and the impact such testing would have on the blood supply. After the meeting, several of the participants, including Dr Donald Francis of the CDC and Dr Louis Aledort and Dr Charles Carman of the National Hemophilia Foundation, wrote letters to the chairperson, Dr Jeffrey Koplan, in support of surrogate testing. The National Gay Task Force also supported the use of anti-core testing in combination with another test, in order to secure a more objective method of screening out high-risk donors.

In their statement of 13 January 1983, the American Association of Blood Banks, the Red Cross, and the Council of Community Blood Centers said that the use of surrogate tests was currently being evaluated in areas of the country where AIDS was most prevalent, and that routine implementation of such tests was not advisable. At a meeting the next day, the National Hemophilia Foundation's medical and scientific advisory council recommended to the manufacturers that they evaluate and, if it were warranted, implement surrogate testing. The industry responded with several arguments against testing, such as the added expense, significant exclusion rates, and potential increases in the price of factor concentrates.

In March 1983, when the Department of Health and Human Services announced new donor-screening recommendations for AIDS, it said that studies should be conducted "to evaluate screening procedures for their effectiveness in identifying and excluding blood and plasma with high probability of transmitting AIDS." At a National Institutes of Health conference on AIDS that month attended by thirty-five scientists, clinicians, and administrators, there was a discussion of several new potential surrogate tests for AIDS. The participants acknowledged that these tests required further study and, consequently, there was no consensus on which one to use. The conference organizers concluded that "[t]here is still no surrogate test for AIDS on which the scientific community can agree."

In July 1983, the National Heart, Lung, and Blood Institute issued a request for proposals to develop tests to identify the AIDS carrier states and to measure the sensitivity of the tests. Shortly thereafter the Irwin Memorial Blood Bank evaluated the anti-HBc test as a surrogate marker for HIV. The study, conducted by Dr Herbert Perkins over a period of three months, yielded uncertain results. Six per cent of donors tested positive for the anti-core test, and, although the prevalence was higher among men, the distribution was more closely linked to ethnicity than to sexual preference. Dr Perkins concluded that the test would have no significant benefit and that the exclusion of 6 per cent of donors could lead to blood shortages.

In December 1983, the Food and Drug Administration's blood products advisory committee reviewed the research on various surrogate tests, including several pilot tests performed at blood banks in high-risk areas. Four studies had been done on anti-core testing, two on Beta-2-microglobulins, and single studies had been made of cytomegalovirus, EBV, immune complexes, Neopterin, T-cell ratio measurement, Thymosinal, and Alpha interferon. Most of the discussion focused on the usefulness of anti-core testing. Dr Johanna Pindyck, for example, summarized the results of anti-core testing done at the Greater New York Blood Program. She reported that 5.5 per cent of male donors under thirty-five years of age were core antibody positive, as were 7.7 per cent of those over thirty-five years. The estimated cost of the test was three dollars, but the cost of discarding the units as well as recruiting efforts to replace the donor required further evaluation. Data from testing 8,049 donors at Irwin Memorial Blood Bank were also discussed. They demonstrated that donors living in an area of homosexually active men were likely to be positive for anti-HBc and that the test could identify 89 per cent of those most at risk of contracting AIDS. The committee members asked whether these data constituted "sufficient evidence to substantiate testing for anti-HBc," and expressed concern about the potential cost of such testing.

Although Dr Donohue, the director of the Food and Drug Administration's division of blood and blood products, had recommended to the committee that anti-core testing be implemented, Dr Michael Rodell, a representative of Armour, suggested that a task force be struck to consider the potential application of the anti-HBc test as an additional risk-reduction measure and to report within three months. This suggestion met with universal approval from the committee members; many representatives of blood products manufacturers had met the previous evening and agreed that the task force would "provide a delaying tactic for the implementation of further testing," which they expected would become a requirement later that year.

By the end of 1983, only one blood bank in the United States had implemented surrogate testing for AIDS. In July 1983, Dr Edgar Engleman introduced T-cell testing at the Stanford University blood bank. The test was difficult to implement because the equipment was costly and the test had to be performed manually, but Stanford was conducting immunological research at the time and had the necessary laboratory equipment. Between July 1983 and June 1985, 33,831 donations were screened in this manner and 586 were discarded. With the introduction of HIV testing in 1985, Dr Engleman discovered that 1.9 per cent of these discarded donations were HIV positive.

The task force on hepatitis B core testing, composed of representatives from the commercial fractionation industry, plasma centres, voluntary blood centres, and the Food and Drug Administration, met on 6 March 1984 and released an interim summary statement a week later. The statement, made by the chairman, Dr Rodell, said that although the majority of task force members were not in favour of testing, they recognized the need to adopt

it if it were performed by other manufacturers. The study group held that a positive test for anti-core was not necessarily indicative of AIDS, but was simply a possible means of identifying persons in high-risk groups. It concluded that if the test were to be used, it should be performed on both plasma and whole blood. Members agreed that a pilot study involving testing for Beta-2-microglobulin levels should be designed, since this test appeared to produce a higher degree of correlation with prodromal or active AIDS.

In the spring and early summer of 1984, several centres in California adopted hepatitis B core testing. Among them were the Irwin Memorial Blood Bank, the Palo Alto blood centre, the Alameda-Contra Costa Medical Association blood bank, and Red Cross centres in San José and the Santa Clara Valley. Of the manufacturers, only Cutter implemented anti-core testing; it did so on 2 April 1984 for a period of nine months. The Food and Drug Administration then issued a statement that said that adoption of the test by these centres was voluntary and that it would be "unwise to adopt anti-core testing to the exclusion of other screening tests," since it was possible that they might ultimately prove to be more predictive and generally useful in enhancing safety. Then, on 23 April, the Secretary of Health and Human Services announced that the AIDS virus had been identified and that a blood test for AIDS would be widely available within six months.

On 16 July 1984, Dr Rodell submitted the task force's final report on hepatitis B core testing to the Food and Drug Administration. It acknowledged that although there was divided opinion about the appropriateness of such testing, the majority of members were not in favour of it. The report set out the following arguments against testing: it was not specific for the disease state, but only an indicator of a population group membership; recent statistics showed that the incidence of AIDS was declining; testing would reject 6 to 20 per cent of the general population; removal of donors positive for anti-HBc would decrease the amount of anti-HBc in plasma pools, thereby increasing the risk for transmission of hepatitis B to even higher levels; testing would result in factor concentrate shortages and price increases; and plasma supplied to fractionators by the voluntary sector would also have to be tested, thereby affecting the supply of packed cells and other components. Those in favour of testing argued that it would identify 60 to 80 per cent of gay men; that it would be helpful in identifying individuals who had been exposed to a number of infectious diseases and who were at high risk of contracting AIDS; and that manufacturers would have an obligation to do all that was necessary and possible to purify the plasma before it was made into blood products. However, now that the Department of Health and Human Services had announced that a specific test for AIDS would soon be available, those members of the task force who had been in favour of the test no longer believed it would be appropriate to implement it. In conclusion, the study group made two recommendations with the unanimous endorsement of the group. These were the development of pilot programs for confidential unit exclusion, and Beta-2-microglobulin testing of these excluded units.

In early 1985, the CDC published a study that demonstrated that 62 per cent of donors to whom the CDC had traced a transfusion-related AIDS case had tested anti-HBc positive. Although the hepatitis B core testing was not required by the Food and Drug Administration until the late 1980s, it was in universal use by 1987, this time as a surrogate test for non-A, non-B hepatitis.

In its assessment, the Institute of Medicine committee found that there were geographic differences that might have made the test useful in some areas of the country. It concluded that it was reasonable to require implementation of surrogate testing in January 1983 and that surrogate testing alone, or in combination with direct questioning about sexual preferences, would have greatly reduced the number of individuals infected with HIV through blood and blood products.

The committee acknowledged that there was considerable uncertainty about the sensitivity and specificity of anti-HBc screening and its consequences for the safety of the blood supply. Some of the participants at the January 1983 meeting in Atlanta took issue with Dr Thomas Spira's data because they did not believe it to be a credible source of information about AIDS and because they considered it was in the CDC's interest to "play up AIDS" in an effort to justify its continued existence. The Institute of Medicine committee also found that there was no agreement about the need for surrogate testing because the data supporting it were either inadequate or unpublished, and no one insisted on better studies. In its report, the committee stated:

[D]uring 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 addition to this uncertainty about the data, critics of the test cited cost, unnecessary deferral of donors, possible blood shortages, and the senseless rejection of non-infectious blood as reasons why the test should not be adopted.

With respect to the blood products advisory committee's role in the failure to adopt surrogate testing, the Institute of Medicine committee observed that it "did not have the social, ethical, political and economic expertise necessary to understand fully the ramifications of the decisions it was making." Moreover, the Institute of Medicine committee continued, the advisory committee "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 favoured their interest at the expense of the public interest."

Screening blood donations: HIV testing

On 13 May 1983, the *Morbidity and Mortality Weekly Report* announced that the retrovirus human T-cell leukemia virus (HTLV) had been isolated from patients with AIDS and that additional study was required to determine if the virus was the cause of AIDS, or merely another opportunistic infection. In the same month, several articles published in *Science* offered two possible explanations. Dr Robert Gallo of the National Cancer Institute believed that HTLV was responsible for AIDS, but Dr Luc Montagnier of the Pasteur Institute believed that AIDS was caused by a third variant of HTLV, the lymphadenopathy-associated virus (LAV). The implications of a retrovirus, whether HTLV or LAV, were of great significance: the presence of the antibodies not only denoted prior exposure but suggested that the virus might continue to be present. A test for antibodies to the virus could therefore be expected to identify persons capable of transmitting the virus by blood transfusion.

In September 1983, the French team led by Dr Montagnier presented its findings to North American researchers at a conference held in Cold Spring Harbor, New York, and suggested that LAV was responsible for AIDS. The following February, when these data were presented to CDC officials, they became convinced that the AIDS virus had been found, and the CDC began collaborating with Dr Montagnier. Using LAV, laboratories at the CDC and the National Cancer Institute developed blood tests to determine if AIDS patients indeed had antibodies to the virus. In March 1984, Dr Gallo and Dr Francis met with Dr Montagnier in Paris to discuss the accumulated data. By then, it was clear that AIDS was caused by a new strain of the human lymphotropic retrovirus, HTLV-III. In April, Secretary Heckler made her public announcement that the AIDS virus had been identified, and that a blood test would be available within six months. A report describing the isolation of the virus was published in *Science* in May. LAV and HTLV-III were later found to be the same virus, and were renamed HIV.

In April 1984, the National Institutes of Health developed and patented a prototype screening test for HIV antibodies and, by May, had solicited applications from various manufacturers interested in the commercial use of the tests. The Food and Drug Administration announced that the test would be regulated as a biological, and not as a medical, device. This meant that before the test kit could be licensed, manufacturers of the kits would have to obtain Investigational New Drug Status, which in turn required Food and Drug Administration approval of the investigation plan by the Institutional Review Board and protocols for informed consent. Such approval had timing implications. As the *Council of Community Blood Centers Newsletter* of July 1984 noted, “[t]his decision would seem to cast doubt on the six-month target announced by Secretary Heckler, which may more realistically be seen as the date when testing will be implemented under IND [investigational new drug] review rather than when all blood donors are routinely tested.”

In June, Secretary Heckler announced that five firms had been chosen to develop and distribute the HIV-antibody test (the AIDS test). These were Abbott Diagnostics, Electro-Nucleonics Inc., Litton-Bionetics Inc., Travenol/Genentech Diagnostics, and du Pont de Nemours and Co., Inc., in association with Biotech Research Laboratories, Inc. In the autumn of 1984, the American Association of Blood Banks and the American Red Cross were asked to participate in the clinical testing of the kits, and several of their blood centres were selected as testing sites. In November 1984, the American Association of Blood Banks, the Red Cross, the American Blood Resources Association, and the Council of Community Blood Centers wrote to Dr Petricciani of the Food and Drug Administration to inform him that they were committed to testing all blood and blood products as soon as a test was available. Out of concern that regions at greatest risk for transfusion-associated AIDS might not be the first to receive test kits, they also requested assistance in implementing a coordinated distribution plan. In December, the Food and Drug Administration received the first application for licence of the test, using an enzyme-linked immunosorbent assay (ELISA). Although early studies indicated that all tests successfully identified HIV reactive samples, they also showed that there was a significant number of false positive results. Nevertheless, it was expected that these tests would be introduced in early 1985.

Although HIV tests were not commercially available in early 1985, the Public Health Service issued provisional recommendations for their implementation. Published in the *Morbidity and Mortality Weekly Report* on 11 January 1985, these recommendations provided that all blood and plasma be tested for the virus and that any blood or plasma units testing positive not be transfused or manufactured into factor concentrates. It recommended that donors be told that their blood would be tested for the AIDS virus and that they would be notified of a positive result on repeat testing and placed on a deferral list. The Public Health Service stated that notification of donors testing positive should be the responsibility of the collection facilities, which should provide information to donors in a manner that ensured confidentiality of both the results and the donor's identity. Donors should be told that the positive results were a preliminary finding that might not represent true infection; they should be given a list of precautions to prevent further transmission and referred to their physicians for evaluation.

The Public Health Service interagency task force on AIDS held meetings on 14 and 17 January 1985 to consider the issue of testing. Representatives of the American Association of Blood Banks, the Red Cross, the Council of Community Blood Centers, and the American Blood Resources Association attended and were invited to comment on the recommendations made earlier in the month. Other issues discussed were disposing of untested blood in stock; informing patients previously transfused with blood from a donor subsequently found to test positive for HIV; new labelling requirements; informed

consent procedures; notifying and counselling donors testing positive; maintaining confidentiality; and deterrents to high-risk groups using blood centres as test sites.

In February, the Public Health Service published a pamphlet to inform donors about the antibody test. The pamphlet provided information about the significance of the test, and included a list of recommendations for those testing positive.

On 19 February 1985, the Food and Drug Administration issued a memorandum about the implementation of the Public Health Service recommendations. It stated that tests would soon be licensed and that blood centres should voluntarily begin testing as soon as supplies became commercially available. Before testing became mandatory, there would be a voluntary phase-in period. Centres should begin to acquire the necessary equipment and to train personnel. During this period, western blot testing (a second test to confirm the results) would be available to blood banks, but because the sensitivity of the tests varied significantly from laboratory to laboratory, it should be regarded as a research tool rather than a confirmatory test.

The Food and Drug Administration memorandum instructed blood banks to give prospective donors information about alternative test sites and to tell all blood and plasma donors that a sample of their blood would be tested; only after the phase-in period would donors be notified if both the ELISA and the confirmatory tests were positive. Donors with a reactive test should be advised to consult a physician, clinic, or public health office, and told that they would be deferred from future donation and that their names would become part of donor deferral registers. With respect to notification, the memorandum suggested that donors might respond best to a personal interview conducted by trained persons who understood the need for confidentiality and appreciated the degree of psychological stress that positive test results might cause. Methods of educating and counselling donors had to be identified and coordinated with local health offices.

The memorandum insisted that all blood products with an initial reactive test result not be distributed for transfusion or further manufacturing into injectable factor concentrates. To comply with good manufacturing practice requirements, it would now be necessary for each blood bank to revise its procedure manual to include HIV-antibody testing, quarantine and disposition procedures for reactive units, procedures for notifying donors of positive test results, and record-keeping procedures, including the maintenance of donor deferral registers. Finally, information concerning HIV-antibody test results should appear in the package insert or container label for blood and blood components intended for transfusion, and donations not tested during the phase-in period should be clearly marked. This same information was distributed to blood-banking organizations at a meeting held by the Food and Drug Administration several days after the memorandum was sent out.

On 2 March 1985, the Department of Health and Human Services announced that test kits manufactured by Abbott had been approved by the Food and Drug Administration. Secretary Heckler stated that the test would be made available not only at blood collection agencies but also at public health and private laboratories; persons who wanted to be tested were urged to use these alternative test sites. In April, Electro-Nucleonics and Litton-Bionetics received licences for their test kits.

Testing for HIV with the new ELISA test began in late March 1985. By April, it had been implemented at about one hundred Red Cross, American Association of Blood Banks, and Council of Community Blood Centers blood banks, which together collected approximately 70 per cent of the nation's blood supply, and at the member laboratories of the American Blood Resources Association. In May, the Public Health Service made a recommendation to all centres that donated blood and plasma should be tested. Testing was implemented at the vast majority of centres in May 1985, and it was in place at all centres by July; it did not become mandatory, however, until December 1987. Although the first ELISA tests detected 96 to 98 per cent of infected blood samples, they did not have a high degree of specificity and, therefore, there was a high rate of false positives. As a result, a second test, the western blot test, was adopted to confirm positive results.

In May 1985, the Food and Drug Administration issued a memorandum to clarify both the terminology on package inserts for antibody test kits and certain aspects of implementing the tests. It said that "repeatedly reactive" and "positive" included those samples positive on both the initial and the repeat testing, and that donations testing positive could not be distributed for transfusion or for manufacture into factor concentrates capable of transmitting infectious agents. In a joint statement issued 7 June 1985 on HIV testing, the American Association of Blood Banks, the Red Cross, and the Council of Community Blood Centers made recommendations about the notification of donors with positive test results. It stated that, ideally, notification of donors testing positive should await the availability of alternative test sites, and that policies should be designed to avoid notification of donors with false positive results. Accordingly, only those donors whose results were verified by additional testing should be notified. Donors whose blood was ELISA-positive, but negative on confirmatory tests, should not be notified, but their names should be entered into a "retest" or "surveillance" list so that they could be readily identified at the time of any future donations.

Informing hemophiliacs of the risk

As consumers of blood products, hemophilia patients were in a better position to learn about and appreciate the risk of AIDS than were patients who received transfusions of blood during surgery. However, when confronted with decisions about their care and treatment, hemophilia patients were often ill-informed about the risk of AIDS.

Treatment recommendations

When the first report of AIDS among hemophiliacs appeared in the *Morbidity and Mortality Weekly Report* in July 1982, the National Hemophilia Foundation stated that the risk of contracting the disease was minimal and that the CDC was not recommending any change in the use of blood products. However, the CDC had not in fact made any comment about treatment methods and was not in the habit of doing so. As a rule, decisions about treatment were left to physicians. At a meeting of the National Hemophilia Foundation's medical and scientific advisory council in October 1982, concerns were expressed about treatment, but it was decided that patients should be urged to continue their current treatment. The council felt that in view of the lack of data, it was premature to question the continued use of prophylaxis or the postponement of elective surgery. On 9 December 1982, the National Hemophilia Foundation informed its members that four new cases among hemophiliacs had been identified, and stated that "while there is insufficient data to directly link the spread of AIDS to concentrates, there is an increased concern that AIDS may be transmitted through blood products." It accordingly said that "patients and parents should be aware of the potential risks."

At the December 1982 meeting of the blood products advisory committee, there was some suggestion that cryoprecipitate might be preferable to concentrates, but no recommendations were made.

The first recommendations about treatment were made by the National Hemophilia Foundation on 21 December 1982. It said that there was no conclusive evidence that the use of cryoprecipitate or fresh frozen plasma would reduce the risk of AIDS, but it recommended that patients who had not yet used concentrates should not begin to do so unless there was an overriding medical indication for so doing. This group included children under the age of four, newly diagnosed hemophilia patients, and those with mild hemophilia. All other patients were advised to continue using concentrates. In January 1983 these recommendations were modified slightly. Physicians were also advised to use DDAVP, or desmopressin, a drug that increases the release of factor VIII in the body, for patients with mild or moderate hemophilia A (persons with a deficiency in the ability to synthesize factor VIII), and to weigh the advantages and disadvantages of postponing elective surgery for all patients.

At the CDC public meeting held on 4 January 1983, there was some discussion of the need for a modification of treatment. It will be recalled that Dr Ratnoff advocated decreasing the risk to hemophiliacs by treating them exclusively with cryoprecipitate, a recommendation he made to all his patients. Although no formal recommendation was made at the meeting, the blood-banking organizations did acknowledge the need for some modification in treatment in their joint statement of 13 January 1983. The American Association of Blood Banks, the Red Cross, and the Council of Community Blood Centers recommended education about blood use and said that there was

a need to prepare for an increased demand for cryoprecipitate. The next day, the National Hemophilia Foundation's medical and scientific advisory council held an emergency meeting to formulate recommendations to physicians, manufacturers, and blood banks. Although it stated that the "potential advantages and disadvantages of cryoprecipitate versus factor VIII concentrates therapy for severe hemophilia A are not clear at the present time," it recommended that cryoprecipitate be used to treat newborn infants and children under the age of four, newly identified patients never treated with factor VIII concentrates, and patients with mild hemophilia requiring infrequent treatment. It also recommended that persons with mild or moderate hemophilia use desmopressin whenever possible, and that elective surgical procedures be evaluated with respect to the advantages or disadvantages of a delay.

Product withdrawals

In 1983, the manufacturers of factor concentrates began to withdraw lots that they thought might contain the causative agent of AIDS. When the first product withdrawal occurred in May 1983, the National Hemophilia Foundation did not re-evaluate the use of factor concentrates. On the contrary, it said that negative media coverage was persuading many patients to disrupt treatment, resulting in a 30 per cent decrease in the use of these products. It urged hemophilia patients to continue using factor concentrates, and stated that AIDS should not cause patients to abandon the appropriate use of blood products. Reports given at a meeting of the medical and scientific advisory committee on 23 October 1983 included an April 1983 survey that demonstrated that 48 per cent of deaths of hemophiliacs during the years 1972–82 had been caused by bleeding; none was reported to have been caused by AIDS. Continued use of concentrates was therefore thought to be justified. When lots of Hyland factor IX and Red Cross factor VIII were recalled in September 1983, and lots of Cutter factor concentrates were recalled in November 1983, the National Hemophilia Foundation advised patients to continue the use of concentrates or cryoprecipitate. When Alpha recalled its factor concentrates in January 1984, the foundation again reaffirmed its recommendation that patients continue using concentrates or cryoprecipitate as prescribed by their physicians. The same advice was given in the autumn of 1984 when Alpha and the Red Cross announced more recalls of factor concentrates, and in December 1984 when the Red Cross announced yet another recall. In May and June 1985, the foundation continued to recommend the use of factor concentrates despite recalls by Armour and Hyland of non-heat-treated concentrates. Not until April 1985 did the National Hemophilia Foundation revise its treatment recommendations. It then advocated the use of desmopressin, licensed a year earlier, for patients with mild or moderate hemophilia A, or, failing that, cryoprecipitate.

Use of heat-treated factor concentrates

Heat-treated blood products were introduced in the United States during the period March 1983 to August 1984. In a December 1983 advisory about the CDC's latest report on AIDS in hemophiliac patients, the National Hemophilia Foundation revised its January 1983 recommendations to suggest that the development of methods to inactivate viruses be expedited. On 17 September 1984, a meeting of the CDC was held to formulate guidelines for treating hemophilia. It concluded that there was not enough information to recommend that hemophiliacs be tested for the AIDS virus, but that treating physicians and patients should consider switching to heat-treated factor concentrates despite insufficient data that they provided protection against AIDS. In October 1984, the National Hemophilia Foundation advised physicians to consider changing the treatment of patients to the use of heat-treated factor concentrates. This advice was reiterated in December 1984 when the foundation informed its members that Alpha, Cutter, and Hyland had been licensed to distribute heat-treated factor IX concentrate. By April 1985, the foundation published revised recommendations. It now informed its members that heat-treated factor concentrates "may be the preferred products" for infants and children under four years of age with severe hemophilia and for newly identified hemophiliacs never treated with factor concentrates, and advised them that desmopressin should be used whenever possible in patients with mild or moderate hemophilia A; in cases where it did not provide adequate treatment, cryoprecipitate should be used. In December 1985, the National Hemophilia Foundation recommended that physicians prescribe only heat-treated concentrates for patients with severe hemophilia.

HIV testing

In April 1984, the National Hemophilia Foundation learned that the CDC had received reports of nine new cases of AIDS among hemophiliacs in the first quarter of 1984, but it did not recommend any change in treatment. On 13 July 1984, the *Morbidity and Mortality Weekly Report* published a preliminary report on HIV testing that found that eighteen of twenty-five asymptomatic hemophiliacs had tested positive for the virus, as did two-thirds of a larger sample size. This information was reported in a National Hemophilia Foundation medical bulletin on 1 August 1984, and was accompanied by the statement that although "testing positive for HTLV-III/LAV [HIV] establishes the presence of antibodies against these agents, it does not suggest a diagnosis of AIDS." Again, in November of that year, it stated that press reports that 70 to 90 per cent of severe hemophiliacs had been infected with AIDS were grossly misleading, and that the fact that a majority of hemophiliacs had tested positive for the virus did not necessarily suggest a diagnosis of AIDS. At this time, it was not yet clear what percentage of persons testing positive for the virus would suffer from AIDS.

In March 1985, with the advent of HIV testing imminent, the National Hemophilia Foundation told its members that because the test did not diagnose AIDS, and because the medical significance of a positive test was unknown, it would not recommend the testing of all hemophiliacs. The results would not change treatment. The foundation reaffirmed its recommendation that patients continue using factor concentrates.

Risk of secondary transmission

In March 1986, the CDC recommended that persons at high risk of contracting AIDS, as well as their sexual partners, undergo HIV-antibody testing. In response to this recommendation, the National Hemophilia Foundation released a notice that reaffirmed its earlier recommendation that patients not be tested. It stated that it would be inappropriate for hemophiliacs to participate in periodic population-wide HIV-antibody screening because negative results might provide a false sense of security and “lead individuals to the erroneous conclusion that safety measures regarding intimate relations are not necessary.”

Although a report of heterosexual transmission from a hemophilia patient to his wife was published in January 1984, the National Hemophilia Foundation told patients in February 1984 that “[i]f there is any risk of heterosexual transmission of AIDS among otherwise healthy hemophiliacs, it is truly remote.” Patients, as well as their physicians, should consider whether condoms should be used strictly as a precautionary, or temporary, measure until more was known about AIDS.

By the spring of 1985, however, the National Hemophilia Foundation had modified its position considerably. Participants at a CDC conference in Atlanta in April 1985 learned that sexual partners of those with AIDS were at risk of acquiring the disease, since there were now two documented cases of AIDS among sexual partners of hemophiliacs. In a medical bulletin to physicians, the foundation suggested that the virus might be sexually transmitted from healthy hemophiliacs to their spouses, and that mother-to-child transmission was a distinct possibility. It accordingly recommended the use of condoms and the postponement of pregnancy. Spouses of hemophiliacs were also told not to donate blood. This advice was repeated in a medical bulletin in July 1985 about practising safer sex. In December 1985, the foundation informed persons with hemophilia that they “should now consider that HTLV-III [HIV] is sexually transmitted.” It urged patients to use condoms regularly, and, because of the risk of perinatal transmission, recommended that spouses of hemophilia patients be tested for HIV before becoming pregnant.

In March 1987, the National Hemophilia Foundation informed members that sexual transmission of the AIDS virus had been confirmed. A joint National Hemophilia Foundation–CDC study found that 10 per cent of sexual partners of hemophiliacs were seropositive and that mother-to-child transmission of HIV had occurred in a “substantial” number of cases. It accordingly

stressed the importance of using barrier methods during sexual intercourse and of deferring pregnancy. One year later, sixteen cases of the transmission of AIDS to spouses of hemophiliacs had been reported, as well as five instances of transmission from mother to child. In November 1989, the foundation recommended that sexual partners of individuals who had received blood components before 1985 be tested. By June 1991, 122 cases of heterosexual transmission of AIDS had been reported.

Conclusions of the Institute of Medicine Committee

The Institute of Medicine committee investigated the way in which physicians and patients obtained information about AIDS, and, although it acknowledged that the decisions about continuing to use factor concentrates were difficult, it concluded that there were serious shortcomings in the communication of risk and the discussion of therapeutic options.

The Institute of Medicine committee found that patients were not informed of the growing concerns about the potential transmission of AIDS by blood and blood products because no organization properly communicated the risks to potential recipients. Many blood bank officials publicly denied the risk of AIDS, and physicians, fearing that patients would refuse medically necessary treatment, often refrained from informing them of the risks. When the risk of AIDS became more widely known among hemophiliacs, the committee found that the risk was underestimated, no doubt as a result of the acceptance of the risk of hepatitis among both patients and physicians. This underestimation of risk resulted in complacency and a failure to act on reports of a new infectious risk. When it finally became clear that the blood supply might in fact be contaminated, physicians were reluctant to discuss the implications of widespread infection with their patients and their families. They were also uncertain about methods of minimizing the risk. Reducing the use of factor concentrates could lead to increased mortality and morbidity, but continued use of these concentrates could potentially increase the risk of AIDS. Unfortunately, the dramatic successes of treatment with factor concentrates in the 1970s heavily favoured the status quo; physicians and hemophiliacs were extremely reluctant to return to former treatment methods. Both physicians and the National Hemophilia Foundation "in their effort to find the right balance between the risks and benefits of continued use of factor concentrates, tended to overweight the well-established benefits of factor concentrates and underestimate the risks of AIDS, which were still uncertain." As a result, although there were means by which dependence on concentrates, and therefore the risk of AIDS, could have been reduced, patients were given little information about these alternatives. The Institute of Medicine committee was especially critical of the foundation's role in distributing useful information. The committee concluded that if the foundation had consulted a wider group of scientific and medical experts, "more explicit and systematic dissemination of a range of clinical options

might well have been possible.” Moreover, the committee found that “financial and other relationships between the National Hemophilia Foundation and the plasma fractionation industry created a conflict of interest that seriously compromised the perceived independence of National Hemophilia Foundation recommendations.”

Informing transfusion recipients of the risk

Between 1984 and 1987 the American Association of Blood Banks, the Red Cross, and the Council of Community Blood Centers issued a number of joint statements about tracing persons who might have received contaminated blood and blood products. The first statement was released on 10 December 1984. To assist in epidemiological studies of transfusion-associated AIDS, and in the absence of a specific blood test, these blood banks recommended that physicians in blood-collecting organizations and transfusion services urge public health investigators and physicians to ask all patients with AIDS whether they had donated blood in the past five years; if they had donated blood, physicians at the blood banks should be informed of both the dates and the locations of the donations. They also said that the decision to notify recipients of the contaminated units or the factor concentrates should be made by the patient’s physician. On learning that a donor has or may have AIDS, blood banks should quarantine all contaminated components and notify manufacturers who might have received plasma from donations made by the donor within the past three years.

When HIV testing was implemented in June 1985, the American Association of Blood Banks, the Red Cross, and the Council of Community Blood Centers released recommendations for notifying donors testing positive for the test as well as recipients of previous donations from infected individuals. With regard to the latter, they did not recommend notifying recipients of potentially contaminated blood products, since “the injury to prior recipients which may be caused by such notification is disproportionate to the benefits which are tenuous and ill-defined.” (At that time, the full significance of a positive test result was unknown.) They did, however, state that components from previous donations still in inventory should be recalled, tested, and destroyed; that the transfusion service director should inform physicians about patients who had received components from those donations; and that the recipients’ physicians were responsible for determining whether the recipients would be informed that they had received components from a contaminated or potentially contaminated donation. They also stated that modified recommendations would be forthcoming pending results of studies to evaluate the health status of the recipients.

In July 1985, the Food and Drug Administration sent a memorandum to blood banks about the use of blood or plasma previously collected from repeat donors who were now found to be HIV-antibody positive. It stated that if any such plasma were intended for use in preparing injectable factor concentrates,

blood establishments must promptly notify consignees of all shipments made within the previous six months. Blood banks preparing factor concentrates for transfusion must also look back at all prior donations within the distribution period and promptly notify consignees, so that the extant factor concentrates might be destroyed.

On 16 June 1986, the American Association of Blood Banks, the Red Cross, and the Council of Community Blood Centers issued a joint statement that dealt with the notification of recipients of contaminated blood and components. The statement said that since the duration of the asymptomatic infectious stage of AIDS was unknown, it was possible that some individuals with a confirmed positive test result might have been infectious at the time of a previous untested donation. The American Association of Blood Banks, the Red Cross, and the Council of Community Blood Centers recommended that all blood banks identify donors with a confirmed positive test for HIV and trace recipients of components made from earlier donations of the infected donor. Blood banks were advised to begin with the most recent donations and to work back until blood donated on two previous occasions was found to be HIV-antibody negative. To accomplish this task, blood banks should establish a mechanism appropriate to their circumstances. Three look-back mechanisms for identifying recipients of previous donations were given as examples: the blood banks would notify the hospital, which in turn would contact the patient's physician; the blood banks would undertake to trace and notify recipients; and the state and local health departments would implement the process for notifying recipients. Although the American Association of Blood Banks, the Red Cross, and the Council of Community Blood Centers acknowledged that the mechanisms used might vary from area to area and might involve the hospitals or transfusion services, the recipient's physician, or public health agencies, these organizations recommended that discussions be held about implementing programs among hospital administrators, transfusion service directors, transfusing physicians, local health departments, and legal counsel. They also recommended that recipients be told that there was a possibility that they might have been infected with HIV, that they should be tested, and that counselling be offered to them.

Finally, in a joint statement issued on 17 March 1987, the American Association of Blood Banks, the Red Cross, and the Council of Community Blood Centers endorsed the CDC's recommendation that patients transfused between 1978 and April 1985 be tested. This recommendation was made after the publication of a study by the CDC showing that there were potentially 2,900 recipients of infected transfusions who might be unaware of their status and whose partners and children might also be at risk.

In 1988, in the wake of the report of the Presidential Commission on the Human Immunodeficiency Virus Epidemic, the Department of Health and Human Services received a presidential directive to formulate a look-back and notification policy for tracing recipients of potentially infected blood

products. The Food and Drug Administration did so, but not until September 1991. The policy required that blood banks search for recipients of donations from HIV-positive donors during the preceding five years and quarantine any suspect blood products.

The Institute of Medicine committee concluded that early guidelines issued by the Public Health Service, such as the Food and Drug Administration recommendations about donor deferral in January 1983 and the Food and Drug Administration recall policy formulated in December 1983, did not contain recommendations about recipients of blood products donated by persons subsequently found to have HIV infection. The committee called this failure to develop a look-back policy “peculiar,” especially since there was no evidence to suggest that resource constraints prevented action, or that any person or organization had sought to influence the Food and Drug Administration to delay the introduction of such a policy.

Conclusions and recommendations of the Institute of Medicine

Conclusions

In addition to the specific assessments already given, the Institute of Medicine committee drew some broader conclusions from its findings. It found that institutional decision-making processes within the blood system in 1983 were inadequate, and that the Public Health Service had not only failed to demonstrate leadership but was not adequately equipped to respond to potential crises within the blood system. Indeed, the committee observed that since the system had not fully dealt with the issue of hepatitis by the early 1980s, it was not surprising that it was ill-prepared to deal with the far greater challenge of AIDS.

The events and decisions reviewed by the Institute of Medicine committee demonstrated the difficulty of decision making when the stakes are high, knowledge is imprecise and incomplete, and decision makers may have personal or institutional biases. The committee concluded that although the management of public health risk necessarily involves a continuing process of decision making in the face of scientific uncertainty, risk assessments are often undertaken with an overabundance of caution:

When confronted with poorly understood and anomalous public health threats, inertia often influences decisions. It is often easier to maintain the status quo than to make a change. In fact, regulatory policy makers, 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.

The Institute of Medicine committee concluded that this conservative response was especially true with AIDS. Although there was sufficient epidemiological evidence by January 1983 to suggest strongly that the agent causing AIDS was transmitted through blood and blood products, the magnitude of the risk for transfusion and blood product recipients was not yet known. There was, therefore, considerable uncertainty about the costs and benefits of the available options to reduce the risk of transmission. This uncertainty caused policy makers within the blood system to choose less vigorous measures over other measures, a response that exposed them to a minimum of criticism.

On the subject of crisis management within the federal bureaucracy, and specifically the role of the Public Health Service in dealing with the challenge of AIDS, the Institute of Medicine committee concluded that the Public Health Service failed to demonstrate leadership, as illustrated by two examples. The first was the 4 January 1983 meeting when CDC scientists expressed concern about the blood supply but received no public support from the directors of the CDC or the office of the assistant secretary for health. The second was the lack of participation by the Food and Drug Administration in the development of a recall policy in July 1983. In the absence of leadership, the Public Health Service relied on standard bureaucratic operating procedures designed for routine circumstances, when a clearly defined decision-making hierarchy would have been more appropriate. As a consequence, competing legal and business considerations inhibited effective government action. The committee concluded that “[f]ocussing efforts and responsibilities, setting timetables and agendas, and assuming accountability for expeditious action cannot be left to ordinary standard operating procedures.”

The Institute of Medicine committee was critical of the use of advisory committees by the Public Health Service. It found that the service did not have a systematic approach to conducting advisory committee meetings. It stated:

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 principal when it allowed statements and recommendations of the BPAC [blood products advisory committee] to go unchallenged, apparently because it could not independently analyze the information.

The committee also found that the Food and Drug Administration’s blood products advisory committee had an overabundance of experts from within the industry and no consumer representation. It suggested that such

committees should “contain fewer topical experts and more members with expertise in principles of good decision making and the evaluation of evidence” to avoid potential conflicts of interest.

The Institute of Medicine committee concluded finally that to be effective, the Public Health Service must have access to information and have the ability to analyse it without reliance on the institutions it regulates. The committee found that in the past this was not always the case. The Public Health Service had failed to assess the costs and benefits of various methods for protecting the blood supply discussed at the meeting held in January 1983, and had neglected to evaluate critically the recall policy created by the blood products advisory committee in July 1983. The Institute of Medicine committee found that few decisions were made with the involvement of high-ranking Public Health Service officials such as agency directors or the assistant secretary for health.

The Institute of Medicine committee stated that if the Public Health Service is to prepare adequately for future threats to the blood supply, it should identify “triggers,” or actions that must be taken when the level of concern exceeds a particular threshold. The committee proposed a number of such triggers. With regard to donor screening, it suggested that whenever epidemiologists identify a high-risk donor group, the Food and Drug Administration should immediately instruct blood banks to defer that high-risk group and to segregate blood and plasma obtained from such groups; whenever a blood bank introduces a donor-screening program, the Food and Drug Administration should require all segments of the industry to do likewise; blood banks, for their part, should use a partially effective intervention that has little or no risk unless they can show that a better method will rapidly supersede it. The committee also suggested that whenever new data or research suggests a possible threat to the blood supply, both patients and physicians should have access to the information; the Food and Drug Administration should perform cost-benefit analyses of any new method to inactivate viruses to evaluate whether it will advance the public health at reasonable costs; and, when a test or treatment enhances the safety of factor concentrates, manufacturers should withdraw all stocks of untested or untreated factor concentrates as quickly as possible.

The conclusions of the Institute of Medicine committee have been criticized by some blood bankers as being biased in favour of persons infected with HIV from blood and blood products. These critics maintain that the report was the result of a flawed process in that the committee failed to interview many of the individuals involved in the decision-making process and preferred to rely on the “hindsight testimony” of persons who were opposed to those decisions, instead of undertaking a comprehensive review of the historical

documents. Moreover, these critics say that because almost half of the infected hemophiliacs were infected before January 1982, and 80 to 90 per cent were infected by January 1983, any of the actions proposed by the Institute of Medicine committee to safeguard the blood supply would have had little influence on the fate of hemophiliacs.

Recommendations

The Institute of Medicine committee made fourteen recommendations, reproduced more or less verbatim below, that were directed primarily to the Public Health Service, the CDC, and the Food and Drug Administration. Recommendations were also made about communicating information to both physicians and patients.

Public Health Service

- The Secretary of Health and Human Services should designate a blood safety director, at the level of a deputy assistant secretary or higher, to be responsible for the federal government's efforts to maintain the safety of the nation's blood supply.
- The Public Health Service should establish a blood safety council to assess current and potential future threats to the blood supply, to propose strategies for overcoming these threats, to evaluate the response of the Public Health Service to these proposals, and to monitor the implementation of these strategies. The council should report to the blood safety director. The council should also serve to alert scientists about the needs and opportunities for research to maximize the safety of blood and blood products. The blood safety council should take the lead to ensure the education of public health officials, clinicians, and the nature of threats to the nation's blood supply, and the public health strategies for dealing with these threats.

Compensation

- The federal government should consider establishing a no-fault compensation system for individuals who suffer adverse consequences from the use of blood or blood products.

Centers for Disease Control

- Other federal agencies must understand, support, and respond to the CDC's responsibility to serve as the nation's early warning system for threats to the health of the public.
- The Public Health Service should establish a surveillance system, lodged in the CDC, that will detect, monitor, and warn of adverse effects in the recipients of blood and blood products.

Food and Drug Administration

- Where uncertainties or countervailing public health concerns preclude completely eliminating potential risks, the Food and Drug Administration should encourage and, where necessary, require the blood industry to implement partial solutions that have little risk of causing harm.
- The Food and Drug Administration should periodically review important decisions that it made when it was uncertain about the value of key decision variables.
- Because regulators must rely heavily on the performance of the industry to accomplish blood safety goals, the Food and Drug Administration must articulate its requests or requirements in forms that are understandable and implementable by regulated entities. In particular, when issuing instructions to regulated entities, the Food and Drug Administration should specify clearly whether it is demanding specific compliance with legal requirements or is merely providing advice for careful consideration.
- The Food and Drug Administration should ensure that the composition of the blood products advisory committee reflects a proper balance between members who are connected with the blood and blood products industry and members who are independent of industry.
- The Food and Drug Administration should tell its advisory committees what it expects from them and should independently evaluate their agendas and their performance.
- The Food and Drug Administration should develop reliable sources for the information it needs to make decisions about the blood supply. It should have its own capacity to analyse this information and to predict the effects of regulatory decisions.

Communication to physicians and patients

- When faced with a decision in which all options carry risk, especially if the amount of risk is uncertain, physicians and patients should take extra care to discuss a wide range of options.
- The Department of Health and Human Services should convene a standing expert panel to inform the providers of care and the public about the risks associated with blood and blood products, about alternatives to using them, and about treatments that have the support of the scientific record.
- Voluntary organizations that make recommendations about using commercial products must avoid conflicts of interest, maintain independent judgment, and otherwise act so as to earn the confidence of the public and patients.

Assistance to persons infected and affected

Government assistance

Although more than 50 per cent of hemophiliacs in the United States were infected through blood products, and despite efforts by them to obtain compensation, no financial assistance has as yet been granted by governments, in contrast to what has happened in all other industrialized countries. Nor has any financial assistance been offered in the United States to persons infected through blood transfusions. As a result, many persons have resorted, usually unsuccessfully, to the courts to seek compensation.

In March 1995, a bill known as the Ricky Ray Hemophilia Relief Fund Act was introduced in the House of Representatives. Its purpose was to authorize the payment of government compensation to persons with hemophilia infected between 1980 and 1987, their survivors, and infected family members. Under the bill, each person infected and his family members would receive either a lump sum of \$125,000 or four payments over a period of five years. In return, persons infected must agree not to sue the Food and Drug Administration.

In June 1996, the bill was referred to the House Judiciary Subcommittee. The first hearing was held on 19 September. By then it had received more than 240 congressional co-sponsors. At the hearing, congressional and federal government officials, hemophilia representatives, and legal experts gave testimony. There was much discussion of the "findings" section, which declares that the government was negligent in its oversight of the blood supply in the early 1980s and that this negligence led to the infection of the hemophilia community. With the exception of the National Hemophilia Foundation, none of the witnesses agreed with this assessment, although the blood safety commissioner and the assistant secretary for health acknowledged that the Institute of Medicine committee report made it clear that the Department of Health and Human Services could have done a better job than it did. At the time of writing, the bill was still being considered by the Judiciary Subcommittee.

In 1987, United States blood organizations tried but failed to persuade Congress to add transfusion injuries to the *National Childhood Vaccine Injury Act of 1986*. Serious consideration was again given to the proposal with the release of the Institute of Medicine committee report, which concluded that, had such a no-fault system existed in the early 1980s, it could have relieved much of the financial hardship suffered by many who became infected. This recommendation has not yet been adopted by the Department of Health and Human Services because it is felt to be "outside the purview and expertise" of the department, an issue that more properly falls under congressional

responsibility. In August 1996, however, a no-fault compensation system similar to the *National Childhood Vaccine Injury Act of 1986* received the endorsement of the Committee on Government Reform and Oversight. No further action has been taken on this issue.

Although no national no-fault scheme for blood injuries has been introduced, a pilot project has been implemented in Arizona. This private dispute resolution mechanism for persons injured by blood or blood products is optional, covers all blood-borne pathogens and transfusion errors, and operates without regard to issues of negligence. The injured person is offered an immediate sum of money to compensate for actual financial losses.

Settlement of civil actions

Experience in the United States illustrates the shortcomings of the tort system for persons harmed by blood. Legal proceedings against blood suppliers and health-care facilities have predominantly been based on the law of strict liability and negligence for factor concentrates. To succeed in a claim for such liability, a plaintiff need only prove that a defect in the factor concentrates caused the injury, and not that the defect arose during the manufacturing process. Forty-nine states have enacted legislation that precludes a finding of strict liability against blood product manufacturers. As a result, claims based on strict liability for factor concentrates have usually failed. This protection was given in an effort to encourage a readily available supply of blood and blood products. Some blood shield statutes define blood as a “service” and not a “sale,” thereby precluding a finding of breach of warranty that applies only to the sale of goods. Enacted in the 1960s and 1970s to protect against hepatitis claims, this legislation has also done much to shield blood banks from strict liability for AIDS. Plaintiffs base their claims on the concept of negligence, in which the standard of care is usually industry custom. As a consequence, blood banks have been successful in AIDS litigation, including the most important cases.

In the early 1990s, it was estimated that more than three hundred actions had been commenced, but, despite widespread sympathy for those infected with HIV from blood or blood components, few of them have been successful. A recent study of transfusion-associated AIDS actions commenced between 1984 and 1993 found that of 163 cases against blood banks, hospitals, and physicians, plaintiffs succeeded in only fourteen and recovered awards totalling approximately U.S.\$75 million. The claims alleged medical negligence (46 per cent), failure to identify high-risk donors (45 per cent), lack of informed consent (39 per cent), and failure to conduct surrogate testing (39 per cent). A 1990 survey by the American Association of Blood Banks found that fewer than twelve cases had resulted in awards for plaintiffs. The difficulties faced by plaintiffs were also underscored in a study of AIDS litigation undertaken by the Department of Health and Human Services (the AIDS Litigation Project) in 1990.

In October 1993, American hemophiliacs brought a class action against four blood product manufacturers – Alpha, Rhône-Poulenc Rorer (Armour), Baxter, and Bayer – for failure to introduce heat treatment in the early 1980s. In October 1993, the Judicial Panel on Multidistrict Litigation consolidated thirteen hemophilia cases before the Honorable Judge John F. Grady of the United States District Court for the Northern District of Illinois (Chicago), and in November 1994 the District Court certified a litigation class action to resolve issues common to all cases. On 16 March 1995, however, in response to a petition filed by the defendant companies, the United States Court of Appeal for the Seventh Circuit held that these issues were improperly certified because they infringed the defendants' Seventh Amendment rights to have a single jury determine all common issues. The court stated that a class action would permit one jury to “hold the fate of an industry in the palm of its hand” and could “hurl the industry into bankruptcy.” It directed that the class action be decertified. In April, the Court of Appeals decided not to reconsider the decision, and in October of that year the Supreme Court of the United States refused to grant leave to appeal. On 16 January 1996, an order decertifying the action was accordingly issued. Despite this ruling, the action proceeded in federal court, having been consolidated in 1993.

On 19 April 1996, the defendants, without admitting liability, proposed a nationwide settlement to all litigants. They offered \$600 million to be divided per capita among the plaintiffs, and an additional \$40 million for legal fees and administration costs. As of April 1996, the blood product manufacturers have been successful in nearly all the thirty-nine individual cases arising out of the distribution of HIV-contaminated factor concentrates between 1982 and 1985.

Under the terms of the settlement offer, every HIV-positive hemophiliac infected between 1978 and 1985, and persons secondarily infected (spouses, monogamous sexual partners, and their infected children), would receive approximately \$100,000 and legal costs, provided that no more than 100 plaintiffs rejected the offer. If accepted by 20 May, the offer would be extended nationwide and every patient, or the families of those deceased, would have the option of accepting or of rejecting it and suing individually. This offer was ultimately rejected by plaintiffs as being too low. In March 1996, three of the defendants had offered 1,800 Japanese hemophiliacs a lump sum of \$420,000 each, in addition to monthly payments for life.

At the end of May the defendants revised their offer, abandoning the requirement that no more than 100 patients opt out of the settlement to pursue private actions and adding an undertaking that companies would not withdraw the offer if the number of opt-outs did not exceed 150. In August 1996, a comprehensive settlement agreement was reached, and the \$640 million settlement was granted preliminary approval by the court. The plaintiffs were then given until 15 October 1996 to inform the claims administrator of their desire to participate in the settlement. As of that date, 6,900 hemophiliacs accepted the

settlement, 800 of whom had actions pending against at least one of the defendants, and approximately 600 individuals chose not to accept the offer, 380 of whom have litigation pending. On 22 November, the defendants agreed to proceed with the settlement, and on 25 November a final fairness hearing before Judge Grady was held to review the terms and conditions. Negotiations have subsequently begun with federal and state authorities to ensure that these payments are not subject to repossession by Medicare, Medicaid, or private insurers. The four defendants have agreed to apportion their contribution based on their share of the hemophilia drug market in the late 1970s and early 1980s. Bayer will accordingly pay 45 per cent; Baxter and Armour, 20 per cent each; and Alpha, 15 per cent.

In May 1997, Judge Grady gave final approval to the settlement. Without this settlement, it is likely that few of the plaintiffs would have received any financial assistance.

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Australia

The blood system in the 1980s

For nearly half a century, blood collection in Australia has been undertaken almost exclusively by the Australian Red Cross Society (Red Cross) through its blood transfusion service, which has a branch in every state capital and in various other cities. Donations of blood and plasma to the Red Cross have always been voluntary and unpaid. Australian law prohibits both payment for blood donations and charges for blood components or blood products supplied to patients.

Until very recently, there were also twenty-seven blood banks operated by public hospitals in New South Wales that maintained their own donor panels and collected their own blood and plasma by voluntary donation. These blood banks have gradually been taken over by the New South Wales Red Cross blood transfusion service, but sixteen independent blood banks have yet to be subsumed within this service. There were also a small number of independent blood donor panels operated by public hospitals in remote towns in Queensland, but the Red Cross has recently assumed responsibility for them.

The Australian Red Cross Society

The Red Cross was established in 1914 as an extension of the British Red Cross Society. Separate branches were established in every state and territory, with some coordination by a national executive in Melbourne. The Red Cross was incorporated in 1941 by royal charter, which provided for the establishment of a division of the Red Cross in every state and territory. In the 1980s there were eight blood transfusion service centres, one in each of the six states and the two territories.

The supply and safety of blood and blood products was entrusted to the national Red Cross. The role of every state blood transfusion service was to recruit blood donors and to produce cryoprecipitate and fresh frozen plasma, which were then sent to Commonwealth Serum Laboratories in Melbourne for fractionation. These state and territorial blood transfusion services were

largely autonomous entities. For example, many divisions owned their blood transfusion facilities, employed staff, and entered into contracts without endorsement by the national Red Cross.

The Red Cross had a national blood transfusion committee that acted as a forum for the development of national policy. The committee had twenty-five members, representing state and territorial blood transfusion services, the Commonwealth Department of Health, Commonwealth Serum Laboratories, and the defence forces, but no representatives of consumer groups.

Except during holiday periods, the Red Cross in most states was able to supply sufficient blood for cellular components and at least 80 per cent of the fresh plasma needed to meet the standard set by the World Health Organization of two international units of factor VIII concentrate per capita.

Commonwealth Serum Laboratories

All blood products were manufactured by Commonwealth Serum Laboratories, a corporation whose shares were owned entirely by the Commonwealth government. It became a public corporation in April 1991 and is now known as CSL Limited.

Commonwealth Serum Laboratories was established during World War I to produce pharmaceutical products for Australia. At the suggestion of the Red Cross, large-scale blood fractionation began in October 1949, with financing from the Commonwealth government. Ten years later, Commonwealth Serum Laboratories began to produce blood products. Although perhaps best known for its factor products, serum albumin, and immunoglobulins, it also produced most of Australia's vaccines for flu, cholera, typhoid, yellow fever, and tetanus.

During the 1980s, Commonwealth Serum Laboratories had a contract with the Commonwealth government to produce factor VIII and factor IX concentrates. The blood transfusion service in every state supplied the necessary plasma, and the laboratories returned the concentrates to each service in proportion to the amount of plasma it had given. The blood transfusion services then supplied hospitals and, in some instances, distributed concentrates directly to patients. Commonwealth Serum Laboratories also made its custom fractionation services available to other countries – New Zealand, Hong Kong, Singapore, Indonesia, Malaysia, and Papua New Guinea. These countries sent plasma for processing, and the products were returned to the country of origin; the plasma from these countries was kept separate from the plasma used for Australian consumption.

The role of government

Constitutional power in the field of health services, including the supply of blood, rests with state and territorial governments. Accordingly, these governments have enacted legislation with respect to the collection of whole blood and

the transplantation of human tissue. Legislation in every state and territory required the consent of donors before donation, and prohibited the buying and selling of human blood and tissue. Although the situation differs somewhat from one state or territory to another, legislation has also been enacted to address the risk of HIV transmission through blood and blood products. Before donating, blood donors must sign declarations stating that they are not at risk of contracting HIV or AIDS, and they may be convicted of an offence for knowingly providing false or misleading information.

The Commonwealth government has never regulated the collection of whole blood, and only recently began to regulate blood products. In 1989, the Commonwealth government enacted the *Therapeutic Goods Act*, legislation that established standards for the safe manufacture, storage, and transport of plasma fractions. Under the *Act* and its regulations, plasma that is fractionated into blood products at Commonwealth Serum Laboratories must come from licensed blood-collecting and processing centres. Although the *Act* applies only to fractionated blood products, because all the plasma used for fractionated products comes from blood or plasma donations collected and tested by the eight blood transfusion service centres, the standards are also observed for some, but not all, aspects of blood components.

The Commonwealth, state, and territorial governments contributed approximately 99 per cent of the costs of the eight Red Cross divisional blood transfusion services, including those for HIV testing, virus screening, blood products fractionation, and payments for damage awards and settlements. The financial agreement between the Red Cross and the Commonwealth government, reached first in 1954, has remained unchanged since the mid-1970s. No funding was given directly to the national Red Cross; it was all distributed to the state and territorial divisions through the state or territorial governments. Capital costs were shared equally between the Commonwealth and the state or territorial governments. State and territorial governments contributed 60 per cent of operating costs; the Commonwealth government, 35 per cent; and the Red Cross, 5 per cent. In recent years, this arrangement has meant that the Red Cross has actually paid 1 to 2 per cent of operating costs, with the remainder paid by the Commonwealth government.

Although governments provided the bulk of funding for blood transfusion services and for the supply of blood components and blood products, they did not exercise control over the related policies and operating procedures. Nor did they exercise much influence over supply and use. The absence of control has been reviewed by the Commonwealth government in recent years, and changes to the financial arrangement have been made.

Public health reporting of disease was undertaken by the six state and the two territorial governments; national coordination was the function of the Commonwealth Department of Health. Reports of AIDS cases were published in the department's bulletin, the *Communicable Diseases Intelligence*. In 1986, the department established a Special Unit in AIDS Epidemiology and

Clinical Research at the National Health and Medical Research Council to monitor HIV surveillance in Australia. In 1990, the unit was expanded to become the National Centre in HIV Epidemiology and Clinical Research.

The Haemophilia Foundation of Australia

The primary consumers of blood products were represented at the national level by the Haemophilia Foundation of Australia, Inc. This organization, founded in 1979, is committed to the improvement of the treatment of hemophilia and rare bleeding disorders. It monitors the development of products, lobbies governments on issues of concern to its members, and operates as a clearinghouse for current information on hemophilia and HIV. It raises over half its annual revenue from donations, both private and corporate, with the remainder coming from the Commonwealth government, foundations, and annual levies on state hemophilia societies.

Prevalence of blood-related HIV or AIDS

In April 1992, the World Federation of Hemophilia reported that of the approximately 1,570 persons with hemophilia in Australia, 1,431 had been tested for HIV antibodies. Of the persons tested, 260 (18 per cent) had tested positive for the virus and 79 (5.5 per cent) had developed AIDS. Fifty-five of that number had died, making AIDS the leading cause of death among adult and child hemophiliacs. Because Australia has long had a policy of self-sufficiency in blood products, these infections are attributed solely to the use of factor concentrates manufactured domestically from Australian plasma. By the end of 1993, 127 cases of transfusion-related AIDS had been reported, representing 2.4 per cent of the AIDS cases in Australia.

Protecting the blood supply from HIV or AIDS

The emergence of HIV or AIDS

The first case of AIDS in Australia was diagnosed in December 1982, but was not officially acknowledged until April 1983. Because the virus had not yet been identified, there was uncertainty whether the symptoms came within the recognized criteria for the disease. By May there were two confirmed cases of AIDS, both in male homosexuals, and by June there were four more suspected, but unconfirmed, reports of AIDS. All these cases were among homosexual men with a history of travel to the United States.

On 11 June 1983, several articles about AIDS were published in the *Medical Journal of Australia*. The authors of the first article stated:

There is a growing feeling that a novel agent is involved, directly or with other factors. The epidemiology suggests the notion of a transmissible agent spread in a way similar to that of hepatitis B infection ... transmission

via blood and blood products seems likely on the basis of AIDS occurring in persons with haemophilia, in intravenous drug users, after blood transfusion, and in a patient after platelet transfusion.

The authors advised homosexuals to “restrict their number of sexual contacts and avoid ‘recreational’ drug exposure.” They said there was an “urgent need” to establish a task force to collect information about possible AIDS cases in Australia. Other articles included a report on the first Australian AIDS case and reports of prodromal AIDS among homosexual men living in Sydney.

An additional six cases of AIDS were diagnosed in 1983, and in 1984 the number of cases began to increase rapidly – 42 in 1984, 112 in 1985, and 212 in 1986. Seventy per cent of these cases occurred in New South Wales, particularly in Sydney, the state capital.

Blood-related AIDS cases began to appear in 1984. The first such case was that of a fifty-two-year-old heterosexual man who was diagnosed with severe pneumonia in July 1984. A year earlier the patient had been treated for Legionnaires’ disease, and his illness was considered a recurrence of Legionnaires’ pneumonia until routine testing revealed that he had almost no T-4 cells. A review of his medical history revealed that he had received four units of red blood cells during his earlier illness. The four donors who had supplied the blood were asked to return to the blood bank to be interviewed. One admitted to being a homosexual, but did not consider himself promiscuous; he had continued to donate blood in 1983 because he did not think a Red Cross exclusion of donors “with multiple sexual partners” applied to him. Blood samples taken from the four donors and the patient were sent to San Francisco, where a rudimentary test had been devised to measure the level of HIV antibodies. The test revealed that both the homosexual donor and the patient were HIV-positive; the other three donors were negative. Because the test occurred more than a year after the blood donation, it could not be proved conclusively that the donor had been carrying the AIDS virus at the time; however, no other possible source of the patient’s infection could be found.

An inspection of the Red Cross’s records disclosed that other blood from the same donor had been sent to Commonwealth Serum Laboratories for manufacture into factor VIII concentrate, which in turn had been distributed to hemophiliacs in Tasmania, Queensland, and the Australian Capital Territory. Thirty persons were found to have received the contaminated product, of whom all but two were traced. No blood tests for antibody were performed, but none of the recipients appeared to have unusual symptoms. As a result of the ensuing media attention, blood banks immediately tightened their criteria for donors, and excluded all men who had had a homosexual contact in the preceding five years.

That autumn more cases of transfusion-related AIDS appeared. On 15 November 1984, the Minister of Health for the state of Queensland announced that three infants had died from AIDS. All three had received transfusions of red cells from the same blood donor in February. The first infant had died in April from a blood clot in the brain, and the other two in September of opportunistic infections. The physician who had treated all three infants eventually suspected AIDS and requested that the donor be traced and tested. The donor was discovered to be a homosexual man who had given blood fifteen times since 1981. The incident was reported in *The Lancet* in December 1984. At the end of 1984 there were no reported cases of AIDS among Australian hemophiliacs, but by May 1985 there were two reported cases among hemophiliacs, and one hemophiliac had died from AIDS-related causes.

Response to the emergence of HIV or AIDS

Before 1983, AIDS had received very limited attention in the Australian media. Some medical specialists and gay activists had, however, been following reports of the disease published in American medical journals; they had also been observing the spread of AIDS during visits to the United States, and expected that AIDS would eventually appear in the substantial and concentrated gay community of Sydney, Australia's largest city. In anticipation of an outbreak, the Department of Health of New South Wales established a medical and scientific committee on AIDS in early 1983. It also funded an immunoepidemiological study of the homosexual and bisexual community to determine factors related to the spread of AIDS.

At the national level, the National Health and Medical Research Council discussed AIDS at its meeting held on 8–9 June 1983. The report of the meeting states that the council “recognized the seriousness of the situation which now exists with evidence of cases of AIDS in Australia,” but expressed the view that publicity may have caused unnecessary anxiety, as “the situation in Australia is at present very different from that in the US [United States], particularly for those who require blood transfusions such as haemophilia sufferers.” The council did, however, establish an expert committee, the Working Party on AIDS, whose functions were to recommend methods to provide diagnostic and treatment facilities for the care of patients, monitor evidence of the spread of the disease, recommend measures aimed at its containment, and keep health professionals and the public informed about new developments.

At its first meeting in July 1983, the working party concluded that “it was likely that the disease was not readily transmitted ... by sexual intercourse or by blood and blood products,” but that “[t]he disease, nonetheless is serious and warrants urgent attention.” The working party adopted the case definition for AIDS then being used by the U.S. Centers for Disease Control, and designed a national data collection system to document the epidemiological and clinical aspects of the disease. Physicians were asked to inform their

state health departments about patients who met the clinical criteria for AIDS, and the health authority in each state and territory was asked to establish an advisory group to receive and investigate reports of suspected cases and to forward information about the cases to the working party for further study.

By October 1983 all states and territories had established AIDS advisory groups, and AIDS had been made a notifiable disease in New South Wales, Victoria, Queensland, South Australia, and the Australian Capital Territory. At the October meeting of the working party, the national reporting form received final approval, and all physicians were then asked to report specific categories of the disease. The earliest state to require reporting was Victoria in May 1983; the last was New South Wales, in August 1984. In Victoria, the *Diseases Notification Regulations 1983*, made pursuant to the *Health Act 1958*, made AIDS notifiable as of May 1983. In Queensland, AIDS was notifiable as of July 1983, and under the *Health Act Amendment Act 1984 (No. 2)*, enacted in December 1984, AIDS was categorized as a sexually transmitted disease. South Australia amended its *Health Act 1935* to include AIDS as a notifiable disease in July 1983. The same month the Northern Territory amended the *Notifiable Diseases Act*, and in August 1983 Tasmania amended the *Public Health Act 1962*. In the Australian Capital Territory the *Public Health Ordinance 1928* was amended to include AIDS as a notifiable disease in September 1983, as was the *Health Act 1911* of Western Australia. Finally, New South Wales amended the *Venereal Diseases Act* in August 1984, and amended the *Public Health Act* in 1985 to include AIDS as a “proclaimed” disease, effective April 1986.

Since late 1984, all new cases of AIDS have been reported to state and territorial health departments, where data are collected and forwarded to agencies of the Commonwealth Department of Health, such as the National Health and Medical Research Council Working Party on AIDS (1983–4), the AIDS Coordinating Unit (1985), and the National Health and Medical Research Council Special Unit in AIDS Epidemiology and Clinical Research. Registration is done using non-identifiable codes.

In response to the deaths of the Queensland infants, the federal Minister of Health held a meeting of all state and territorial health ministers in Melbourne on 19 November 1984 to develop a national AIDS strategy. At that meeting, the health ministers endorsed the introduction of state legislation to punish donors who made false declarations about their eligibility to give blood, but rejected the proposal of prohibiting all male donors for fear that it would pose too great a threat to the blood supply (men gave about 60 per cent of the blood used in Australia). It was also decided that the offer from the U.S. Centers for Disease Control to train Australian AIDS workers would be accepted; that A\$2.7 million would be allocated for the introduction of HIV screening tests in blood transfusion centres; and that an additional A\$300,000 would be given to Fairfield Hospital in Melbourne to establish a national AIDS monitoring centre where employees could be trained in screening procedures.

In November 1984, the working party on AIDS was replaced by a National AIDS Task Force, composed of medical and scientific experts and senior Commonwealth and state health administrators. The task force was asked to give advice on research guidelines and priorities for the diagnosis and care of persons infected with the AIDS virus and to monitor the spread of the disease. It has developed and issued a number of guidelines and bulletins addressing a wide spectrum of public health issues relating to AIDS. Also in November 1984, the federal Minister for Health established a National Advisory Committee on AIDS consisting of representatives of the community, high-risk groups, and governments. This committee has exchanged information with state and territorial health authorities and community groups, participated in the organization of two national conferences on AIDS, developed a blood donor recruitment campaign, published informational booklets and brochures, and conducted a national AIDS education campaign.

Excluding persons at risk: Donor screening

In early 1983, the Red Cross's national blood transfusion committee decided to postpone any decision about donor screening until the release of guidelines in the United States, where the problem of protecting the blood supply from HIV infection was being discussed. Donor-screening guidelines were released by the U.S. Food and Drug Administration in March 1983, and methods to promote the voluntary self-exclusion of donors were introduced in Australian blood banks soon thereafter.

In April, after the first case of AIDS in Australia was confirmed, the director of the New South Wales blood transfusion service, Dr Gordon Archer, issued a directive prohibiting homosexual men from donating blood as of 1 May 1983 because it was "a virtual certainty that AIDS was already in the blood supply." In response, the chairman of the national blood transfusion committee made the following statement: "The position will continue to be kept under close review but it is considered that there is no cause for alarm at present and it is not felt necessary to request any particular group in the community outside NSW [New South Wales] to refrain from donating blood." The Red Cross instead undertook to monitor the situation closely. Other blood bankers expressed concern that the move would reduce confidence in the blood supply, and gay activists, offended by Dr Archer's policy, picketed the blood bank. In the early 1980s, gay activists were involved in efforts to have homosexuality decriminalized.

At a meeting of the Red Cross working party on factor VIII and factor IX concentrates on 27 May 1983, members decided that two documents should be prepared. One should list donor-screening guidelines for blood transfusion services, and the other should be a press statement to help educate the public about AIDS. Both documents were released several days later. On 2 June the chairman of the national blood transfusion committee issued a press statement reassuring the public that "no case of AIDS has yet been seen in

any recipient of blood in this country, including haemophiliacs." He said that the risk of the transmission of AIDS through blood or blood products in Australia was "greatly reduced" by the exclusive use of volunteer blood donors and the long-standing policy of self-sufficiency in blood products; moreover, he announced that donor-screening recommendations had been distributed to all Red Cross blood banks. The Commonwealth Department of Health also made a statement about AIDS which said that homosexual males, intravenous drug users, and persons requiring frequent treatment with blood products were at risk of contracting AIDS, and concluded that "[a]t this stage it is considered it would be prudent for male homosexuals NOT to donate blood."

The statements made by the Red Cross and the Commonwealth Department of Health were unanimous in recommending that blood transfusion services refrain from collecting blood from persons with signs and symptoms suggestive of AIDS, sexually active homosexual or bisexual men with multiple partners, past or present intravenous drug users, and sexual partners of persons at increased risk of contracting AIDS (that is, persons in the listed categories). Directors of state and territorial blood transfusion services were instructed to begin donor screening. Although the donor-screening guidelines from the Red Cross suggested the use of "information leaflets for donors, lectures to common interest groups, and articles in selected papers and magazines," state and territory blood transfusion service directors were accorded a certain degree of latitude in selecting the most appropriate deferral method for their centres.

Pamphlets and notices were introduced to encourage voluntary self-exclusion in most states and territories, and donors were asked to read them as a condition of donating. By the autumn of 1983, all blood transfusion service centres except those in Tasmania and the Northern Territory had introduced pamphlets about AIDS, although they did not do so simultaneously or in any uniform fashion. Most leaflets referred to "sexually active homosexual or bisexual men with multiple partners" as a risk group, but not all blood transfusion services used this language. In New South Wales, for example, the blood transfusion service sought to exclude homosexuals with "multiple partners"; its counterpart in Victoria sought to exclude homosexuals with "many partners"; while in Western Australia the risk factor was more broadly described as "active homosexuality."

These measures were not without controversy. The gay community in Sydney reacted angrily to the exclusion of homosexuals from the donor pool. It accused the blood transfusion service of discriminating against gay men on the basis of sexual preference rather than potential high risk. In August 1983, the chairman of the Red Cross's national blood transfusion committee sought to explain the Red Cross's position to a forum of gay groups convened in Sydney, but was met with hostility.

In October 1983, the Red Cross reviewed donor-screening policy at a meeting of the executive subcommittee of the national blood transfusion committee. The chairman told the committee that even though the Australian situation differed from that in the United States, it seemed wise to discourage all homosexuals from giving blood. The suggested policy was not adopted, and for the next year blood transfusion centres in the states and territories continued to exercise their own discretion as to what constituted appropriate donor-screening measures, with mixed results. For example, by the autumn of 1984, blood transfusion services in Victoria and Queensland had broadened the risk group to include "males who have engaged in homosexual activity at any time in the previous 5 years"; the blood transfusion service in South Australia excluded all "sexually active homosexual or bisexual men"; and the blood transfusion service in New South Wales excluded "all homosexuals and bisexuals." It was not until the deaths of the Queensland infants were reported in November 1984 that some measure of uniformity in donor screening was introduced.

The federal and state health ministers, meeting in response to the infant deaths, agreed on 19 November 1984 that, as part of a national approach to AIDS, the Red Cross would prepare a uniform donor declaration to be used by all blood banks. The executive subcommittee of the national blood transfusion committee drafted the declaration on 4 December and, two weeks later, it was approved by the health ministers at a second meeting. Each minister was asked to introduce legislation requiring donor declarations and imposing penalties for false declarations. New South Wales was the first state to enact such legislation and, before the end of 1984, most states and territories had introduced similar legislation.

The legislation required each potential donor to answer a questionnaire attesting to the fact that he or she was not at risk of contracting AIDS, and set out the manner in which this was to be done. For example, the *Blood Contaminants Act 1985* of South Australia states that blood shall not be taken unless the donor has signed a donor declaration in a prescribed form, and the *Blood Donation (Limitation of Liability) Act 1985* of Western Australia requires that the declaration be made before a designated officer under the *Human Tissue and Transplant Act 1982* – that is, a medical practitioner, a staff member of the Red Cross blood transfusion service, or a registered nurse employed in the taking of tissue.

The declarations asked donors to state that neither they, nor their spouse or sexual partners, had engaged in male-to-male sexual activity during the past five years; had used intravenous drugs; were suffering from night sweats, weight loss, persistent fever, diarrhea, or swollen glands; had reason to believe they were suffering from AIDS or any related diseases; or had received blood products or a blood transfusion in the past five years. To minimize embarrassment to a donor who was unable to sign the declaration, questions about

conditions unrelated to HIV or AIDS were added after discussions with spokespersons for homosexuals, including active blood donors.

The donor declaration legislation in the states and territories also imposed penal sanctions for signing a false or misleading declaration. The *Human Tissue (Amendment) Act 1985* of New South Wales, for example, imposes a penalty of A\$5,000 or imprisonment for one year, or both, for signing a false or misleading declaration.

At most blood banks, the declaration was signed in the presence of a staff member who could answer any questions the donor might have. Elsewhere, donors who were unsure of their potential risk were referred to a physician. Before the declarations came into use, previous donors in Victoria, South Australia, the Australian Capital Territory, Tasmania, and New South Wales received letters from the directors of the state blood transfusion services advising them of the new procedure and reminding them of risk factors for HIV or AIDS.

In transfusion-related AIDS litigation, it has been argued, with some success, that the early efforts at voluntary self-exclusion were inadequate because states and territories were permitted too much latitude in defining risk groups and in identifying ways in which to exclude them. Lawyers acting for persons infected have stated that this uneven implementation of voluntary self-exclusion in 1983 and early 1984 is one of the reasons why Australia had the highest rate of transfusion-related AIDS in the developed world in 1984. The use of donor declarations and the imposition of criminal penalties for false declarations, however, has generally been viewed as an effective measure to prevent the spread of HIV within the Australian blood system. Faced with the possibility of criminal penalties, many homosexual men are said to have stopped giving blood. Moreover, soon after declarations and penalties were introduced, many donors called blood banks, asking them to discard their donations.

Inactivating viruses in blood products

In an attempt to reduce the risk of transmission of non-A, non-B hepatitis through factor concentrates, Commonwealth Serum Laboratories first examined the possibility of dry heat treatment in February 1983. Next it investigated a method developed by the Scottish National Blood Transfusion Service which involved wet heating factor VIII concentrate at 60°C for ten hours. The results of these experiments, received in late 1983, were not encouraging, for factor VIII concentrate subjected to this method showed a 50 per cent loss in activity.

In mid-1984, Commonwealth Serum Laboratories resumed its investigation of dry heat-treatment methods. In October, the director of research visited the Centers for Disease Control in the United States and, on his return, reported to his colleagues about the preliminary work being done there to inactivate

the HIV virus. Arrangements were made to have concentrates produced by Commonwealth Serum Laboratories spiked with HIV at the U.S. Centers for Disease Control and heated at 60°C for seventy-two hours – experiments that ultimately proved successful. That month, the AIDS working group of the national blood transfusion committee of the Red Cross recommended that Commonwealth Serum Laboratories introduce heat-treated factor VIII concentrate. In early November, a committee convened by the Commonwealth Department of Health asked that Commonwealth Serum Laboratories begin heat treating factor VIII concentrate at 60°C for seventy-two hours, that existing stocks of factor VIII concentrate be heat treated before distribution, and that patients receiving heat-treated factor VIII concentrate be made aware of the effects of heat treatment on the product. By February 1985, all factor VIII concentrate manufactured by Commonwealth Serum Laboratories was routinely heat treated at 60°C for seventy-two hours. Where possible, unused non-heat-treated factor concentrates in circulation were returned to Commonwealth Serum Laboratories and were heat treated, but some non-heat-treated products were still being used in early 1985.

In December 1984, Commonwealth Serum Laboratories modified its product warning labels for factor concentrates. The new product label stated: “This product has been subjected to heat treatment at 60°C for 48 hours to inactivate viruses such as hepatitis B, non-A non-B hepatitis and AIDS which may be present in the starting plasma from which AHF is manufactured. The extent of virus inactivation is not accurately known and some deleterious changes in the product cannot be excluded.” Before this date, the package warning informed consumers of the risk of intra-muscular hemolysis, but did not mention the risk posed by HIV.

Surrogate testing for AIDS

The matter of surrogate testing was first raised when Dr Archer released a statement in May 1983 requesting homosexual men not to donate blood. Organized homosexual groups responded, in part, by issuing a pamphlet, *What Is Wrong with Dr Archer's Proposed Banning of Gay Donors*. In this pamphlet, the authors argued that “it is the blood and not the donors that needs to be screened,” and stated that in the United States it had been discovered that tests for hepatitis B core (anti-core) and other tests “identify accurately all at-risk blood.” When Dr Archer contacted Dr Joseph Bove, the chair of the American Association of Blood Banks transfusion transmitted diseases committee, to inquire about the tests, he was told that the American association was not recommending their use.

The matter of surrogate testing was discussed at an AIDS symposium held in Perth on 23 July 1983, where there was considerable support for a study of the effects of testing for antibody to the hepatitis B core antigen. However, no decision about testing was made.

In July 1984, Dr Archer attended the congress of the International Society of Blood Transfusion in Munich, where he learned that Cutter Biological Division of Miles Laboratories Inc., an American blood product manufacturer, had recently introduced anti-core testing; that anti-core testing was being implemented at the Irwin Memorial Blood Bank in San Francisco; and that German blood product manufacturers would soon begin using the test. This news, combined with the mistaken belief that the U.S. Food and Drug Administration had recommended anti-core testing, and the report of the first Australian transfusion-related AIDS case in July 1984, caused Dr Archer to decide to implement anti-core testing at the New South Wales blood transfusion service. In early September, the first shipment of test kits arrived from Organon Teknika Ltd. in Belgium, new staff were hired to undertake the testing, and by 5 October anti-core testing began at the New South Wales blood transfusion service.

Screening blood donations: HIV testing

Australia was one of the first countries in the world to introduce nationwide comprehensive blood-screening tests. In November 1984, the Australian Prime Minister announced that the Commonwealth had asked the U.S. Department of Health and Human Services to make available the HIV-antibody screening tests that were still under development. In January 1985, the Minister for Health and senior officials visited London, San Francisco, Atlanta, Washington, and New York to gain some understanding of AIDS programs. While in Washington, the Minister of Health arranged for Australia to participate in the Food and Drug Administration's evaluation of antibody test kits. Australia was the only foreign country to participate in this evaluation.

Meanwhile, in Australia, the National AIDS Reference Laboratory undertook its own evaluation of the test kits during January and February 1985, and data from the Food and Drug Administration was also used to accelerate regulatory approval. By April, the Commonwealth government had arranged for the purchase and distribution of kits to all Red Cross blood transfusion service centres and had authorized state and territory laboratories to perform testing. States and territories also established alternative test sites where persons could voluntarily be tested for HIV antibodies and receive counselling. Funding for the testing of all hemophilia patients had already been granted by the Commonwealth government in October 1984. Routine screening of blood donors for the AIDS virus was fully implemented at all blood banks in May 1985.

Informing transfusion recipients of the risk

Since the first case of transfusion-induced AIDS in 1984, the Red Cross has conducted various programs to trace persons who may have become infected by the blood supply. These measures include "trace-backs" (tracing and testing donors of blood received by a patient who has become positive for HIV or hepatitis), "look-backs" (identifying and testing all recipients of previous

donations from a donor found to be positive for HIV or hepatitis), and “universal look-backs” (inviting any person transfused in a given period to come forward to be tested). Universal look-back was implemented in New South Wales and Western Australia for HIV when HIV screening was introduced.

Despite these efforts, a 1995 report on blood transfusion services in Australia commissioned by the Commonwealth government judged national tracing mechanisms for blood products to be inadequate. The authors of the report pinpointed two areas of concern. First, ensuring the safety of allogenic blood (anonymous pooled blood from many donors) was a divided role. Second, the eight largely autonomous divisional blood services had developed incompatible information systems. As a result, it had been impossible to establish an adequate national blood donor data system, thereby impeding effective efforts to trace blood donations. The authors also found that the failure to develop efficient automated hospital record systems was seriously limiting the effectiveness of hepatitis C trace-back procedures; they recommended that the Australian Health Ministers’ Advisory Committee request Red Cross blood transfusion services to make “specific provision” for the trace-back of blood donors who may have been infected with the hepatitis C virus.

Assistance to persons infected and affected

Government assistance

By late 1985, the Haemophilia Foundation of Australia had decided that members with HIV or AIDS needed financial help and it asked the Commonwealth government for compensation. The federal government’s National Advisory Committee on AIDS established a Working Party on Compensation for People with Medically Acquired AIDS that, in late 1986, endorsed the idea of compensation in a report to the government. It recommended that the Commonwealth pay some form of no-fault compensation or make *ex gratia* payments to these patients. The Commonwealth failed to respond by 1988, prompting the Haemophilia Foundation to mount a public campaign for financial assistance. The Minister of Health made it clear that the Commonwealth would not give compensation, but would instead consider granting some financial assistance in recognition of the costs associated with both hemophilia and HIV. Finally, in November 1989, as a result of lobbying efforts by the Haemophilia Foundation, transfusion-related AIDS organizations, politicians, and private citizens, the Commonwealth government announced the establishment of the Mark Fitzpatrick Trust, named in memory of a young boy infected by blood products, and made an initial grant of A\$13.2 million (Can\$12 million).

Under the trust, financial assistance was made available to individuals, families, or guardians of persons (alive or dead) who had acquired HIV as a result of the transfusion of infected blood or blood products between 1 January 1979 and 1 May 1985, or as a result of the transplantation of infected human tissue during that period. In January 1991, the trustees extended the

eligibility criteria by including any child infected with HIV in utero or through breast feeding, provided the mother had acquired HIV through medical procedures during the course of the relevant pregnancy. In April 1991, eligibility was further extended to permanent Australian residents who had acquired HIV overseas through medical procedures during the period covered by the trust deed.

Payments to applicants are made on the basis of need and hardship. Persons infected receive between A\$1,000 (Can\$915) and A\$8,000 (Can\$7,325) per annum. The Mark Fitzpatrick Trust made its first payments to persons with hemophilia in November 1990. As of February 1992, it had 353 approved registrants and had paid out more than A\$3.8 million (Can\$3.4 million). These payments give some measure of financial assistance to those infected, but they are not intended as compensation for suffering and loss caused by HIV or AIDS.

Only one state has given similar help. In March 1992, the New South Wales government announced a financial assistance plan of A\$50,000 (Can\$45,260) for each HIV-infected person. The funds are distributed by the Mark Fitzpatrick Trust on the state's behalf.

The payments were not considered adequate by persons infected. Because they had not been required to waive their right to bring civil actions as a condition of accepting the awards, many claimants chose to bring actions against their state or territory, the Red Cross, Commonwealth Serum Laboratories, and various public hospitals for damages.

Settlement of civil actions

There have been many actions brought by persons with blood-related HIV or AIDS. The first case, *H. v. Royal Alexandra Hospital for Children and Others*, was tried in the Supreme Court of New South Wales in January 1990 and was unsuccessful. The plaintiff had been administered factor VIII concentrate at the Royal Alexandra Hospital in 1982 and 1983, and in June 1985 was diagnosed with AIDS. The claim was based on the alternative hypotheses that "H" had been infected in March 1982 or in September 1983. Although serological tests for establishing whether blood is positive for the HIV antibody could not be performed in 1982, the fact that the patient had had symptoms consistent with a seroconversion in April 1982, along with the low probability that the 1982 batches of concentrates had been contaminated with HIV, suggested that infection had occurred from cryoprecipitate in March 1982, and not from factor VIII concentrate. Mr Justice Badgery-Parker held that before March 1982 there was no evidence that the exclusion of donors known to be at high risk for hepatitis B was an effective method of removing likely carriers of unrecognized viruses; thus, neither the blood bank nor the manufacturer, in using plasma from such a donor pool, was negligent. With respect to the hospital, the court concluded that the administration of factor VIII concentrate was appropriate and that it was not reasonable to expect the treating physicians to warn "H" of the remote risk of infection by an unknown virus.

The second case, *E. v. Australian Red Cross Society and Others*, was also unsuccessful. In this case the plaintiff, who had contracted AIDS from a post-operative blood transfusion in early October 1984, brought an action against the treating hospital, the local health service, and the Red Cross New South Wales blood transfusion service. The plaintiff alleged that blood and blood products were goods supplied in trade or commerce and, therefore, that the laws relating to product liability applied. The court rejected the contention that blood and blood products were commercial goods. The plaintiff also alleged that the Red Cross had negligently failed to implement surrogate testing for antibody of the hepatitis B core antigen in a timely manner; that testing should have been implemented by early 1984. The Federal Court of Australia (General Division) ruled that the Red Cross could be found negligent only if the court "were satisfied that a prudent person ... would have determined that the concern for contamination outweighed the difficulties which would ensue from reducing the blood supply." In the opinion of the court, since the first transfusion-related AIDS case did not appear in Australia until July 1984, before August 1984 no prudent blood banker would have determined that it was better to accept the loss of 5 per cent of the blood supply than to risk possible HIV contamination of the blood supply. The court therefore ruled that "it was not unreasonable for the Red Cross to wait until after a transfusion AIDS case had appeared" to begin testing.

The next year, *PQ v. ARCS & Others* was decided. The case, brought in the Supreme Court of Victoria in August 1990, lasted eighty-seven days, making it the longest civil jury trial in Australian history. The plaintiff was successful in his action against the defendant hospital, but the action against the Red Cross and Commonwealth Serum Laboratories was dismissed. The plaintiff was awarded A\$870,000 (Can\$806,229), of which A\$500,000 (Can\$463,350) were general damages.

It was after the conclusion of this action in 1990 that settlements began to be offered to plaintiffs in other actions. Litigants in Victoria received two large settlements. These were significant because, for the first time, the Red Cross and Commonwealth Serum Laboratories had agreed to settle. In March 1991, the case of a young girl who became infected from a blood transfusion in October 1984 was settled for A\$300,000 (Can\$226,910). In December of that year another action was brought against the Red Cross, a hospital, and Commonwealth Serum Laboratories on behalf of a boy with severe hemophilia who had received HIV-infected blood products in July 1984. It was settled for A\$600,000 (Can\$530,640) after an eight-day trial.

Motivated by the judgment in the *PQ* case and the significant costs of defending these actions, state and territorial governments began settling actions in May 1991 and have since settled more than 430 outstanding claims of persons with blood-related HIV or AIDS. The Red Cross state and territorial blood transfusion services were indemnified by state governments, Commonwealth Serum Laboratories, and the Commonwealth government. With the

exception of a Western Australia settlement in which persons infected received identical awards, every claim was assessed on an individual basis, taking into consideration the law and the likelihood of success had the case proceeded to trial. Settlements have included awards to infected spouses, the payment of medical expenses, and small, retrospective payments on behalf of persons who have died. These settlements, in chronological order, are as follows:

Western Australia In May 1991, the government settled all outstanding claims for A\$5.4 million (Can\$4.8 million). Each of the twenty-two persons in the state with blood-related HIV received the sum of A\$280,000 (Can\$249,116), plus free health care.

South Australia and the Northern Territory In October 1991, settlements were made by both governments. Payments ranged from A\$150,000 (Can\$132,660) to A\$600,000 (Can\$530,640), in addition to payment of medical expenses.

Victoria In December 1991, the state paid 112 residents A\$22.5 million (Can\$19.8 million) and undertook to pay the medical costs of A\$40 million (Can\$35 million) for persons infected. Payments ranged from A\$150,000 (Can\$132,660) to A\$600,000 (Can\$530,640). The state's contribution was about A\$8 million (Can\$7 million). Legal costs of approximately A\$2 million were also paid.

Queensland In December 1992, persons infected with HIV reached an agreement with the federal and state governments. The thirty-four infected persons were awarded A\$7.2 million (Can\$6.3 million).

New South Wales In April 1994, the government paid A\$36 million (Can\$35.6 million) as compensation to 230 people infected with HIV. The Commonwealth government undertook to allocate a further A\$25 million (Can\$24.7 million) for continuing medical expenses. Infected persons received from A\$100,000 (Can\$99,040) to A\$400,000 (Can\$396,160) each, the majority between A\$150,000 (Can\$148,560) and A\$250,000 (Can\$247,600). The amount of the payment depended on potential loss of earnings, the number of dependants, and the likelihood of success had the action proceeded to trial.

Actions in Tasmania were settled in late 1993, and in the Australian Capital Territory in 1993–4. Details about these settlements are not available.

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France

The blood system in the 1980s

The French blood system has been operated by the state since 1952. During the 1980s, it consisted of the Centre national de transfusion sanguine (National Blood Transfusion Centre), located in Paris, and 163 local blood transfusion centres. There were seven fractionation plants. Donations of blood and plasma were, and continue to be, voluntary and unpaid. The French government fixed prices for blood products, and these costs were reimbursed under the national health insurance scheme.

In recent years, the blood system has been entirely transformed. The most important change was the creation of the Agence française du sang (French Blood Agency) in 1992.

Blood transfusion centres and the Centre national de transfusion sanguine

During the 1980s, blood donors were recruited locally by the blood transfusion centres with the help of two donor organizations – the Fédération française des donneurs de sang bénévoles (French Federation of Voluntary Blood Donors) and the Croix-Rouge française (French Red Cross). Approximately half these centres were public entities and were affiliated with the hospitals in which they were located; the other half were private associations with boards of directors. Each centre managed its own operations without any direction from the Centre national de transfusion sanguine. The centres not only recruited blood donors but also gave donors medical examinations, stored blood, prepared preserved blood and liquid plasma, conducted blood typing procedures, and supplied plasma to the nearest regional fractionation plant. The six regional fractionation plants were located in Lille, Lyon, Bordeaux, Strasbourg, Nancy, and Montpellier and each one was operated by the local blood transfusion centre.

The non-profit Centre national de transfusion sanguine was established as a Fondation d'utilité publique in 1975; it was an autonomous agency, operating independently of governmental authorities. Although the Centre's primary purpose was to undertake research in blood transfusion and to

promote education about the subject, it also operated a fractionation plant at Les Ulis near Paris, the largest in France. In 1982, the Centre was given a monopoly on the import of blood and blood products.

During the 1980s, the Centre national de transfusion sanguine was influenced by a number of internal and external bodies. These bodies included the Fondation nationale de la transfusion sanguine (National Blood Transfusion Foundation), an organization that made suggestions about blood transfusion policy; the Société nationale de la transfusion sanguine (National Blood Transfusion Society), a professional association of transfusion experts; and the Comité national de l'hémophilie (National Hemophilia Committee), which included representatives from the Centre national de transfusion sanguine, the Société nationale de la transfusion sanguine, the Laboratoire national de la santé (National Health Laboratory), the Association française des hémophiles (French Hemophilia Association), and a number of treating physicians.

The role of government

In the Ministère des Affaires sociales et de la Solidarité nationale (Ministry of Social Affairs and National Solidarity), two agencies were concerned with blood transfusion and blood products. These agencies were the Direction générale de la santé (Health Branch) and the Laboratoire national de la santé.

Legislation governing blood transfusion was first enacted in 1952 and remained in force until 1993, when new legislation relating to the Agence française du sang came into force. The 1952 legislation provided for the establishment of blood transfusion centres in each département (administrative region). These centres were placed under the control of the Direction générale de la santé and reported to the prefect of the département in which they were located, although the function of the blood transfusion centre director was day-to-day management. (Prefects, appointed by the French government, coordinated social and health services within départements.) The legislation also provided that all donations must be voluntary, anonymous, and unpaid.

The Direction générale de la santé licensed transfusion centres and established standards for blood donation and blood products. By order of 23 December 1983, monitoring the quality of blood transfusion was added to the functions of the Direction générale de la santé, although the Laboratoire national de la santé also played a role in "monitoring" blood products, even though at that time blood products were not regulated as drugs. The power to recall unsafe blood products from the market was shared by the Direction générale de la santé and ministers of the government. Legislation enacted in July 1983 authorized "those ministers concerned" and the minister responsible for consumer affairs to suspend distribution of a potentially hazardous product and to recall it from the market.

The Direction générale de la santé was assisted by several advisory bodies. The Commission consultative de transfusion sanguine (Advisory Commission on Blood Transfusion) gave advice from experts such as directors of blood transfusion centres, hospital directors, physicians, and representatives of the Fédération française des donneurs de sang bénévoles and the Croix-Rouge française. The Association pour le développement de la transfusion sanguine (Association for the Development of Blood Transfusion) and the Société nationale de la transfusion sanguine gave expert advice from scientists and physicians employed by the blood transfusion centres.

Monitoring the spread of AIDS was also a function of both the Direction générale de la santé and the Laboratoire national de la santé. The surveillance of infectious diseases and public health was the role of the epidemiological unit at the Laboratoire national de la santé. Reports of communicable diseases received by it were sent to the bureau for communicable diseases within the Direction générale de la santé, and summaries were published in the *Bulletin épidémiologique hebdomadaire*. In 1984, a network for communicable disease surveillance was created to transmit information among the Direction générale de la santé, the Unité de recherches biomathématiques et biostatistiques (Biomathematics and Biostatistics Research Unit), and the Laboratoire national de la santé, as well as among medical inspectors of health, national reference centres, physicians, and laboratories. In 1985, this group was assisted by the creation of a formal network of general practitioners to act as “sentinels” for the surveillance of communicable diseases.

Association française des hémophiles

The Association française des hémophiles was established in 1955 to represent the interests of persons with bleeding disorders. During the 1980s, it had a national office, located in Paris at the Centre national de transfusion sanguine, and a number of regional committees. The goal of the organization is to alleviate many of the difficulties faced by persons with hemophilia and to help them live normal lives. The Association is active in a number of areas. It works to educate the public about hemophilia, contributes to scientific and medical research related to hemophilia, gives members information about new products, assists members in obtaining medical and social assistance, and publishes a quarterly newsletter called *L'hémophilie*. The Association also plays an important role at the national level as an advocate for the interests of hemophiliacs before government. During the 1980s, the Association received funding from the Centre national de transfusion sanguine.

Prevalence of blood-related HIV or AIDS

France has the highest incidence of AIDS resulting from the use of blood and blood products among all Western European countries. Between 1985 and 1993 there were 1,926 cases of blood-related AIDS, or an incidence rate of

3.2 per 1,000,000 each year – a number significantly higher than that of the next highest country, Spain. The majority of persons infected were recipients of blood transfusions.

It is estimated that more than 1,250 of the country's 4,000 hemophiliacs became infected with HIV. According to the European Centre for the Epidemiological Monitoring of AIDS, as of 31 December 1996 there were 527 reported cases of AIDS among hemophilia patients, representing 1.2 per cent of all AIDS cases in France and its overseas départements (French Guyana, Guadeloupe, Martinique, and Réunion), and 1,662 reported cases of AIDS among transfused patients, representing 3.8 per cent of all AIDS cases in France and its overseas départements.

Protecting the blood supply from HIV or AIDS

“L'affaire du sang contaminé”

Perhaps the most controversial and well-documented public examination of HIV infection among hemophiliacs is “l'affaire du sang contaminé,” which resulted in the conviction of public officials. The issue first came to the attention of the French public in April 1991 when Dr Anne-Marie Casteret, a physician and journalist, published a series of articles in the magazine *L'Événement du Jeudi*. In these articles, she reported that the Centre national de transfusion sanguine had made a decision to sell lots of factor concentrates that were known to be contaminated with HIV before it introduced heat-treated factor concentrates to the market. This revelation by Dr Casteret precipitated the resignation of the Centre's director, Dr Michel Garretta.

In June 1991, the French government commissioned the general inspector of social affairs, Michel Lucas, to investigate the matter. Mr Lucas's report, *Transfusion sanguine et SIDA en 1985: Chronologie des faits et des décisions pour ce qui concerne les hémophiles* [*Blood Transfusion and AIDS in 1985: The Chronology and Events of AIDS and Hemophiliacs*, or the Lucas Report], was submitted to the government in September 1991. The next month, charges were brought against four individuals: Dr Michel Garretta, who had been director general of the Centre national de transfusion sanguine since October 1984; Dr Jean-Pierre Allain, a practising physician who served as the director of research and deputy director of the Centre national de transfusion sanguine; Professor Jacques Roux, the director general of health; and Dr Robert Netter, the director of the Laboratoire national de la santé. Dr Garretta and Dr Allain were charged with “fraud concerning the essential quality of merchandise sold,” in contravention of the *Act of August 1, 1905* and section L675 of the *Public Health Code*, and Professor Roux and Dr Netter were charged with failure to assist a person in danger, pursuant to section 63 of the *Penal Code*.

Efforts by infected hemophiliacs to obtain damages were already well under way by this time. On 31 March 1988, Pascal Fiedler, Thierry Choquet, Laurent Choquet, and Jean-Louis Tellini each brought an action alleging fraud. On

21 April 1988, Christian Garvanoff, an HIV-positive hemophiliac, lodged three complaints: the first against the Centre national de transfusion sanguine; the second against the Association française des hémophiles; and the third against the regulator, the Laboratoire national de la santé. In addition to the law on fraud, Mr Garvanoff invoked the provisions of the *Penal Code*, specifically failure to help a person in danger, and in a separate complaint he accused Dr Garretta of manslaughter for the death of his brother Gabriel Garvanoff, who had died earlier that month. The various proceedings were consolidated by an order issued on 24 March 1989. In May and June of that year, the court received additional complaints from HIV-infected hemophiliacs; these complaints were also consolidated with the first action in March 1990. By virtue of the French *Code of Criminal Procedure*, which provides that bringing a civil action before criminal courts is a right accessory to public action “by anyone who has personally sustained damage directly caused by the offence,” and French case law, which has broadly interpreted this definition to include individuals who can point to “the possibility of an injury resulting directly from the offences with which the accused are charged,” these actions were joined with the criminal action initiated by the state in 1991.

The trial of Dr Garretta, Dr Allain, Dr Netter, and Professor Roux began on 22 June 1992 in the Tribunal de grande instance de Paris and continued throughout most of the summer. The primary issues at trial were, first, the delay in manufacturing heat-treated factor concentrates, and, second, the distribution between March and October 1985 of non-heat-treated blood products from the Centre national de transfusion sanguine which were known to be contaminated with HIV. The decision of the trial court was appealed to the Cour d’appel de Paris, and a decision by that court was rendered in July 1993. The findings of the courts are discussed throughout this chapter and in the section “The courts.”

The emergence of HIV or AIDS

The first French case of unusual opportunistic infection was observed in a young male homosexual in August 1981 by Professor Willy Rozenbaum, who at that time was a senior hospital lecturer at the Claude Bernard Hospital in Paris specializing in infectious and tropical diseases. Professor Rozenbaum noticed that the patient’s symptoms were similar to those described in the *Morbidity and Mortality Weekly Report* of 5 June 1981. The patient was suffering from malaise and loss of weight. He also tested positive for cytomegalovirus and had an inverted T-lymphocyte helper-to-suppressor cell ratio. His only apparent risk factor was the fact that he had visited New York in February 1980 and had experimented with amyl nitrite.

By 1982, a number of AIDS cases among French homosexuals had been reported. Between 31 March and 29 December 1982, twenty-nine confirmed cases were reported to epidemiologists in the Direction générale de la santé. Of the twenty-nine persons with AIDS, ten had travelled to Africa in the

previous five years, nine to the United States, and six to Haiti. By March 1983, an additional ten cases were reported. All but two of the patients had been living in Paris, although many had travelled to equatorial Africa, the United States, or Haiti. (Almost all those with a history of travel to the United States were homosexual.) Nine of these cases were seen before June 1981, a fact that led the epidemiologists to conclude that “the illness and the supposed infectious agent(s) are not new in France.” An article published in the French medical journal *Presse médicale* in April 1983 reported that four French homosexuals with the disease had all spent some time in the United States and had signs of past or present cytomegalovirus infection. The author of the article stated that these infections might have been caused by a transmissible agent that was now present within the French homosexual community.

By May 1983, there was some evidence to suggest that the disease might be sexually transmitted. A Haitian heterosexual couple living in Paris was reported to have died of AIDS in 1982. The wife had lived in the United States between March and September 1980 and, during that period, had had sexual relations with another Haitian who had AIDS. According to the authors of this article, these three cases of AIDS “support[ed] the view that the hypothetical viral agent associated with AIDS can be transmitted through intimate contact.” In October 1983, the World Health Organization reported that France had the highest number of cases of AIDS among fifteen European nations. The *Bulletin épidémiologique hebdomadaire* reported that, by the end of 1984, AIDS cases were increasing at a rate of four per week, and that 90 per cent of AIDS cases diagnosed in France were in Paris.

Blood-related AIDS cases were first reported in mid-1983. In May 1983, a survey of 2,388 hemophiliacs (representing approximately 60 per cent of the hemophiliac population) revealed no cases of AIDS. The next month, however, the AIDS virus (in France known as the lymphadenopathy-associated virus, or LAV) was isolated in two French hemophiliacs, and a study of blood transfusion and AIDS submitted to the Commission consultative de transfusion sanguine reported that there were six suspected cases of AIDS in French hemophiliacs, three of whom had been treated with domestic factor concentrates. Because these six cases were not cases of full-blown AIDS, however, the authors concluded that “we have been unable to identify any official case of the disease in France attributable to the injection of a blood product.” The next month a French hemophiliac died of AIDS – the first fatal case of AIDS in a hemophiliac. Published reports of other cases appeared later. A report of a case of AIDS in a hemophilia B patient appeared in the *Revue française de transfusion et immuno-hématologie* in 1984, and a report of two cases of AIDS in patients with hemophilia A in the *Annales de médecine interne* in 1986.

In 1983, *The Lancet* reported a case of AIDS in a French man who had received a blood transfusion four years earlier in Haiti. The first AIDS case in patients who had been given a blood transfusion in France involved a woman who had

received numerous transfusions in 1981 after a motor vehicle accident. She died in January 1984 of *Pneumocystis carinii* pneumonia. It was later discovered that one of the donors was infected with the AIDS virus, but had been asymptomatic at the time of donation. The case was reported in the *Revue française de transfusion et immuno-hématologie* in February 1985. At a meeting of the Commission consultative de transfusion sanguine on 22 November 1984, Dr Jean-Baptiste Brunet, an epidemiologist at the Direction générale de la santé, presented a paper on the risk of transmitting AIDS through blood transfusions. He reported that there were 221 cases of AIDS in France, three in persons who had received blood transfusions.

Response to the emergence of HIV or AIDS

France was the first European country to establish an epidemiological surveillance system for AIDS. The discovery of AIDS cases in late 1981 led to the creation of an informal study group to examine the syndrome. It consisted of physicians and researchers working in a wide range of specialities, including immunology and infectious and tropical diseases, and physicians who were treating AIDS patients. In the spring of 1982, with a grant from the Direction générale de la santé, Dr Brunet began the task of creating a national surveillance system.

For every case referred to the multidisciplinary group, a preliminary report form was completed to verify that the patient did indeed suffer from AIDS. At that time, AIDS was defined as “biopsy-proven Kaposi’s sarcoma in a patient under 60 years old and/or life-threatening opportunistic infection confirmed by biopsy or culture but no known underlying illness or history of immunosuppressive therapy.” In verified cases, the attending physician completed a questionnaire to evaluate the patient’s exposure to risk factors. Retrospective cases were included only when there was sufficient information to confirm that they fell within the definition of the syndrome. Patients with a history of symptoms such as polyadenopathy, persistent or undulating fever, and weight loss were not included, but were monitored.

In August 1983, the Direction générale de la santé established an information network to promote the development of an AIDS surveillance system at the local level. Then, in November 1984, the World Health Organization, with the support of the French government, established the European Centre for the Epidemiological Monitoring of AIDS in Paris. The reporting of AIDS cases became obligatory in June 1986, although there was no similar requirement to report persons who tested HIV positive.

French health authorities were not aware of the risk posed by blood and blood products in the transmission of AIDS until the spring of 1983. On 24 March, Dr André Chippaux, the assistant director of the Laboratoire national de la santé and director of the blood section, addressed the Commission consultative de transfusion sanguine on the subject of AIDS and blood and, on 11 May 1983, informed both Dr Netter and Professor Roux of the risks to

hemophiliacs. On 13 May 1983, Dr Netter forwarded to Professor Roux a report that stated that “AIDS represents a potential danger for people receiving blood or derivatives,” but said that screening donors would be difficult because the causal agent was unknown and the incubation period appeared to be long. At the meeting of the Commission consultative de transfusion sanguine on 9 June 1983, Dr Bahman Habibi, an employee of the Centre national de transfusion sanguine, presented a report about blood transfusion and AIDS in which he pointed out that although there were six suspected cases of AIDS among hemophiliacs, there were as yet no confirmed cases.

By the autumn of 1983, this initial concern about blood and blood products intensified. In a memorandum dated 2 September 1983, the Laboratoire national de la santé requested the Ministry to “strengthen the sector responsible for reviewing the tests applied to non-heat-treated blood products to take into account the emergence of AIDS.” On 8 October 1984, Dr Brunet attended a meeting of the Laboratoire national de la santé to give officials current information about the epidemiology of the disease and to inform them that AIDS was appearing among hemophiliacs. That month the *Bulletin épidémiologique hebdomadaire* reported that HIV was transmitted through blood and blood products and by sexual contact.

At the trial of Dr Garretta and the others, Judge Foulon heard contradictory testimony about precisely when experts became aware of the potential risk of the transmission of AIDS through blood and blood products. According to Professor Rozenbaum, it was clear in mid-1982 that AIDS was of concern to hemophiliacs and patients receiving blood transfusions. By that time, the theory of a viral agent had been advanced and the existence of a retrovirus had been announced. Dr Luc Montagnier of the Institut Pasteur (Pasteur Institute) stated that the risk of transmitting the virus to hemophiliacs was certain by August 1983, although he acknowledged that the scientific community was not convinced of this risk until his work was universally recognized in the spring of 1984. Dr Brunet was of the view that French scientists were divided about the origin of the disease, some believing that it was viral, and others that it was environmental. He testified that this difference of opinion persisted until the end of 1984, even after Dr Montagnier discovered the virus.

Excluding persons at risk: Donor screening

On 24 May 1983, Dr Garretta’s predecessor, Professor Jean-Pierre Soulier, published a circular about AIDS for distribution to blood donors. The circular stated that the following persons were at high risk of transmitting AIDS or hepatitis: male homosexuals having multiple sexual partners, intravenous drug users, and persons who had travelled to areas such as the Caribbean, Haiti, the west coast of the United States, and equatorial Africa. Attached to the circular was a questionnaire for donors to complete. It asked whether donors had used intravenous drugs or had had multiple homosexual partners, and

inquired about symptoms of AIDS, such as loss of weight, fever, night sweats, and swollen glands. Physicians supervising the collection of donations were asked to prepare a report at the end of the first month of screening that outlined the responses given and the reaction by donors to the questionnaire. The results of one month of screening were published in the *Revue française de transfusion et immuno-hématologie*. Of 7,235 donors who completed the questionnaires, twenty-eight responded that they had had multiple homosexual partners, and an additional eight said that they had used intravenous drugs.

The next month, the Direction générale de la santé sent donor-screening guidelines to all blood transfusion centres. On 20 June 1983, Professor Roux issued a directive, or "circulaire," requesting blood transfusion centres to begin screening donors for AIDS. Although he acknowledged the "minimal" risk of AIDS transmission, Professor Roux gave specific instructions about how this donor screening should be undertaken. First, all blood donors should be examined for suspicious symptoms (asthenia, unexplained weight loss, prolonged fever, copious night sweats, and polyadenopathy). Second, donations from homosexuals or bisexuals with multiple partners, intravenous drug users, persons of Haitian or equatorial African origin, and sexual partners of these persons would be restricted to use for plasma fractionation, except for any preparation of factor concentrates. Third, physicians supervising the collection of blood should be informed that it was important to distribute information to donors before they donated. A sample donor pamphlet attached to the circular stated that the syndrome may be transmitted by blood even in the absence of an apparent illness in the blood donor. It requested donors who were at risk of contracting AIDS or who had symptoms of AIDS to inform the attending physician of these facts. Fourth, blood transfusion services should strive for self-sufficiency in factor VIII concentrate so that the use of imported products might be avoided. Transfusion services might achieve this goal by minimizing the unjustified use of fresh frozen plasma and by increasing the production of plasma used for preparing cryoprecipitate. Three days later, the Committee of Ministers of the Council of Europe also recommended measures for donor screening. One of its recommendations was that governments of member states "provide all blood donors with information on the Acquired Immune Deficiency Syndrome so that those in risk groups will refrain from donating." Attached was a sample donor leaflet. A second circular that included hemophiliacs as a group at risk of contracting AIDS was published on 26 August 1983 by the Direction générale de la santé.

The recommendations set out in the June and August 1983 circulars from the Direction générale de la santé were not always implemented by blood transfusion centres. On 22 November 1984, Dr Brunet submitted a report to the Commission consultative de transfusion sanguine about the risk of transmission. In it, he stated that the donor-screening recommendations issued in June 1983 had largely been ignored, and that 10 per cent of persons infected

with the AIDS virus developed AIDS in five years. In response, Professor Roux issued another directive to blood transfusion centres on 16 January 1985, in which he informed them that the “potential of transmission by blood transfusion has been established” and that cases of transfusion-related AIDS had been reported in France. Professor Roux stated that blood transfusion services had not acted on the recommendations he had issued in June 1983 about the screening of donors for AIDS, and he demanded strict application of this directive. He also stated that the centres would soon be receiving an AIDS pamphlet to be distributed to donors. The transfusion centre directors were told that, during the medical interview preceding a donation, they were to ensure that donors had assimilated the information, and were to ask donors whether they were members of a risk group. Donors who answered in the affirmative were to be asked not to donate. Finally, Professor Roux warned that blood transfusion establishments that failed to implement the preventive measures recommended might be held accountable. Enclosed with the circular was a copy of the recent epidemiological bulletin produced by the Secretary of State for Health that outlined the current statistics for AIDS in France.

Collection centres located in penitentiaries did not introduce donor-screening measures until mid-1985, and no action was taken to halt collections until late 1985. The donor-screening circular issued in June 1983 was not distributed to penitentiaries. In fact, in January 1984 the head of French penitentiaries authorized the transfusion centres to collect more frequently in the penitentiaries. Some persons thought that donating blood helped to facilitate prisoners’ rehabilitation. At a meeting of the Société nationale de la transfusion sanguine in February 1984, however, a few physicians expressed concern about using the blood collected in penitentiaries because of the high prevalence of hepatitis among inmates. Yet, when the second donor-screening circular was issued in January 1985, Professor Roux did not prohibit blood collection in penitentiaries, even though the penal administration had requested guidance about the matter.

By mid-1985, however, it was becoming clear that a significant number of prisoners were at high risk of contracting AIDS. In May, the head of French penitentiaries was informed that a study conducted at the Fresnes penitentiary revealed that 12.6 per cent of all new inmates to the penitentiary, and 60 per cent of Fresnes inmates who were drug addicts, were HIV positive; the next month, Dr Brunet told government advisers on blood transfusion that 16 per cent of incoming prisoners at the Bois-d’Arcy penitentiary were HIV positive; and in August, French government authorities learned that 7 per cent of potential donors at the Fresnes penitentiary were HIV positive.

A committee composed of officials from the ministry of justice and the ministry of health was established to examine ways of improving health conditions in penitentiaries, and, at a meeting in June 1985, the committee concluded that a reduction in blood collection in penitentiaries would result in a serious shortage for the Centre national de transfusion sanguine. It therefore

recommended that collections in penitentiaries should continue, provided that the blood centres were made aware of the risks involved. Blood continued to be collected in French penitentiaries during the summer of 1985, and it was not until October that governors of penitentiaries were informed that collections were to be temporarily suspended. From studies done at the time, it was estimated that as many as a quarter of the contaminated donations collected in 1985 originated with prison inmates.

The trial court did not comment on the implementation of donor screening for AIDS. The Cour d'appel de Paris, however, found that the donor-screening circulars distributed by Professor Roux in June 1983 were "imperfectly implemented" because physicians at blood transfusion centres were reluctant to subject donors to the questionnaires. It also found that blood transfusion centres located in neighbourhoods with a high incidence of AIDS and in penitentiaries continued to collect blood long after this date.

Inactivating viruses in blood products

In 1983, French scientists became interested in the heat treatment of blood products as a way to reduce the transmission of AIDS, although there was as yet no consensus that the process would be effective. On 11 May 1983, Dr Chippaux wrote to Dr Netter and Professor Roux to advocate the introduction of heat treatment, even though doubts persisted about its effectiveness, stating that it could "reduce as far as possible the risk of transmitting AIDS." In June 1983, Dr Allain informed the Commission consultative de transfusion sanguine that he had launched a study to evaluate heat-treated factor concentrates; and on 8 October 1983, officials from the Centre national de transfusion sanguine, the Institut Pasteur, the Direction générale de la santé, and the Laboratoire national de la santé met to discuss the safety of blood products and the inactivation of viruses. In July 1984, a number of officials from the Centre national de transfusion sanguine attended the congress of the International Society of Blood Transfusion in Munich, where the issue of heat treatment was a subject of much debate. With a few exceptions, most of the persons attending the conference were not persuaded about the merits of heat treatment. In fact, in September 1984, when Dr Allain reported the results of the August meeting of the World Hemophilia Congress in Rio de Janeiro to the Association française des hémophiles, he said that there was no proof that heat treatment inactivated retroviruses.

The same month, however, a study published in *The Lancet* demonstrated that heat did kill retroviruses, and immediately thereafter the U.S. National Hemophilia Foundation recommended the use of heat-treated factor concentrates. The importance of introducing heat-treated factor concentrates was also underscored by Dr Brunet at a meeting of the Commission consultative de transfusion sanguine in Paris in November 1984. In his presentation, Dr Brunet highlighted the risk of HIV transmission, stated that 10 per cent of persons infected with HIV developed AIDS within five years and that

donor-screening recommendations issued in June 1983 were seldom applied, summarized studies demonstrating the effectiveness of heat treatment at 68°C for twenty-four hours on a retrovirus similar to the AIDS virus, and drew attention to the recommendations of the U.S. National Hemophilia Foundation that heat-treated concentrates be used. In December 1984, an article published in *The Lancet* concluded that despite continuing uncertainties about the heat treatment process, "it is reasonable to switch to heat-treated factor VIII concentrates," and that to do otherwise would be "indefensible."

During 1984, several seroprevalence studies were undertaken to determine whether hemophiliacs were becoming infected. These studies produced additional evidence of the efficacy of heat treatment. The first study was conducted by Dr Allain from September 1983 to March 1984 and involved 405 patients who used various heat-treated and non-heat-treated factor concentrates. When it was completed, the study showed that 45 per cent of the 405 hemophiliacs studied were HIV positive and that eighteen hemophiliacs treated solely with a heat-treated factor VIII concentrate, Hemofil-T, manufactured by the U.S. fractionator Travenol Laboratories Inc. (Travenol), remained free of HIV infection. This information was immediately communicated to Dr Garretta. The second study, conducted by Dr Christine Rouzioux and Dr Montagnier and published in *The Lancet* in February 1985, examined eighteen hemophiliacs treated exclusively from December 1982 to June 1984 with Hemofil-T. None of the subjects had seroconverted.

Despite the mounting scientific evidence demonstrating the effectiveness of heat treatment, it was not until April 1985, at the International Conference on AIDS in Atlanta, that Dr Garretta became convinced of the need to provide heat-treated factor concentrates. After the conference, he implemented an "emergency strategy" to ensure that heat-treated factor concentrates could be distributed as early as July 1985.

Conversion to heat-treated products

The acquisition of heat treatment technology by the Centre national de transfusion sanguine was a protracted process. On 3 December 1983, a letter of intent for the transfer of the technology was signed between the Centre and Immuno AG, an Austrian blood product manufacturer. Negotiations were resumed again in January 1984, and a third meeting was held in July 1984 at the congress of the International Society of Blood Transfusion in Munich, but it was not until January 1985 that negotiations with Immuno were finally completed. As a result of the delays, the Centre national de transfusion sanguine did not produce heat-treated factor VIII concentrate at its own plant until September 1985; before that date, plasma from the Centre was shipped to Vienna for fractionation and then returned to France.

In 1984, however, one fractionation centre in France began to develop its own heat treatment technology. Professor Maurice Goudemand and Professor Huart, physicians with the blood transfusion centre in Lille, had also attended

the Munich congress in July and had returned home convinced of the need to introduce heat treatment methods. On 1 August, Professor Goudemand wrote to Professor Soulier, then the head of the Centre national de transfusion sanguine, proposing that the two fractionation centres cooperate in the scientific and technical development of heat treatment. Professor Soulier replied on 11 September that the proposal had been forwarded to Dr Garretta and Dr Allain, and that it was for them to decide whether to meet with Professor Goudemand to discuss the feasibility of a joint heat treatment study. However, Dr Garretta did not contact Professor Goudemand with regard to his proposal. Nevertheless, Professor Goudemand proceeded with the project, and by December the Lille blood transfusion centre had begun to produce heat-treated factor VIII concentrate that was distributed to patients within the area in June 1985.

Meanwhile, on 10 May 1983, Travenol had informed the Centre national de transfusion sanguine that its factor concentrates would soon be heat treated to reduce the risk of contamination, and it offered to sell the Centre heat-treated factor concentrates. The Centre declined Travenol's offer. The offer was renewed in May 1984, and thereafter the Centre accepted occasional imports of Hemofil-T, although the quantity remained small. On 13 August 1984, Dr Garretta sent his colleagues a memorandum stating that imports of factor concentrates had been stopped and could not be resumed except on an individual basis with authorization from him and from Dr Allain. In January 1985, Dr Garretta wrote to Dr Netter, informing him that "a decision has been made to import new therapeutic factor concentrates only for national clinical testing or isolated use." Later that month, when Dr Garretta met with senior officials at the office of the Secretary of State for Health to discuss imports, it was decided that it was too expensive to import heat-treated factor concentrates on a large scale. Only the blood transfusion centre in Strasbourg negotiated an import licence with Travenol, in December 1984. The reason for this rejection of imports was Dr Garretta's adherence to the policy of self-sufficiency. In his testimony, at trial, Dr Allain stated that the Centre national de transfusion sanguine could not import because it "had to show the Ministry that the French system was able to cope with the demand without resorting to imports, that it was independent." Dr Garretta also said that the decision not to import blood products was influenced by the fact that the American factor concentrates were inherently unsafe, owing to the "mercenary," or commercial, nature of blood collection in the United States.

Contamination of non-heat-treated factor concentrates

The first testing of blood samples for the AIDS virus in France was conducted in October 1984 by Dr François Pinon, the head of the blood bank at the Cochin Hospital in Paris, and Dr Jacques Leibowitch, an immunologist at the Garches Hospital in Paris. They used an immunofluorescence test that Dr Leibowitch had developed in July 1984, and their work became known as the "Cochin

study.” The test was a very simple one, subject to a large margin of interpretative error. By 12 December, Dr Pinon and Dr Leibowitch had tested 2,000 donors. They found that AIDS antibodies were present in six of every 1,000 Parisian blood donors who had been screened for AIDS in accordance with the recommendations made by the Direction générale de la santé on 20 June 1983. In light of these results, Dr Pinon and Dr Leibowitch estimated that approximately 2,500 patients a year would become infected from contaminated blood donated by French donors.

On 10 January 1985, when Dr Pinon sent a copy of the preliminary results to the Direction générale de la santé, he stated that “there is a definite possibility of transmitting AIDS through blood transfusion ... Preliminary results indicate that LAV [HIV] antibodies are present in 5/1,000 Parisian blood donors.” Dr Pinon also said that it would be “prudent to reduce, try to avoid, at all times possible the use of blood products for therapeutic reasons.”

By March 1985, the preliminary results had been confirmed by ELISA testing, and by radio-immuno-precipitation testing undertaken at Dr Max Essex’s laboratory in the United States. On 7 March, Dr Brunet sent a copy of the Cochin study to the Commission consultative de transfusion sanguine and referred to the “apparently disturbing” results. The study showed that patients who had received blood from nineteen seropositive blood donors at Cochin Hospital had become infected, and it confirmed that blood products manufactured from donations made by donors in Paris were heavily contaminated. A copy of the results was also sent to Professor Roux. In his letter to Professor Roux, Dr Brunet observed that transfusion was an effective method of transmitting HIV infection, and that the blood was infectious whether or not donors were ill or asymptomatic; he concluded that “[i]f the proportion of LAV-positive [HIV-positive] donors found in the Cochin study is representative of the situation in Paris, it is probable that all blood products prepared from pools from Paris donors are now contaminated.” Professor Roux sent this document to the Minister of Health “through the usual channels.”

On 7 March 1985, at a meeting of the Commission consultative de transfusion sanguine, Dr Brunet reported the results of the Cochin study and informed participants that seven multiply transfused patients had acquired AIDS from transfusions between 1977 and 1982. In view of these results, it was decided that the Centre national de transfusion sanguine should be responsible for establishing a working group of experts to study all the problems posed by AIDS and by the transfusion of blood and blood products. The results of the Cochin study were published in the French newspaper *La Libération* on 8 March 1985.

Introduction of heat-treated factor concentrates

As discussed above, Dr Garretta finally became convinced of the efficacy of heat treatment in reducing the risk of the transmission of AIDS when he attended the Atlanta conference in mid-April 1985. On his return to Paris, he

immediately developed an “emergency strategy” to accelerate the production of heat-treated factor concentrates, which were originally scheduled to come on stream as late as December 1985. Under this plan, heat-treated factor concentrates from Immuno and the Lille blood transfusion centre would begin as early as mid-July, and the first heat-treated lots of factor VIII concentrate manufactured by Immuno from plasma supplied by the Centre national de transfusion sanguine would be distributed on 30 August. However, the strategy also contemplated the use of all non-heat-treated factor concentrates before heat-treated factor concentrates were introduced. As an internal memorandum of the Centre national de transfusion sanguine stated, “[t]his [strategy] naturally assumes that the entire inventory of infectious products will be distributed before offering heat-treated products as an alternative.” On 7 May 1985, Dr Garretta wrote to Dr Netter to inform him of the potential contamination of domestic non-heat-treated factor concentrates and of his emergency strategy with respect to the introduction of heat-treated products. He expressed concern about delaying the implementation of heat treatment, stating that 50 per cent of French hemophiliacs were infected, that the annual increase in infection might be estimated at 10 to 20 per cent, and that a delay of three months in the production of heat-treated concentrates would in all likelihood cause the death of five to ten hemophiliacs. On 9 May 1985, Dr Garretta sent a similar letter to the Direction générale de la santé.

On 10 May 1985, Professor Roux sent a memorandum to the Minister of Health about the implementation and the cost of screening tests and heat treatment. With respect to heat treatment, he said that 50 per cent of the country’s 4,000 hemophiliacs were seropositive and that the annual increase in infection might be estimated at 10 to 20 per cent. He did not raise the issue of a transition period, the possibility of prohibiting the use of non-heat-treated factor concentrates, or of importing heat-treated factor concentrates. Professor Roux did not appeal to the Minister for a swift decision, but concluded the memorandum by stating that “[i]t will be up to the Minister of Health to take a position on the various measures listed above.” The same day, the Association française des hémophiles met to discuss the introduction of heat-treated factor concentrates and agreed on 1 October 1985 as the date for full conversion. Dr Allain was present at the meeting, but made no mention of the fact that lots of non-heat-treated factor concentrates from the Centre national de transfusion sanguine were likely contaminated.

On 14 May 1985, Dr Allain, Dr Habibi, and Dr Anne Marie Couroucé, the latter two physicians both with the Centre national de transfusion sanguine, met to discuss the preliminary *AIDS and Blood Transfusion* report prepared by the expert group. The group concluded that hemophiliacs were at high risk of contracting AIDS and made a number of important recommendations: when testing for AIDS was introduced, donated blood found to be HIV-antibody positive must not be used for therapy; large lots of plasma must be considered potential sources of infection and must be subjected to viral

inactivation methods such as heating; if one of the donors was later found to be infected, the factor concentrates made from his or her blood must be recalled immediately; use of factor concentrates currently being distributed could be allowed only if there was no possibility of replacing them with factor concentrates that were presumed to be non-infectious; and, during the transition period, measures must be devised urgently to make available factor concentrates prepared from seronegative donors or imported inactivated factor concentrates. The data showing the extent of contamination of lots from the Centre national de transfusion sanguine were discussed.

On 29 May 1985, a confidential meeting of officials from the Centre national de transfusion sanguine was held to determine the “attitude to adopt concerning LAV-positive [HIV-positive] donations identified during the validation phase of the [AIDS] test ... and their effect on manufactured blood products” – that is, whether to recall lots containing plasma found to be positive for the AIDS virus. During the meeting, the participants were told that “with two or three LAV-positive [HIV-positive] donors per thousand, a figure now confirmed, and pools of 1,000 litres derived from 4,000 to 5,000 donors, all our lots are contaminated.” Three possible courses of action were presented and discussed: complete recall (causing serious financial problems); replacement with imports (which might carry other risks of infection); or no recall (since heat-treated factor concentrates would soon be distributed). Dr Habibi presented the position of the group of experts that factor concentrates must be recalled whenever possible, and he also stated his own view, that physicians, not the Minister, should make this ethical decision. Dr Garretta, however, argued that there should be no recall of factor concentrates because all pools were by now contaminated, and he concluded that “it is up to the regulatory authorities to assume their responsibilities for this serious problem and perhaps prohibit us from distributing products, whatever the financial consequences.”

On 30 May 1985, Dr Habibi forwarded a copy of the experts’ report on *AIDS and Blood Transfusion* to the Minister of Health. The report said that “the probability is sufficient to consider that all lots are potentially infectious.” It recommended that large lots of plasma should be virally inactivated; that where a donor was shown to be infected after donating, all factor concentrates manufactured from that donor’s blood should be recalled; and that existing factor concentrates should be used only in circumstances in which it was impossible to replace them with non-infectious factor concentrates. It concluded that “since in all probability all lots were infected, a decision must be made to either recall and halt distribution, or refrain from any intervention.” A middle option was also offered – that of recalling only those lots which had been proven to be contaminated and had not yet been distributed. On the issue of recall, Dr Habibi called into question both the value of mounting an exchange at this “late date” and the availability and safety of imported replacement factor concentrates. He informed the Minister that since the experts were “unable to reach a unanimous decision” about the issue, the “problem

is thus placed before national health authorities." In contrast to the experts' preliminary report, the final report did not include statistics demonstrating the extent of the contamination and the potential risk of infection. Also absent was a recommendation that health authorities take immediate action, and any mention of a halt in the use of these products pending a possible decision to prohibit distribution.

On 3 June 1985, Dr Garretta wrote to Dr Netter, informing him that "the probability of not having contaminated lots is unfortunately very low" and that the "figures make plain that all the plasma pools we have used and are now using are liable to be contaminated with the LAV [HIV] virus." He added that persons in charge of the various divisions at the Centre national de transfusion sanguine had decided that raw material that had not yet been manufactured would be discarded, but that they would not "intervene" with respect to plasma units that had been used "whether in regard to stable products that have been distributed or in regard to clinical investigations." This was the first time that Dr Netter had been informed of the extent of the contamination, and he forwarded the letter to Professor Roux and the Secretary of State for Health on 14 June. The same day the extent of the potential contamination of the lots of domestic non-heat-treated factor concentrates was communicated to treating physicians in the Brittany-Loire region.

When the Comité national de l'hémophilie met on 19 June 1985, there was agreement that heat-treated factor concentrates should be used, that there should be a transition period of a few weeks when both heat-treated and non-heat-treated factor concentrates would be distributed, and that domestic or imported heat-treated factor concentrates should be distributed as soon as possible to HIV-negative hemophiliacs. According to the record of the meeting, there was no reference to the extent of contamination, nor any indication that hemophilia patients were aware of it. The same day, Dr Garretta asked the blood transfusion centre directors in his area to give some thought to their liability insurance policy in order to "adapt it to the increased risks."

The next day, a meeting of the Commission consultative de transfusion sanguine was held. Dr Garretta and Dr Allain were present, and Professor Roux and Dr Netter were represented by their deputies. Dr Garretta reported that the Comité national de l'hémophilie had agreed to accept a brief transitional period when both heat-treated and non-heat-treated factor concentrates would be distributed. He said that "the possibility of not having contaminated lots is very low," because of the frequency of two seropositive donors per 1,000 and lots consolidating the plasma of 5,000 donors, and that it was essential that seronegative hemophiliacs and young hemophiliacs be given heat-treated factor concentrates.

On 26 June 1985, Dr Garretta issued a memorandum to an official at the Centre national de transfusion sanguine outlining the policy with respect to heat-treated factor concentrates. He informed the Centre that during the transition period (until 1 October 1985) both non-heat-treated and heat-treated

factor concentrates would be given to patients. He stated that “distribution of non-heat-treated products remains the standard procedure as long as they are in stock,” and that with the exception of patients with “LAV-negative [HIV-negative] serology,” heat-treated factor concentrates would be distributed “systematically after stocks of non-heat-treated factor concentrates are used up.” On 3 July Dr Habibi, the official at the Centre responsible for the distribution of blood products, also issued a memorandum clarifying Dr Garretta’s instructions about the use of non-heat-treated and heat-treated stock. This memorandum read as follows:

For patients known to be LAV-positive [HIV positive], non-heat-treated concentrates must be used until inventories are exhausted ... As a cautionary measure and except in special cases, the amount of heat-treated factor concentrates delivered must not exceed the volume required for one month of treatment. [Translation.]

Later that month, an order was signed by an executive assistant of the Minister for Social Affairs and National Solidarity and the Secretary of State Responsible for Health establishing 1 October 1985 as the final date on which health insurance agencies would reimburse the cost of non-heat-treated factor concentrates.

The distribution of contaminated stock continued throughout the summer and early autumn of 1985. A Centre national de transfusion sanguine internal memorandum about non-heat-treated stock, dated 23 August stated: “[T]ry to distribute [it] to LAV-positive [HIV-positive] hemophiliacs, through Orsay and Saint Antoine.” In a letter sent to Professor Roux dated 24 September, Dr Garretta expressed regret that the use of non-heat-treated factor concentrates had diminished much faster than he had expected. Attached to the letter was a document summarizing the distribution of non-heat-treated factor concentrates. It showed that although most of the concentrates in question had been distributed by 5 August, distribution continued until 15 September. However, the Cour d’appel de Paris found that non-heat-treated factor concentrates were distributed to some blood transfusion centres after 1 October 1985, the date of full conversion to heat-treated factor concentrates.

Although several persons protested against the use of these contaminated factor concentrates and made efforts to halt distribution, no one was successful in dissuading Dr Garretta from distributing the supplies of non-heat-treated factor concentrates. Dr Allain stated that he had had many disputes with Dr Garretta about the distribution of non-heat-treated factor concentrates, and that, after January 1985, he had repeatedly urged Dr Garretta to heat treat factor concentrates. On 16 January he wrote a letter to both Dr Garretta and Professor Jacques Ruffié, the chair of the board of directors of the Centre national de transfusion sanguine. In his letter, he stated that 47 per cent of hemophiliacs were infected, and he urged them to conclude negotiations

with Immuno for the transfer of heat treatment technology. He also said that any delay would lead to the need to import huge quantities, and he told Dr Garretta that “the Centre national de transfusion sanguine bears a heavy responsibility for hemophiliacs, their physicians and the Ministry of Health in the prevention of this fatal disease.” Dr Helen Lee, the head of the laboratory at the Centre, also testified that “he [Dr Allain] wanted to work from the inside to change things and that he had had many violent confrontations with management on this subject.”

At a meeting attended by blood transfusion specialists in April 1985, Dr Lee was reprimanded for publicly questioning the policy to distribute non-heat-treated lots. She had protested that if factor VIII concentrate was not heat treated, or if heat-treated factor concentrates were not imported, twenty to fifty people would be at risk each month.

A number of treating physicians also objected to the policy of distributing potentially contaminated stock. On 27 June 1985 Professor Ducos wrote to Professor Roux:

I am very concerned about the situation in which we find ourselves. We know that every day we are injecting blood products from LAV-positive [HIV-positive] donors which will cause seroconversion in the recipient, who may in turn infect his family. For how many cases of AIDS will we be responsible in this way? [Translation.]

In July, Professor Ducos received a letter from another physician, Professor Bernard Boneu of the Toulouse blood transfusion centre, who found the practice of continuing to administer non-heat-treated factor concentrates unacceptable. Professor Boneu objected to the division of hemophiliacs into two groups and the delay in implementing the use of heat-treated factor concentrates caused by the rejection of imports. In his letter, he stated:

My professional conscience dictates that as of today we must prohibit the distribution of non-heat-treated products to all hemophiliacs, even if this means importing large amounts of heat-treated products as an interim measure for one or two months for hemophiliacs until the French transfusion network is self-sufficient. I ask you to pass this letter on to the competent authorities so that the distribution of non-heat-treated products is stopped immediately and they are replaced by heat-treated products manufactured in France or abroad. [Translation.]

By way of summary, in late 1984, French physicians began to request heat-treated factor concentrates for their patients, but, despite repeated requests to Dr Allain, they were able to obtain imported heat-treated factor VIII concentrate for only a few hemophiliacs – those who were participating in clinical trials. The recommendation of the Comité national de l'hémophilie made in

June 1985 that heat-treated factor concentrates be given to hemophiliacs who were not yet infected was not strictly followed since most hemophiliacs were not aware of their status until the fall of 1985. The Centre national de transfusion sanguine continued to produce non-heat-treated factor concentrates until May 1985. The first lots of heat-treated factor IX concentrate were distributed on 27 June 1985, but the first lots of heat-treated factor VIII concentrate were not distributed until mid-September. By 1 October the conversion to heat-treated factor concentrates had been completed.

To decide when it was reasonable for officials of the Centre national de transfusion sanguine to introduce heat-treated factor concentrates, both the Tribunal de grande instance de Paris and the Cour d'appel de Paris reviewed what was known about heat treatment through the years 1983 to 1985 and what efforts were made to apply that knowledge. They determined that, in 1983, when heating as a means of inactivating viruses in blood products was introduced, there was a healthy scepticism about the safety and efficacy of the process, but that "in late 1984 a pragmatic approach recommended using heat-treated concentrates even though some scientific doubt might still persist." They also held that any lingering doubt about the effectiveness of heat treatment should have been eradicated by domestic seroprevalence studies completed during this period.

The Tribunal de grande instance de Paris examined whether conversion by the Centre national de transfusion sanguine to heat-treated factor concentrates could have been accomplished sooner, and whether, in fact, the wait for the Centre's own heat-treated factor concentrates had been necessary at all, given the availability of foreign heat-treated factor concentrates. It found that the Centre national de transfusion sanguine had been given the opportunity to acquire heat treatment technology from the Lille blood transfusion centre, but had failed to do so. As for imported factor concentrates, although the Lucas Report raised the possibility that foreign heat-treated factor concentrates might have been in short supply, the court was unable to find any documentary evidence to support such a contention. It concluded that "the Centre national de transfusion sanguine was never faced with a refusal to export because of shortage by any foreign firm."

The courts' assessment of the role of the accused in the distribution of non-heat-treated factor concentrates known to be contaminated appears below in the section entitled "The courts."

Removing products from the market

As discussed above, in late May 1985 the decision whether to recall potentially contaminated factor concentrates manufactured by the Centre national de transfusion sanguine was placed before the regulatory authorities. In the absence of any decision on their part, the Centre continued to distribute these products until the stock was depleted. On 2 October 1985, one day after the conversion to use of heat-treated factor concentrates, Professor Roux ordered

the return of all non-heat-treated factor concentrates from blood transfusion centres. However, withdrawals of non-heat-treated factor concentrates were undertaken by the blood transfusion centres in Rouen and Lille well before this date.

The trial court found that as Director General of Health, Professor Roux “had a duty and the authority to intervene” as soon as he was aware that the products delivered by the Centre national de transfusion sanguine were potentially contaminated, but did not do so. Professor Roux testified that he did not have the legal means to demand a recall, and, moreover, that it was the responsibility of the Centre to withdraw hazardous products from sale. The court stated that Professor Roux could have written to Dr Garretta, reminding him of his duty to recall products and requesting him to halt distribution of the non-heat-treated products. The Cour d’appel de Paris affirmed this decision, stating that Professor Roux should have issued a circular warning hospitals, physicians, and hemophilia patients of the risks posed by the contaminated products, and that he should have prohibited their use. However, it held that Dr Garretta, too, was responsible for the continued distribution of the contaminated factor concentrates, and stated that he had “an obligation to halt immediately and definitively the distribution of products which he knew to be contaminated ... even if this meant replacing them with imported heat-treated products.”

Surrogate testing for AIDS

No surrogate testing for AIDS was undertaken in France.

Screening blood donations: HIV testing

In February 1983, Dr Montagnier and his team at the Institut Pasteur cultured cells from a lymph gland taken from a patient with AIDS and, from this culture, they isolated a retrovirus that they called the lymphadenopathy-associated virus, or LAV. The virus was isolated from two French hemophiliacs in June 1983 and, by the autumn, Dr Montagnier was able to demonstrate that this virus was indeed the cause of AIDS. This discovery was published in *Science* in April 1984. In May, Dr Robert Gallo of the National Cancer Institute in the United States also published the results of his research on HTLV-III in *Science*, and his findings were consistent with those of Dr Montagnier. Both LAV and HTLV-III were later found to be the same virus and were renamed HIV.

In August 1983, Dr Montagnier submitted a request to the Prime Minister for a grant to build a laboratory for handling the virus and developing test kits. This application was approved in January 1984 and the laboratory became operational in June of that year. On 28 February 1985, the Institut Pasteur submitted an application to the Laboratoire national de la santé for approval of its test kit.

The Institut Pasteur was not alone in seeking to have its test kit licensed in France. On 11 February 1985, the U.S. corporation Abbott Laboratories Ltd. (Abbott) also applied to have its HIV test kit licensed by the Laboratoire national de la santé, but encountered several obstacles in obtaining approval. In March 1985, Dr Netter informed Professor Roux that the Abbott submission was “incomplete” and demanded that it be deferred. Professor Roux, in turn, informed Abbott of this fact and, on 25 April, Abbott submitted the necessary information. Dr Netter then wrote to the Minister of Health and suggested that approval be deferred until the Pasteur test was approved. Dr Netter stated: “[I]t is not possible under current circumstances to postpone this approval much longer without risking a referral to the Council of State for abuse of power ... I intend to grant Institut Pasteur its approval immediately, and to postpone Abbott’s until 13 May 1985.”

On 30 April 1985, Professor François Gros, the scientific adviser to the Prime Minister, wrote a memorandum stating that the approval of the Abbott test could be delayed for some time. Professor Gros then held a meeting of Cabinet advisers on 9 May 1985, when it was decided that the Abbott registration file should be delayed at the Laboratoire national de la santé until the Pasteur test was approved. This delay would ensure that the Institut Pasteur received at least 35 per cent of the national market.

On 9 May 1985, Dr Garretta alerted the Minister of Health to the need to implement a screening test quickly for HIV antibody, the cost of which would have to be met through special financing. At the request of the Commission consultative de transfusion sanguine, a report was produced in May 1985 canvassing “all the problems that AIDS creates for the blood transfusion organization, screening tests, factor concentrates preparation and so forth.”

On 19 June 1985, the Prime Minister announced in the National Assembly that systematic blood donor testing would begin on 1 August at a cost of Fr 200 million. On 21 June, the Pasteur test was licensed by the Laboratoire national de la santé.

On 3 July 1985, Professor Gros wrote to Louis Schweitzer, the Prime Minister’s chief of staff, stating that the Laboratoire national de la santé would not be able to delay for much longer the approval of the U.S. blood test, and that after its approval it would flood the French market. On 23 July a ministerial order was issued, stating that blood donor testing would be compulsory on 1 August. The next day, 24 July, the Laboratoire national de la santé approved the Abbott test for use in France.

In July 1985, the Minister of Health met with a group of experts to make recommendations about implementing blood donor testing, and in particular the method of informing seropositive blood donors of their status. These experts concluded that donors must be told of their status, for the following reasons: donors might have implicitly requested the information; the disease was transmissible; and infected persons could benefit from early detection and treatment. They recommended that all donors found to have an irregularity

through the systematic screening process be sent a letter advising them of the situation and requesting them to make an appointment with a physician at the transfusion centre or to submit the name of a physician to whom the centre could forward the test results. Pursuant to an order enacted 23 July 1985, HIV testing was implemented at all blood transfusion centres beginning on 1 August 1985.

In October 1985, the blood transfusion centres received a circular from the Direction générale de la santé that gave guidance for testing procedures and for informing persons found to be seropositive. In July 1987, legislation was enacted requiring every département to designate at least one consultation centre as an alternative test site for anonymous diagnostic testing at no cost.

In his investigations, Mr Lucas found evidence that ministers and officials had deliberately attempted to delay the approval of the Abbott test kit pending the approval of the Pasteur test, and, on 11 November 1991, President François Mitterrand publicly conceded that “[t]here was a certain delay in the decision-making.” Because the matter did not relate to the charges before them, the Tribunal de grande instance de Paris and the Cour d’appel de Paris did not deal extensively with the issue of AIDS testing. Nevertheless, evidence of an attempt to delay registration of the Abbott test was put before the courts. The Tribunal de grande instance de Paris held that Dr Netter had received orders to delay registration of the tests, and “could and should have opposed any delay in putting screening tests on the market.” The delay in implementing HIV testing has since been the subject of further investigation. (See the section “Later investigations” below.)

Informing hemophiliacs of the risk

On 18 November 1982, Professor Soulier, then the director of the Centre national de transfusion sanguine, wrote an open letter to members of the Association française des hémophiles warning them about the use of American blood products. He stated that “[m]ysterious viral diseases are liable to be transmitted in fractions derived from plasma taken from paid donors” because remuneration served to attract the “poorest classes in the population.” He advised the Association that “French hemophiliacs would perhaps do well to tone down a little their enthusiasm for imported factor concentrates made with plasma from paid donors, which expose them to the transmission of viral agents more than other products do.”

In late 1982 and the early months of 1983, Dr Netter expressed concern about hemophiliacs’ preference for the use of factor concentrates over cryoprecipitate. The minutes of the meeting of the Commission consultative de transfusion sanguine in March 1983 show that the ratio of cryoprecipitate use to factor concentrates use had reversed in favour of factor concentrates, so much so that distribution in 1983 was expected to be 75 per cent factor concentrates and 25 per cent cryoprecipitate. In May 1983, Dr Netter sent a report to Professor Roux that stated that because of the risk of AIDS, the Association française des hémophiles and physicians treating hemophiliacs must be convinced that

“reducing the potential risk should take precedence over comfort,” and that they should be encouraged to reduce the use of imported concentrates. He added that discontinuing imports of blood products was being contemplated.

At the general meeting of the Association française des hémophiles in early June 1983, it was reported that only Professor Soulier and a few of his Belgian colleagues called for a reduction of imports and an increase in the use of cryoprecipitate, an idea that was met with resistance by hemophiliacs, who regarded it as a “step backwards.” The Association passed a motion in favour of the continued use of concentrates that stated:

Assessed objectively, the potential risk of AIDS is not such as to change present substitutive therapeutics or the corresponding methods of obtaining supplies. Consequently, we believe it to be necessary to continue importing, which could not be interrupted or significantly reduced in present circumstances without serious consequences. [Translation.]

The motion was published in the edition of the *Revue de l'hémophilie* of September 1983.

In the autumn of 1983, Professor Soulier attempted to alert the medical community to the risks of AIDS. In an article published in the *Revue française de transfusion et immuno-hématologie*, he stated that the mortality rate for AIDS in the United States approached 100 per cent; that a recent study (the preliminary phase of the Cochin study) had revealed that four out of every 1,000 Parisian donors were at risk for the disease; and that the use of volunteer donors was no assurance of safety, given the large pool sizes.

On 11 October 1984, the president of the Association française des hémophiles made the following public statement: “We should continue to place strong trust in our physicians and in the products they prescribe ... there is no miracle product in other countries.”

As early as September 1983, Dr Allain and a team of investigators began a seroprevalence study of 405 hemophiliacs. They completed their research into the effects of different heat-treated and non-heat-treated factor concentrates in March 1984, though their findings were not published in *The Lancet* until February 1985.

On 13 March 1984, the Centre national de transfusion sanguine sponsored a scientific conference at which Dr Couroucé reported that there was a “high incidence” of HIV antibody among 133 hemophiliacs tested at the Institut Pasteur. These results, however, were neither published nor made known to the Ministry of Health or the Association française des hémophiles.

In September 1984, the results of a study of seropositivity among 245 hemophiliacs conducted by Dr Couroucé and Dr Rouzioux, a virologist at the Claude Bernard Hospital in Paris, were released. The study demonstrated that seropositivity levels increased with the frequency of treatment and that French factor concentrates caused HIV infection.

During the autumn of 1984, Dr Allain released the results of his seroprevalence investigation to a meeting of the AIDS Hemophilia French Study Group he coordinated. His study revealed that of 405 hemophiliacs tested, 45 per cent were seropositive, and 35 per cent of those treated with French concentrates had seroconverted. Dr Allain also found that eighteen hemophiliacs treated solely with Hemofil-T did not seroconvert. Dr Garretta was immediately informed of these results. Dr Allain stated that he called a meeting of the physicians in attendance to ask whether they should inform patients about the treatment risks, but the physicians decided against informing patients because the tests were still in the “experimental stage” and not “definitive.” The results of Dr Allain’s study were known by or made known to only the twenty-seven participants at the meeting, a group that included the directors of major hemophilia and transfusion centres in France, immunologists, virologists, and Dr Montagnier. The results were also sent to the Centre national de transfusion sanguine. On 19 December 1984, the results of the AIDS Hemophilia French Study Group were presented to a meeting of the Ministère de l’Industrie et de la Recherche and at the Atlanta AIDS conference. In March 1985, the AIDS Hemophilia French Study Group reported that 48 per cent of 1,670 patients were seropositive.

In April 1985, the seroprevalence study undertaken by Dr Couroucé and Dr Rouzioux was published in the *Annals of Internal Medicine*. On 9 May 1985, Dr Garretta wrote to the Direction générale de la santé, stating that “the frequency of LAV [HIV] antibodies indicating the presence of the virus is about 50 per cent in the 4,000 French hemophiliacs receiving multiple transfusions.”

It is apparent that, by the spring of 1985, many officials in the blood system were well aware of the infection rate among hemophiliacs. However, it was not until the summer of 1985 that French hemophiliacs began to learn about the rate of infection among their ranks. On 1 June 1985, at the conference of the Association française des hémophiles, a rumour circulated that four-fifths of hemophiliacs were seropositive. The ensuing panic led treating physicians to decide to inform patients individually of their HIV status, though patients were not informed until September 1985 or later. At the conference, although treating physicians also made a recommendation that all hemophiliacs and their sexual partners be tested for the AIDS virus, they stated that “[t]he treating physician remains the sole judge of whether or not to reveal to those concerned the results of the screening tests and how to take preventive measures.” Dr Allain disseminated this recommendation in favour of testing among his colleagues on 4 June 1985, but no mention was made at the conference of the extent of the contamination of factor concentrate produced by the Centre national de transfusion sanguine.

On 25 June 1985, a letter was circulated to all members of the Association française des hémophiles stating that French factor concentrates were potentially contaminated; that blood tests were available; that hemophiliacs should

be tested; that those who were seropositive should take precautions, specifically with relation to sexual contacts; and that those who were seronegative should use heat-treated factor concentrates. By September 1985, most hemophiliacs had been tested, and in October the results of the AIDS Hemophilia French Study Group were published in *Blood*. It was only then that the executive of the Association française des hémophiles learned that the domestic lots were contaminated. It alerted the media and called for a ban on the use of non-heat-treated factor concentrates.

In reviewing the use of factor concentrates by hemophilia patients, the Tribunal de grande instance de Paris found that, although a number of specialists had advocated limiting the consumption of these products, few treating physicians adopted this practice. The court determined that Professor Soulier's letter of November 1982 showed that the Association française des hémophiles had been informed of the risk associated with the use of imported factor concentrates, and that hemophiliacs were reluctant to revert to the use of other products because they considered them "a step backwards."

As for the disturbing results of the Cochin study, the court found that Professor Roux had been notified of the risk of mass contamination and of the risk to hemophiliacs. The court also stated that when he sent a copy of the Cochin study to the Minister of Health, Professor Roux should have included a memorandum emphasizing the urgent nature of the problem and proposing a solution. The court held that the failure to do so was "one of the elements that points to his criminal responsibility."

The courts also examined whether hemophiliacs were ever told that the factor VIII concentrate they were using might be contaminated. At trial, Dr Garretta had maintained that physicians, the entire scientific community, and hemophiliacs knew that domestic non-heat-treated factor concentrates were contaminated. The Tribunal de grande instance de Paris concluded, however, that although some physicians and scientists were aware of the risk of transmitting AIDS through blood products, only a very small group of people with inside information, mainly in Paris, knew of the high rate of infection among the hemophiliac population and the extent of the contamination of lots from the Centre national de transfusion sanguine. The Cour d'appel de Paris held that Dr Garretta had a duty to inform hemophiliacs and their physicians immediately of the danger associated with the use of these products, and that he should have issued a news release to this effect.

The courts also found that, as a direct result of their lack of knowledge, hemophilia patients did not question the policy formulated by the Centre national de transfusion sanguine until the autumn of 1985. Until that time, the members of the Association française des hémophiles were never clearly informed about the extent of the contamination of lots of factor concentrate produced by the Centre national de transfusion sanguine and were kept ignorant of the rate of infection among their ranks. The Tribunal de grande instance

de Paris stated, “not only did patients not know the true extent of the risks they were running, but their association put forward proposals rooted in industrial or commercial concerns completely extraneous to their interests.”

Informing transfusion recipients of the risk

In September 1992, the Secretary of State for Health issued a circular recommending that all patients who had undergone a transfusion be tested for the AIDS virus. In December 1992, a second circular was issued, requesting health establishments to take all necessary measures to identify patients who had received blood transfusions between 1980 and 1985, and in March 1993, another circular was issued to address some of the practical difficulties in locating these persons. As of December 1992, it was estimated that almost 50 per cent of transfused patients had not yet been tested for the AIDS virus.

The courts

The Tribunal de grande instance de Paris

The Tribunal de grande instance de Paris rendered its decision on 23 October 1992. It concluded that the four accused had failed to prevent the infection of hemophiliacs caused by the distribution of potentially contaminated factor concentrates, but found only three of the accused guilty of the offences as charged. With respect to the charges of fraud against Dr Garretta and Dr Allain, the court held that “the deliberate nature of the actions of Dr Garretta and Dr Allain and their intent to deceive the victims is amply demonstrated by the investigation [evidence].” It stated:

Both accused, to an equivalent degree, were personally aware before the period of the charge that the products distributed by the CNTS [Centre national de transfusion sanguine] were seriously infectious ... By their silence, their reluctance to give out information and even their manoeuvres in the sense of behaviour and attitudes, they consistently pursued one goal: to mislead hemophiliacs, to “deceive” them until “the inventory was used up.” [Translation.]

The court found that, “as physicians, they had greater power to deceive, and they disregarded a basic rule of the ethics which forbade them to cause patients to run an unwarranted risk which was entirely avoidable from the start of the period of the charge.” It also concluded that Dr Garretta was “the inspiration and chief architect of this policy” and stated:

Garretta exercised his prerogatives as Director to the full and cannot claim to have been impeded in his duties in any way. He used the powers vested in him or assumed by him as adviser to the public authorities to place the interests of the CNTS before those of patients and of the blood transfusion organization in general. He ignored, thrust aside or short-circuited

opponents to his policy — Prof. Ruffié, Prof. Roux, Dr Allain and some prescribing physicians. Ultimately, taking advantage of the fact that many others were silent, negligent or indifferent or consciously refused to act, by his action he amplified a needless tragedy. [Translation.]

Although the court granted Dr Allain “the benefit of mitigating circumstances, since he was acting as a clearly subordinate official,” it was critical of his failure to oppose Dr Garretta:

Dr Allain, in addition to his responsibilities as a prescribing physician, was especially well informed because of his research within the CNTS. He collaborated actively in the policy laid down by Dr Garretta ... Dr Allain remained totally faithful to the action initiated by Dr Garretta. In his capacity as an expert on hemophilia and as a prescribing physician trusted by his patients, he not only supported but substantiated the lie in their minds. He knew better than anyone the danger of the policy that he not only allowed to continue but actually gave decisive public support to. [Translation.]

In finding Professor Roux guilty of the charge of deliberately failing “to prevent either an action identified as a crime or an offence against the physical well-being of a person” pursuant to section 63(1) of the *Penal Code*, the court found that Dr Brunet’s note to Professor Roux in March 1985 was proof that Professor Roux was aware of the extent of contamination of the Centre’s factor concentrates and of the risk posed to hemophiliacs. It held that Professor Roux’s subsequent memorandum to the Minister on the subject should have been accompanied by a note, stressing the emergency and proposing a solution. It made the following assessment:

Prof. Roux, Director General of Health, the tutelary authority for transfusion, and a member of the CNTS board of directors, manifestly refrained from exercising this power to prevent Dr Garretta from acting as he did ... Prof. Roux’s knowledge of the specific risk represented by the products distributed by the CNTS has been amply demonstrated. He obtained that knowledge early and it is well documented ... The Director General of Health had considerable latitude to ward off that danger or attempt to do so ... We are in fact dealing with deliberate abstention and refusal to act on the part of someone who was fully aware of the issues and knew perfectly well that an offence was being committed. He had the means of preventing or trying to block it without any risk to himself. His refusal to act clearly results from a combination of the early and accurate information received by him on the one hand and on the other, the extent and diversity of actions open to him and even, in view of his public duties, incumbent on him, as

regards both the Ministerial offices and the blood transfusion network in general and the CNTS in particular. The law does not require that the abstention be motivated by malice or forethought. It is not concerned with motive ... It is enough to observe that in this case, Prof. Roux's failure to act in the duties devolving on him at the time of the charge, in view of the information and means available to him can only be analyzed as a conscious and deliberate refusal to act to try to prevent the obvious committing of an offence. [Translation.]

The court acquitted Dr Netter of the same charge because of the efforts he had made to alert his superiors:

While the Court has explored the reasons which led it to consider that this text [charge] is applicable to Prof. Roux, the situation is very different for Dr Netter. To be sure, Dr Netter could have done more and better: undoubtedly intervening "downstream" with the CNTS, although the forms of such intervention remained somewhat imprecise. Neither do we see much involvement on the part of his subordinate and representative, Dr Chippaux, even though he attended the two successive meetings of the Comité and the Commission of 19 and 20 June 1985. The fact remains that Dr Netter did act "upstream" and within a reasonable period informed both the Director General of Health and adviser to the Minister, both of whom undoubtedly had the means to react. Finally, as regards means, and although the argument is more one of fairness than of law, we must acknowledge that the means available to Dr Netter were definitely not commensurate with the mission attributed by the law to the service he headed ... In conclusion, while we must acknowledge that a malfunction of service has been established and that the LNS [Laboratoire national de la santé] did not fulfil its role, or not adequately, we cannot, on the other hand, assert that there is sufficient evidence that Dr Netter deliberately refrained from preventing the commission of offences by Dr Garretta and Dr Allain or from providing or obtaining assistance to a person in danger. [Translation.]

The court sentenced Dr Garretta to imprisonment for four years for failing to alert his superiors. Dr Allain was sentenced to imprisonment for four years, with a two-year suspended sentence, for failure to promote heat treatment and for failure to warn hemophiliacs in May 1985. Professor Roux was given a four-year suspended sentence for failing to challenge Dr Garretta and to warn his superiors. The charge of manslaughter against Dr Garretta was dismissed. With respect to damages, the court ordered damages for "moral injury," ranging from Fr 10,000 to Fr 300,000, holding the Centre national de transfusion sanguine, Dr Garretta, and Dr Allain jointly responsible for payment.

The Cour d'appel de Paris

The decision of the Tribunal de grande instance de Paris was appealed to the Cour d'appel de Paris. In July 1993, the court affirmed the judgment against Dr Garretta and Dr Allain, but reduced Professor Roux's suspended sentence from four years to three, and gave Dr Netter a suspended sentence of one year.

Although Dr Allain was released from prison in August 1994 and Dr Garretta in May 1995, both remained at the centre of the controversy for some time afterward. In June 1994, public prosecutor Jean Perfetti requested the court to order criminal retrials of Dr Garretta and Dr Allain. In August, the Cour de cassation ruled that it would not quash the earlier judgment, but left the door open for laying separate charges of poisoning, a ruling to which the Paris Bar Association objected on the basis that the matter had already been adjudicated. On 7 August 1994, Dr Garretta and Dr Allain were placed under investigation with respect to possible charges of poisoning. Dr Garretta subsequently attempted to have these charges withdrawn, arguing that there was no intent to poison; the Cour d'appel de Paris denied his request because the question of intent was in fact the subject of the investigation that could lead to a new trial.

Later investigations

The trial of the four officials did not end "l'affaire du sang contaminé." Although the trial served to publicize the circumstances surrounding the distribution of contaminated factor concentrates, it also raised issues about the role of the government itself, thereby opening the door to further litigation. During the trial, it was suggested that HIV testing might have been unnecessarily delayed because of an interest in ensuring that the French test, developed by the Institut Pasteur, was given preference in the French market over the rival test manufactured by Abbott. The court learned that although Abbott applied for regulatory approval several weeks before the Institut Pasteur, as a result of a decision by ministers to delay registration of the Abbott test, the Pasteur test was approved first, on 21 June 1985, and the Abbott test received approval one month later, on 24 July 1985. Because the testing issue did not directly involve the actions of the accused, it was not dealt with extensively at the earlier trial, but the nature of the evidence was such that it led to public complaints about ministerial accountability. In the trial judgment, the court observed that "the actions of the accused ... necessarily take place within a framework strongly influenced and sometimes determined by politics," but stated that it could pass judgment only on the criminal responsibility of those accused. A remark by a former minister that she may be "responsible, but not guilty," also caused debate about the nature of ministerial accountability.

To make ministers legally accountable, the National Assembly amended the constitution in July 1993 not only to permit charges against current and former ministers but to create a court expressly for that purpose, the Cour de

justice de la République. Charges were then laid against ministers and their advisers. In January 1994, Ludovic Bouchet, a hemophiliac, brought poisoning charges against the former Minister of Health, Edmond Hervé, the former Minister of Social Affairs, Georgina Dufoix, and the former Prime Minister, Laurent Fabius. In September 1994, these former ministers were charged with conspiracy to poison by delaying approval of testing from May to July 1985. By the spring of 1995, the French government had widened the scope of its investigation and had laid charges against a number of ministerial advisers and health officials involved in the decisions about the introduction of testing. In March 1997, the prosecutor general of the Cour de justice de la République concluded his investigation into the conduct of former ministers. He recommended that the charges against former ministers be withdrawn, stating in his report that there was insufficient evidence to substantiate charges of "complicity in poisoning." The Cour de justice de la République, however, announced that it had received new documentary evidence and that it would need to examine the evidence before making a decision about the prosecutor's recommendation. As of the date of writing, the matter continues to be investigated by the court.

Assistance to persons infected and affected

In early 1987, the Association française des hémophiles asked the Minister of Health to establish a special fund to assist hemophiliacs with HIV or AIDS and their infected family members. At the time, the government took the position that it had no legal obligation to give compensation to persons infected through contaminated blood and blood products. However, in December 1987, a report issued by the Parliamentary Commission for Cultural, Family and Social Affairs (Hannoun Report) recommended that compensation be given to persons infected through blood transfusions. As a result, in November 1988, the Ministry of Health and the Ministry of Social Welfare agreed to give financial assistance. A public fund was approved by the government in April 1989. Lump-sum payments were made ranging from Fr 30,000 to Fr 170,000 (Can\$5,600 to \$31,800), depending on an individual's loss of income and familial responsibilities. The fund made no provision for persons with asymptomatic HIV infection.

In July 1989, an agreement was finalized between the Association pour le développement de la transfusion sanguine, the Association française des hémophiles, and the representatives of the insurance companies that were involved. It provided for the creation of two funds. The first, the Public Solidarity Fund, was established in July 1989 to make lump-sum payments to hemophiliac patients with AIDS and to surviving families of deceased hemophiliacs, and was financed by the state. For hemophiliac patients with asymptomatic HIV infection whose HIV-antibody seropositivity had been diagnosed before 31 December 1989, HIV-infected spouses with clinically overt AIDS, and surviving spouses and children, a Private Solidarity Fund

was established in August 1989, financed by insurance companies. Grants were also made to patients with hemophilia who were living in France and who had been treated over long periods with blood coagulation factor concentrates from the Centre national de transfusion sanguine.

The Public Solidarity Fund was governed by a committee composed of officials from the government, various AIDS organizations, and the Association française des hémophiles. The amounts of money it paid varied from Fr 30,000 (Can\$5,418) to Fr 170,000 (Can\$30,702), depending on the severity of illness, the age of the patient, the loss of income, and familial responsibilities. The Private Solidarity Fund was administered by a foundation with representatives of the blood transfusion service, insurance companies, and the Association française des hémophiles. This fund also made lump-sum payments. Hemophiliacs with asymptomatic HIV infection received Fr 100,000 (Can\$18,700); infected spouses with overt AIDS the same amount; and surviving spouses and children as much as Fr 250,000 (Can\$46,800), depending on family status. Additional lump-sum payments were made in case of death. Widows received Fr 170,000 (Can\$31,800), and each child Fr 40,000 (Can\$ 7,500). Recipients of these payments were required to sign a "letter of agreement" stating that they would not bring any civil actions against blood transfusion services or their insurance companies. Payments from both solidarity funds were tax exempt and were disregarded when assessing eligibility for public welfare benefits.

The financial assistance provided by the solidarity funds proved inadequate to cover the expenses of hemophilia patients with HIV or AIDS and the needs of wives and children of very ill or deceased patients. The Association française des hémophiles lobbied the government for a more comprehensive compensation plan. In December 1989, at the time the first payments were being made from the solidarity funds, the Association française des hémophiles wrote to its members to warn them that a four-year deadline to bring civil actions against the Ministry of Health was approaching. (Since most hemophiliacs learned about their infection in 1985, the deadline was December 1989.) As of December 1989, more than six hundred infected hemophiliacs wrote to the Ministry of Health and requested compensation. The Ministry refused to give any compensation. The Association française des hémophiles then advised its members with HIV or AIDS to make claims for compensation in administrative courts, and more than three hundred HIV-infected patients with hemophilia did so. In December 1991, the first judgment by an administrative court imposed liability on the state and held the state responsible for all infections occurring after 14 March 1985.

In April 1990, a proposal for a compensation law was submitted to the National Assembly. At the time, approximately seven thousand persons were infected from blood and blood products, some twelve hundred of

whom had hemophilia. In April 1991, the revelation that the Centre national de transfusion sanguine had knowingly distributed potentially contaminated blood products did much to accelerate passage of this legislation. During a meeting with the Association française des hémophiles that spring, President Mitterrand announced that a compensation scheme would be established, and, indeed, legislation to do so was soon introduced.

On 31 December 1991, the legislation was enacted by the National Assembly. The legislation provided for the creation of a compensation fund for persons who had become HIV infected through the use of blood or blood products before 1 January 1990. This new fund, which replaced the earlier solidarity funds, was established early in 1992 with a grant of Fr 100 million (Can\$22 million).

The compensation legislation was supplemented by a Décret d'application (regulation) on 26 February 1992. Under this decree, the compensation fund was created as an independent agency, chaired by a senior judge and financed by government grants, with contributions to be made by insurance companies. A Compensation Commission was set up to rule on eligibility and the amount of the awards, assisted by a council of consultants. The council included representatives of victims' associations, legal experts, and the French government. Both agencies were created in March 1992, and by the end of 1992 all applications made by patients with hemophilia had been reviewed. To qualify for compensation, HIV-infected persons were required to submit their applications, together with medically certified proof that they were HIV infected and that they had received a transfusion of whole blood or blood products.

Payments from the new fund were also made by lump sum, depending on a patient's age, family status, and number of dependants. The awards were intended to compensate for pain and suffering from HIV infection and AIDS. The Compensation Commission fixed the maximum total payment to an individual at Fr 2 million (Can\$441,400) for adults. It established that payments be made in four instalments (25 per cent upon acceptance of the compensation offer; 25 per cent in each of the next two years; and 25 per cent at the onset of AIDS), but at the request of the Association française des hémophiles it permitted the option of receiving payment in a lump sum. For hemophiliac children, the Compensation Commission proposed to convert the maximum sum of Fr 2 million into a life pension that would be payable to the age of eighteen years. All payments were tax exempt, although any interest derived from this money had to be declared. Persons who accepted the compensation were not precluded from bringing civil actions.

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Germany

The blood system in the 1980s

The former Federal Republic of Germany (West Germany) had a mixed, decentralized blood system. Blood and plasma were collected by the German Red Cross blood banks, local public blood transfusion services, and blood banks operated by manufacturers of plasma derivatives. Although donations were made on a voluntary basis, some plasmapheresis centres paid donors a token amount to compensate them for the time they took to donate. Germany, however, was not self-sufficient in blood products. In recent years, the blood system has not changed significantly, although much has been done to decrease reliance on imported blood products and to improve blood safety.

The German Red Cross

The German Red Cross Blood Donation Service (Deutsche Rot Kreuz Blutspendedienst) (Red Cross) began in Düsseldorf as a small organization in 1952. Since then, it has developed into a wide network of modern centres, producing 75 per cent of the blood and blood components used in Germany. Today the network comprises twelve Red Cross centres, with forty blood banks, including twenty-two in the former West Germany and seventeen in the former German Democratic Republic (East Germany). It has a staff of 4,000, in addition to approximately 200,000 volunteers who work for the local associations to advertise and prepare blood donation drives. After the reunification of Germany, the Red Cross also extended in 1991 into the new federal states (Länder) of the German federation.

According to the World Federation of Hemophilia, Germany is self-sufficient in red blood cells only. The supply of plasma falls short of the country's needs by approximately 60 to 70 per cent and must be supplemented by imports (90 per cent of which come from the United States). Of the 30 to 40 per cent of the plasma that is produced domestically, donations of whole blood are the source of 80 per cent, and the remaining 20 per cent is obtained through plasmapheresis. In recent years, Germany has produced only 30 to 45 per cent of the domestic need for factor VIII concentrate.

Community and commercial blood banks

Twenty-five per cent of Germany's blood and blood components are collected by eighty public blood banks operated by the state, communities, and universities, and a number of commercial blood banks owned by pharmaceutical corporations. Historically, most of the plasmapheresis has been undertaken by the commercial centres, although the community blood banks and the Red Cross have recently begun to perform this function. Donors are not remunerated by the community blood banks, but are paid a small amount by the commercial centres.

Blood product manufacturers

Several blood product manufacturers carried on business in Germany during the 1980s. They were Alpha Therapeutic GmbH, Armour Pharma GmbH, Bayer AG, Baxter Deutschland GmbH, Behringwerke AG, Biotest AG, Immuno GmbH, and Tropon AG. Some of them continue to operate today. Hospitals pay manufacturers directly for blood products supplied.

The role of government

The principal regulator of blood and blood products is the federal government, although state governments also play a role. The federal Ministry of Health and affiliated institutes carry out this task.

The Federal Health Office (Bundesgesundheitsamt), a quasi-autonomous agency affiliated with the Ministry of Health, historically regulated the blood supply pursuant to the *Pharmaceutical Act (Arzneimittelgesetz)*, although in 1994 the regulatory function was transferred to the Paul Ehrlich Institute, a federal research institute. During the 1980s the Federal Health Office conducted much of the research on HIV test kits. Since July 1994, however, it has also been given the task of licensing blood products. The states inspect blood banks.

The *Pharmaceutical Act* defines blood products as pharmaceuticals if they are made from or contain blood or stored blood, plasma or serum, blood components, or preparations made from blood components. Whole blood is defined in the *Act* as stored blood to which stabilizers have been added. Under the *Act*, all human body components become pharmaceuticals if they are "intended to replace an active ingredient produced by the human body," or "if their purpose is to treat, mitigate, prevent or identify – through their use on or in the human body – disease, pain, bodily injuries or pathological conditions." The purpose for which blood and blood products is intended is thus significant; only when they are "dedicated" do blood and blood products become pharmaceuticals. Under this definition, red blood cell and platelet concentrates, fresh frozen plasma, human albumins, clotting factor preparations, and immunoglobulins are pharmaceuticals. The *Act* also provides that all pharmaceuticals are subject to strict liability.

Under sections 21 and 30 of the *Pharmaceutical Act*, blood products must be licensed by federal authorities, and when they are licensed, they must be monitored for adverse effects (referred to as “post-market surveillance”). Although licensing of blood products is done by the Federal Health Office, until June 1994 the task of post-market surveillance was shared by both the federal and the state governments, the former being responsible for ensuring compliance with the law, and the latter for monitoring practices. Under section 69(1) of the *Act*, the federal government may only recommend that blood products be recalled, while the states have exclusive jurisdiction to initiate such a recall. In practice, this meant that although the federal government had the authority to withdraw its regulatory approval of a blood product, it could not order a recall of products still on the market. Under professional guidelines, physicians are required to report any adverse reactions to drugs to the Pharmaceutical Commission.

To ensure that licensed blood products continue to comply with the provisions of the legislation, the federal government may initiate a “multi-stage plan” pursuant to section 63 of the *Pharmaceutical Act* and the regulations made thereunder. Under a multi-stage plan, the federal government and all institutions involved in the marketing or use of pharmaceuticals work together to monitor, collect information on, and evaluate the risks associated with the use of the products. The regulations provide for two regular meetings per year, and more if there is a well-founded suspicion of a health hazard.

The importation of plasma is also regulated under the *Pharmaceutical Act*. According to the *Act*, drugs and biologics entering the country must bear a certificate confirming that they have been manufactured in compliance with good manufacturing practices sanctioned by the World Health Organization or the Convention on Inspection of Pharmaceutical Industries. The federal Ministry of Health may, by decree and with the consent of the Council for the Minister-Presidents of the German States (Bundesrat), prohibit the importation of blood products from countries that are not members of the European Community if it is deemed necessary to do so to prevent risks to health. The permission for the importation of plasma or concentrates is given by the local customs authorities on confirmation by state authorities that good manufacturing practices have been observed. There are no restrictions on the export of plasma. Germany exports some plasma. Plasma collected in Germany is manufactured into blood coagulation concentrates by pharmaceutical manufacturers in Austria that maintain their own plasmapheresis centres in Germany.

During the 1980s, the national institute for infectious diseases, the Robert Koch Institute in Berlin, monitored outbreaks of disease and conducted disease surveillance. It collected data on AIDS cases, and since September 1987 has received reports of cases from laboratories performing HIV tests.

The German Hemophilia Society

The German Hemophilia Society (Deutsche Hämophiliegesellschaft zur Bekämpfung von Blutungskrankheiten), now located in Hamburg, was founded in Heidelberg in 1956 by Dr R. Marx, a professor of medicine who was then teaching in Munich. In the former East Germany, a similar hemophilia support group was founded by Professor D.W. Remde as a section of the Society of Hematology and Blood Transfusion of the German Democratic Republic (Sektion Hämophilie der Gesellschaft für Hämatologie und Bluttransfusion der DDR). These two organizations were united in November 1990. The German Hemophilia Society now has approximately 3,000 members and is funded by membership fees, donations, and government grants.

The goal of the society is to improve the lives of persons with hemophilia. It provides care and counselling to patients, undertakes medical research, and disseminates information both to members and to the public. The society has worked to increase the safety of blood products, lobbied for financial assistance for persons infected with HIV or hepatitis C, and sought assurances of adequate psychosocial care for HIV-infected persons and their families. To facilitate its work, the society has a medical advisory board, in addition to a number of working groups, such as the working group on blood coagulation concentrates and the working group on HIV and HCV financial assistance. The German Hemophilia Society also publishes a journal, *Hämophilie-Blätter*, that is distributed to all members three times a year.

Prevalence of blood-related HIV or AIDS

Almost half the 6,000 hemophiliacs in Germany were infected with HIV. According to a report of the World Federation of Hemophilia, the first HIV testing in 1985 revealed that 47 per cent of patients with hemophilia were infected. By the end of 1994, 43 per cent of regularly treated hemophilia patients were HIV infected, the majority being hemophilia A patients. It is thought that most hemophiliacs were infected by imported concentrates.

Recent data published by the European Centre for the Epidemiological Monitoring of AIDS show that in Germany, as of 31 December 1996, 515 hemophiliacs and 260 transfused patients had AIDS.

The discussion of historical events in this chapter is confined to events in the former West Germany; it does not include a review of events in the former East Germany.

Protecting the blood supply from HIV or AIDS

Inquiries into the blood supply

An examination of the events of the early 1980s was first undertaken in 1992 by the Health Committee of the German Parliament (Parliamentary Committee). Its first or interim report, *On the Risk of HIV Infection through Blood Products*, was submitted to the Minister of Health in November of that year.

In October 1993, the Parliamentary Committee produced a second report. Although the Parliamentary Committee addressed a broad range of issues, including the introduction of heat treatment, recall of blood products, tracing of recipients, compensation, self-sufficiency, and blood usage, its members felt that a more comprehensive study of the blood supply was warranted. They therefore recommended that yet another parliamentary committee be struck to investigate the matter thoroughly.

On 29 October 1993, the Speaker of the German Parliament established the Third Investigation Committee (Investigation Committee) to examine the role of the federal government in the transmission of HIV through blood and blood products. Specifically, the Investigation Committee was asked to consider whether the Federal Health Office (in West Germany) had failed to fulfil its statutory obligations under the *Pharmaceutical Act*; whether the federal government had failed to rectify shortcomings of the *Pharmaceutical Act* pertaining to drug safety; whether the federal government had properly exercised its technical and legal supervision of the Federal Health Office and its institutes; whether and how pharmaceutical manufacturers had influenced decision making; whether the federal government was responsible for the structural, organizational, and personnel shortcomings of the Federal Health Office; whether the federal government was responsible for failing to assist persons infected in asserting their claims; to what degree the federal government should be held responsible for spreading the infection by not having provided persons with sufficient information and for having failed to take appropriate measures; whether the federal government, by neglecting to create a domestic supply of blood and blood products, was guilty of failing to reduce the risk of infection; and, finally, to what extent the federal government should be held accountable for any past errors or omissions. In examining these issues, the Investigation Committee was urged to consider the following: the measures adopted; the adequacy of the measures; the date when the measures were introduced; the time lapse between the recognition of risk and the measures to reduce risk; the decision-making processes; and whether any employees of the federal Ministry of Health had had conflicts of interest. The Investigation Committee was also charged with the task of identifying any deficiencies within the present system and recommending improvements. Finally, it was required to address the question whether additional financial assistance should be granted to persons infected and affected. Unlike investigatory bodies in other countries, the Investigation Committee considered events in Germany until the time of its report. It also reviewed infections that resulted from heat-treated factor VIII concentrate, used primarily in the treatment of type A hemophilia, and from other factor concentrates usually used in the treatment of type B hemophilia. The Investigation Committee issued an interim report on 31 January 1994 and a final report on 25 October 1994. The findings and recommendations of both the Parliamentary Committee and the Investigation Committee are discussed in some detail later in this chapter.

The emergence of HIV or AIDS

When three cases of immune deficiency were discovered in hemophilia patients in the United States in July 1982, no such cases had yet been reported in Germany. On 15 October 1982, an article describing the “Gay Related Immunodeficiency Disease” was published in the *German Medical Weekly (Deutsche Medizinische Wochenschrift)*. This article listed the groups at risk for the disease, including hemophiliacs. In November, the same journal reported on the first cases of *Pneumocystis carinii* pneumonia in German homosexual men.

In November 1982, Dr Joanna L’age-Stehr, an epidemiologist with the Robert Koch Institute, visited members of the AIDS Task Force at the Centers for Disease Control (CDC) in Atlanta to learn more about AIDS. Shortly thereafter, she prepared a memorandum for the German medical profession about AIDS in hemophiliacs. With Dr Manfred Koch, a member of the AIDS working group in the Federal Health Office, and Dr Wilhelm Weise, the head of the Blood Type Research and Blood Donor System Directorate in the Federal Health Office, Dr L’age-Stehr published a report about AIDS in the *Federal Health Bulletin (Bundesgesundheitsblatt)* entitled “Unknown Pathogen the Cause of Fatal Immune Deficiencies?” The authors documented the increasing number of AIDS cases observed by the CDC since the middle of 1981, stated that the recipients of factor VIII concentrate were particularly affected, and noted that AIDS appeared to be caused by an unknown infectious agent that was transmitted through blood and blood products – as was hepatitis B. Readers were also informed that a reporting questionnaire would soon be sent to medical practitioners. On 18 February 1983, the article was reprinted in the *German Medical Gazette (Deutsches Ärzteblatt)*, a journal that was distributed to all physicians.

In mid-March, Dr L’age-Stehr attended a conference in New York on Kaposi’s sarcoma and opportunistic infections in homosexual men. At this conference she learned that thirteen cases of AIDS had been confirmed in hemophiliacs in the United States, and that six suspected transfusion cases were under investigation. The next month, she published an article in the *Federal Health Bulletin* entitled “Acquired Immune Deficiencies – A New Infectious Disease AIDS (Acquired Immune Deficiency Syndrome).” In the article, she described the clinical symptoms and progression of the disease, and stated that it could be transmitted by blood and was probably transmitted by an infectious agent. She described as “alarming” the discovery of eight cases of AIDS in American hemophiliacs, and the results of three studies that had revealed a significant decrease in the T-cells of hemophiliacs. She also said that the CDC had received a report in December 1982 of an infant with opportunistic infections who had been transfused at birth; this case was possibly the first case of transfused AIDS, she continued, and two similar cases of transfusion-related AIDS were currently being investigated.

On 30 April 1983, Dr L'age-Stehr learned of two German hemophiliacs with AIDS, one of whom had died a year earlier (known subsequently as the "Bonn patient"). On 16 June, Dr L'age-Stehr wrote to the treating physician in Bonn to request that a CDC AIDS questionnaire be completed; the physician refused to do so. After consulting a colleague, he explained, he no longer classified the patient as an AIDS case because the patient had suffered from progressive multi-focal leucoencephalopathy, or PML, a condition not usually associated with AIDS. In a report about AIDS in West Germany that appeared in *The Lancet* in December 1983, however, the Bonn patient was described as the first hemophilia AIDS case in Germany.

Several other hemophilia AIDS cases occurred in 1983. In a report submitted to the Health Ministry in June 1983, the Federal Health Office stated that two hemophiliacs had become infected. In August 1983 the Robert Koch Institute received reports of two additional cases of hemophiliacs with AIDS, and a report of AIDS in a female patient who had received unidentified blood products.

By mid-1984, a total of seven cases of AIDS in hemophiliacs had been reported to federal health authorities. In October 1984, Dr Koch reported that of forty-one hemophiliacs tested, twenty-six were HIV positive. In the scientific community the significance of these findings was vigorously debated. It was unclear whether the results reflected active infection or simply an immune response to a virus. The theory suggesting an immune response was supported by the fact that, at the time, only a few of the hemophiliacs had become ill. Nevertheless, by December 1984, the number of reported cases of AIDS in hemophiliacs had risen to eight, and by the autumn of 1985 there were sixteen hemophilia AIDS cases in Germany. The report of the first fatal case of AIDS in a hemophiliac was published in the *Neurologist* (*Nervenarzt*) that year. By September 1986, the total number of German hemophilia patients with AIDS had risen to sixty-six. Of these, seven were hemophilia B patients.

Cases of AIDS among patients who had been treated with PPSB, prothrombin complex preparations, became known to federal health authorities in 1986. PPSB is a factor concentrate that contains several clotting factors, including factor IX. It is used to treat persons with hemophilia B and others who require treatment for a bleeding episode. On 7 October 1986, Dr Koch reported to the Pharmaceutical Institute that a woman in Mutlangen who had been treated with PPSB had died of AIDS, and that a similar case was under investigation.

The Investigation Committee found that although the first hemophilia AIDS case in Germany was reported to Dr L'age-Stehr in April 1983, a diagnosis of PML and a lack of cooperation on the part of the treating physicians impeded the investigation of the case, and the ensuing delay in confirming the case enabled physicians and the pharmaceutical industry to deny the existence of AIDS in Germany. It concluded that treating physicians should have known in June 1983 that the Bonn case in May 1982 was the first fatal

AIDS case in a German hemophiliac and that a diagnosis of PML did not disqualify it. The Investigation Committee also found that by the end of 1983 there had been several hemophilia AIDS cases in Germany that were not reported to the Federal Health Office. The committee stated that the facts demonstrate that physicians treating hemophilia patients at that time either knowingly disregarded, or simply did not recognize, concrete indications of HIV infection in their patients.

Response to the emergence of HIV or AIDS

On 20 April 1983, the AIDS Commission of the Federal Health Office held its first meeting, which was attended by immunologists, virologists, epidemiologists, and clinicians. Dr L'age-Stehr reported that AIDS cases had been diagnosed among hemophiliacs in the United States, and said that the current epidemiological profile of Germany was similar to that of the United States in 1981. Two German physicians treating hemophiliacs reported two suspected cases of AIDS among their patients, as well as evidence of lowered T-cell ratios. In discussing these reports, the participants devoted much time to determining who was at risk of contracting AIDS. In a memorandum to the Minister of Health after the meeting, Dr Helmut Göing of the Federal Health Office stated that although there were twelve to fifteen cases of AIDS among hemophiliacs in the United States, there was none in Germany, despite its reliance on American concentrates. He also said that there was then no need to require the reporting of AIDS cases. The participants also discussed methods to exclude donors who were at risk of contracting AIDS, but they could not agree on how this should be done.

On 18 June 1983, the blood product manufacturer Immuno held a meeting in Frankfurt to discuss AIDS, opportunistic infections, and hemophilia. Invited guests included treating physicians from Germany, Austria, Switzerland, France, and Spain, as well as immunologists and microbiologists. Two treating physicians from New York were also present. There was considerable discussion whether AIDS was an infectious disease, whether additional factors were involved, and whether the lowering of the T4/T8 ratio was an indication that a person had contracted AIDS. The Bonn case was presented by the treating physician, but the physicians from the United States stated that they did not believe it met the criteria for AIDS cases. AIDS was added to the list of known risks associated with use of factor VIII concentrate, but the participants concluded that the risk to hemophiliacs was negligible.

On 20 July 1983, the U.S. Food and Drug Administration contacted the Federal Health Office to inquire whether Germany, like France, was considering a ban on imports of American blood products. The Federal Health Office informed the Food and Drug Administration that although it would not be imposing a ban on imports from the United States, import restrictions were being considered. As a consequence of the inquiry about imports,

the Federal Health Office began to develop a policy to deal with the risk of AIDS known as the “multi-stage plan concerning AIDS transmission through factor VIII products.”

As a first step, federal health officials held a number of internal meetings to review what was known about the disease and to assess the risk posed by blood and blood products. The first meeting took place on 7 September 1983 at the Robert Koch Institute. The members of the institute who attended the meeting concluded that the use of factor VIII concentrate posed the greatest risk because it was manufactured from large pools containing 1,000 to 10,000 donations; of second importance were fibrinogen products; and third, other blood products used for replacement therapy. They also reviewed measures adopted by foreign jurisdictions to reduce risk, such as reducing the size of plasma pools, banning blood products imported from regions with a high incidence of AIDS, and developing procedures to inactivate pathogens.

On 13 September 1983, the president of the Federal Health Office, Professor Dr Karl Überla, held a meeting with his senior officials. They also concluded that factor VIII concentrate posed the greatest risk and had to be the government’s first priority; that other blood coagulants were of secondary importance; and that blood transfusions were “virtually risk-free.” In accordance with this assessment, a decision was made to focus efforts exclusively on reducing the risk of using factor VIII concentrate. The officials also agreed that the Federal Health Office should convene a meeting with organizations involved in the blood system to discuss ways in which this reduction in risk could be achieved.

Two weeks later, the Federal Health Office wrote to representatives of all the participants in the blood system, inviting them to a meeting to be held on 14 November 1983 “to assist in the development of a multi-stage plan to prevent the transmission of AIDS through factor concentrates.” The participants also received a list of questions they were asked to answer before the meeting. On 26 September 1983, the Federal Health Office asked blood product manufacturers and the Red Cross to inform the Federal Health Office how much factor VIII concentrate was being used by each treatment centre; whether any measures had been taken to reduce the transmission of AIDS; and from which geographic regions they obtained their source plasma. They were also asked to submit copies of package inserts and labelling, as well as reports of adverse reactions resulting from the use of factor VIII concentrate, including cases of AIDS. Answers were to be sent to the Federal Health Office by 15 October 1983.

Federal health officials met once more before the November public meeting. On 25 October 1983, a meeting was held at the Federal Ministry for Youth, the Family and Health. At this meeting, the Federal Health Office reported that AIDS might be caused by a virus; that it was transmitted by blood and blood products; that hemophiliacs and transfused patients were at risk of contracting the disease; and that, as a “worst-case scenario,” the

spread of AIDS would be similar to that of hepatitis B, affecting 5 to 8 per cent of the population. However, a press release issued by the Ministry after the meeting stated that a panel of "highly qualified experts" had unanimously concluded that transmission by way of blood or blood products "appears to be so unlikely in practice, that, according to the current state of scientific knowledge, with common precautions in the blood donor system, there is no reason to fear the spread of AIDS beyond the known risk groups." The press release did not mention that hemophilia patients or transfusion recipients were groups at risk.

On 14 November 1983, federal health officials held a meeting with the Red Cross, pharmaceutical companies, hospitals, and members of the scientific community to discuss what was known about the risk of HIV transmission from the use of factor VIII concentrate and to suggest possible measures to reduce the risk. At the meeting, Dr Weise stated that although there were three suspected cases, there were no confirmed cases of AIDS resulting from the use of blood or blood products in Germany. He also told the participants that the epidemiology of AIDS was similar to that of hepatitis B; that AIDS might be caused by a virus; that AIDS was transmitted predominantly through sexual contact via blood and bodily fluids; and that hemophilia patients and transfusion recipients were at risk of contracting the disease.

Much of the information presented at the meeting was greeted with scepticism. Most participants considered that the danger of bleeding far outweighed the risk of AIDS, and that the risk to hemophiliacs was negligible. Some participants said that AIDS could not result directly from blood and blood products, but that other predisposing risk factors also had to be present. The representative of the Pharmaceutical Manufacturers Association stated that German hemophiliacs were treated extensively with factor VIII concentrate imported from the United States, and that if factor concentrates truly were a mode of transmission, many German hemophiliacs would have already contracted the disease, but this was not the case. He also said that, weighed against the risk of fatal bleeding, the risk of the potential transmission of AIDS was negligible. A representative of Immuno rejected the theory that AIDS was transmitted by an infectious agent.

At the meeting, several methods of minimizing the risk of transmission were discussed. The federal health officials informed the participants that a recall or reduction of imported blood products was not then under consideration, but that the introduction of other measures, such as mandatory testing for antibody to the hepatitis B core (also referred to as "anti-core" or anti-HBc testing), batch testing, and donor-screening guidelines were being examined. The blood product manufacturers suggested that blood and plasma not be collected in areas with a high incidence of AIDS, that regulations requiring the tracing of plasma from the recipient to the donor be enacted, and that mandatory batch testing be introduced. Dr L'age-Stehr discussed the potential benefits of anti-core testing, but received little support. Several participants

argued that testing would increase the cost of a unit by as much as 5 to 10 per cent, and that it would exclude too many donors. The possibility of restricting treatment to the use of cryoprecipitate was discussed, but rejected. A suggestion to ban imports was also dismissed because the domestic supply was inadequate to meet the needs of hemophiliacs. A representative of the German Hemophilia Society stated that its members were not in favour of reducing the use of U.S. factor concentrates, and that they were "prepared to accept the risk of AIDS." There was some discussion of the heat treatment process used by Behringwerke, and a suggestion was made that hemophilia patients be treated exclusively with its heat-treated factor VIII concentrate (Behring HS). This proposal was rejected, however, because there was insufficient clinical evidence that the process inactivated all viruses while retaining the efficacy of the product. It was also felt that the use of the heat-treated product might lead to allergic reactions and the formation of antigens, which would render further treatment with factor concentrates impossible. Moreover, supplies were insufficient to treat all patients, and the use of heat-treated factor concentrates was not universally an insured service. Health insurance companies reimbursed the cost of products only to infants and to persons who tested negative for hepatitis B. A suggestion by the Federal Health Office that plasma pool sizes be restricted to 6,000 donations was rejected because the participants were not convinced that such a measure would increase safety.

The participants at the November 1983 meeting also discussed the surveillance and reporting of AIDS cases, but decided against the introduction of mandatory reporting. Although the reporting of HIV infection became compulsory in September 1987, the reporting of AIDS cases is voluntary in Germany.

On 8 June 1984, the Federal Health Office issued an Order (*Bescheid*). Part A of the Order provided that, effective 1 December 1984, blood product manufacturers would be required to identify the country of manufacture, the origin of the plasma, the number of donors who had contributed to the plasma pool, and the amount of plasma processed. With respect to any side-effects associated with the use of the factor concentrates, manufacturers would be required to warn that the factor concentrates might cause non-A, non-B hepatitis and AIDS. Part B of the Order required that plasma be tested for syphilis, anti-HBc, HBsAg (surface antigen of hepatitis B), and GPT (glutamate pyruvate transaminase) or ALT (alanine amino transaminase) as of 1 January 1985. There was no requirement that blood products be subjected to viral inactivation procedures.

During the summer of 1984, without the endorsement of the national president of the Red Cross, almost all provincial Red Cross associations lodged objections to the Order, as did many of the blood product manufacturers. The Red Cross associations argued that there was no justification for the required tests. Anti-core testing would lead to loss of neutralizing antibodies in the plasma pool, thereby increasing the risk of hepatitis, and ALT tests were unreliable. The blood product manufacturers opposed the requirement of

factor concentrate warnings because they did not want their products associated with the transmission of AIDS. They regarded the prohibition against mixing plasma from various countries as superfluous, and several of them demanded transition periods during which the supply of existing products could be exhausted and new lots manufactured in accordance with the new guidelines. Finally, they objected to the fact that important donor guidelines, such as questioning donors about symptoms of AIDS and conducting physical examinations, had been omitted from the Order, as had any requirement for inactivating viruses.

On 1 November 1984, the Federal Health Office held a meeting to discuss the objections lodged against the Order. The Order was revised in late November, and in December 1984 the Federal Health Office issued a ruling on the objections to the Order (*Widerspruchsbescheid*). The Federal Health Office stated that the Order made June 1984 would be amended. In contrast to the original Order, the amended Order would not include the provisions requiring the identification of the country of origin, batch testing, and the prohibition against the mixing of plasma from different countries. Anti-core testing would only be required in the absence of HIV testing, which must be implemented by 1 July 1985. Finally, a new provision was introduced. Although there was no requirement that factor concentrates be subjected to heat treatment, manufacturers would be required to state whether, and how, the factor concentrates had been virally inactivated.

The Parliamentary Committee stated that the amended Order of December 1984 could have applied to blood products other than factor VIII concentrate, since many of the provisions dealt with the collection of plasma generally and no distinction was made at the time of donation with respect to later use. The blood product manufacturers, however, did not share this view. They regarded the requirements as binding for factor VIII concentrate exclusively. The fact that the Order did not expressly apply to blood products other than factor concentrate was brought to the attention of the Federal Health Office on several occasions, but the matter was never addressed.

The Parliamentary Committee endorsed the approach taken by the Federal Health Office in limiting the multi-stage plan to factor VIII concentrate. It stated that this restriction was made "because, according to medical information available at the time on the HIV risk and the use of blood factor concentrates, the risk was highest when such drugs were used and therefore precautions were most urgently needed there." It concluded that this approach was scientifically sound, because the plasma used to produce clotting factor concentrates yielded not only factor VIII but also other factors. Therefore, any safety measures for factor VIII concentrate necessarily would apply to these other clotting factor concentrates.

The Investigation Committee concluded that the U.S. Food and Drug Administration's inquiry to the Federal Health Office about banning blood products manufactured in the United States was a catalyst for action, and that it forced

federal health officials to consider the threat of AIDS to the blood supply. However, the Investigation Committee could not understand why, in September 1983, the officials in the Robert Koch Institute estimated the risk of non-factor VIII concentrates (PPSB, factor IX) to be minimal, when the risk of hepatitis transmission was twice that of factor VIII concentrates, and when factor concentrates were also produced from large pools and were consumed by a larger number of patients. The Investigation Committee also questioned why the Federal Health Office had concluded that non-factor VIII blood products were of “less importance” and that blood transfusions presented “hardly any risk.” It stated that, by November 1983, federal health officials had been told that the risk of transmission existed with all blood products, including factor IX concentrate, PPSB, fibrinogen, and blood transfusions, but they did not interpret this information as a reason to expand the multi-stage plan to include all blood products. This omission was regarded by the Investigation Committee as “an incomprehensible scientific and administrative error in judgment.”

Excluding persons at risk: Donor screening

At the meeting of the AIDS Commission of the Federal Health Office in April 1983, the members discussed the issue of identifying groups at risk. However, they “could not find common ground concerning suitable and practical measures to exclude blood donors suspected of AIDS.”

On 7 June 1983, the Red Cross released a position statement on AIDS. The statement said that the disease primarily attacked homosexuals and drug users, and, more rarely, hemophiliacs, a pattern that “indicate[d] that the still unknown pathogen is able to be transmitted via blood.” Consequently, the Red Cross blood banks had incorporated questions into their blood donor questionnaire that were intended to elicit information about early symptoms of the disease.

The new donor-screening questionnaire informed donors that there were approximately forty cases of AIDS in Germany; that it must be assumed that AIDS was caused by an unknown infectious agent transmitted in a manner similar to the way in which hepatitis B was transmitted; that the incubation period could be as long as three years; and that persons most at risk of contracting the disease were male homosexuals, prostitutes, immigrants from Haiti, intravenous drug users, and recipients of blood and blood products, particularly factor VIII concentrate. Donors were asked whether they had any of the symptoms of AIDS (such as unexplained weight loss, swelling of the lymph nodes, unexplained fever, night sweating, dry coughing, diarrhea, or lymphopenia), and any donors having one or more of these symptoms were excluded from donation. The donor was also required to certify by his or her signature that the information given during the medical interview was true.

In the autumn of 1983, the Federal Health Office released a public statement about AIDS. On 6 September, it issued a press release, stating that all blood donors must be informed of the AIDS virus and that persons belonging to risk groups should be asked not to donate blood. It also warned that imported blood products produced from paid donations carried a special risk of contamination. As of 1 September 1983, donors were given an information sheet about AIDS. It described the symptoms of AIDS and identified groups most at risk of acquiring the disease as being intravenous drug users, homosexuals or bisexuals, and persons who had had intimate contact with persons belonging to these groups or with persons who had AIDS. Donors were also asked to sign a form, acknowledging that they had read and understood the information sheet. The issue of excluding donors at risk was discussed at the November 1983 meeting of the Federal Health Office, where it was suggested by the Pharmaceutical Manufacturers Association that blood and plasma should not be collected in areas with a high incidence of AIDS.

By 1984, the AIDS information sheet identified the following groups as at risk of contracting AIDS: men who after 1977 had sexual contact, once or more than once, with another man as well as with their own sexual partners; intravenous drug users and their sexual partners; hemophiliacs and their sexual partners; immigrants from central Africa, western Africa, and Haiti who entered Germany after 1977 and their sexual partners; women or men who had sexual contact with persons with AIDS; women or men infected with HIV and their sexual partners; men and women who had engaged in prostitution since 1977; and male and female sexual partners of persons belonging to the above groups. Donors were asked to indicate whether they were members of any of the risk groups by marking one of two boxes – one, that their blood might be given to the sick and injured; and two, that it should not be given to the sick and injured. The form was then signed by the donor.

The Order made in June 1984 did not address the question of donor screening. Many organizations in the blood and blood products industry objected to the fact that questions about AIDS symptoms and guidelines for physical examinations were omitted from the Order. On 12 December 1984, the Federal Health Office published the amended Order. Part B of the Order, to come into effect on 1 July 1985, stated that imported factor concentrates might be used, provided that the donor-screening guidelines of the country of origin had been observed.

The Federal Health Office did not require the direct questioning of donors about their membership in a group at risk of contracting AIDS until the second strain of the AIDS virus (HIV-2) appeared in Germany in 1988. On 14 July 1988, the Federal Health Office wrote to manufacturers, informing them of its intention to impose mandatory direct questioning of donors about their sexual contact with West Africans. On 11 December 1988, the

Federal Health Office announced that, effective immediately, all donors who had had sexual contact with West Africans or their sexual partners were to be excluded from donation.

In its final report, the Investigation Committee did not make any findings with respect to donor screening. It did observe, however, that although donor-screening guidelines were considered at the November 1983 meeting, they did not find their way into the Order.

Inactivating viruses in blood products

During the late 1970s, the German pharmaceutical manufacturer Behringwerke began to develop a method of inactivating hepatitis viruses. The process involved heating concentrates in a solution at 60°C for ten hours. By 1978, Behringwerke had begun clinical trials of this new heat-sterilized factor concentrate, which it named "Factor VIII HS." The results were published by N. Heimburger and colleagues in the German journal *Die gelben Heften* in 1980. The results were impressive. The clinical trials, conducted at several German hemophilia centres, demonstrated that the process inactivated not only hepatitis B but also non-A, non-B hepatitis. As of the date of publication, none of the forty-four patients treated with the new factor concentrate showed signs of hepatitis. In 1981, Behringwerke published the results of other studies performed using its new heat-treated factor concentrate. The studies proved that the structure of the protein was unchanged by heat inactivation and that the viral inactivation process yielded factor concentrates of higher purity. On 5 February 1981, heat-treated factor VIII concentrate manufactured by Behringwerke was licensed by the Federal Health Office, with the condition that a clinical report be submitted after two years.

Although Behringwerke had succeeded in producing a demonstrably safer factor VIII concentrate product, Factor VIII HS was not used extensively by hemophiliacs in Germany. The inactivation was achieved at the expense of a 40 per cent loss in clotting activity. This loss meant that twice the amount of plasma was needed to produce the factor concentrate, and the cost doubled. As a consequence, only German hemophilia patients who tested negative for hepatitis B were eligible to receive the factor concentrate free of charge under their health insurance plans.

During the early 1980s, several other blood product manufacturers also began to incorporate a viral inactivation measure into their manufacturing processes. They sought and obtained regulatory approval for the distribution of their heat-treated factor concentrates on the German market. On 22 October 1982, the Federal Health Office licensed Armour Pharma to distribute H.T. Factorate, and on 13 December 1982 it licensed the dry heat-treated factor VIII concentrate produced by Travenol Laboratories Inc. The next year several other manufacturers, including Immuno, were licensed to manufacture and distribute heat-treated factor VIII concentrate in Germany.

Despite the approval of the regulatory authorities, many experts were opposed to the use of these factor concentrates because they believed that heat treatment might damage the nature of clotting factor concentrates and lead to the formation of factor antibodies. On 11 July 1983, at a meeting of the working group of the Scientific Council of the German Medical Association, it was stated that hemophiliacs who had been given Behringwerke's heat-treated factor VIII concentrate were more likely to develop "inhibitors" that would cause resistance to factor VIII concentrate than were patients receiving non-heat-treated factor VIII concentrate. It was also reported that Behringwerke's heat-treated factor concentrates had led to cases of non-A, non-B hepatitis, a fact that reinforced doubts about the efficacy of heat-treated factor concentrates.

By the autumn of 1983, the federal health authorities began to consider whether the manufacturers of factor concentrates should be required to subject their products to some type of viral inactivation process. On 26 September 1983, when manufacturers were invited to a meeting about current inactivation methods used to prevent the transmission of hepatitis B, it was revealed that a majority of manufacturers were already using some method of viral inactivation. At the meeting convened by the Federal Health Office in November 1983 to address the potential transmission of AIDS by factor VIII concentrate, it was proposed that hemophilia patients be treated exclusively with heat-treated factor concentrates manufactured by Behringwerke. This proposal did not meet with universal approval and was rejected. Some participants stated there was no clinical evidence that the process inactivated all viruses while retaining the efficacy of the concentrates, and that use of heat-treated factor concentrates might lead to allergic reactions and to the formation of inhibitors, rendering further treatment with factor concentrates impossible. Furthermore, supplies of heat-treated factor concentrates were insufficient to treat all patients, and heat-treated factor concentrates were not an insured service for all hemophiliacs.

The Order published by the Federal Health Office in June 1984 did not deal with the subject of heat treatment – a fact that was of some concern to many of the blood product manufacturers. In June 1984, the general manager of Immuno wrote to the Federal Health Office stating that it was "essential" to include a requirement of viral inactivation in the Order. This view was shared by others, and the matter was again brought to the attention of the Federal Health Office in August 1984. The blood product manufacturer Tropon stated that the Order did not take into account heat treatment and the discovery of the AIDS virus. Behringwerke also protested the absence of mandatory heat treatment, pointing out that viral inactivation was more important than any of the measures mentioned in the Order.

The debate over whether to require viral inactivation of factor concentrates continued into the autumn of 1984, despite the fact that large treatment centres had already begun to distribute heat-treated factor concentrates. On

27 November 1984, Federal Health Office officials held a meeting to discuss amendments to the Order, including the possible inclusion of viral inactivation requirements. There was a wide divergence of views among the participants. Dr Weise was of the view that the requirement should apply only to imported factor concentrates or those manufactured from imported plasma. He stated that the Red Cross could not introduce viral inactivation processes on such short notice, and that it might lose part of its market to imported products. An official from the Pharmaceutical Institute proposed that the Order be amended to ensure that only virally inactivated factor concentrates be approved for marketing. A member of the AIDS working group in the Federal Health Office considered that drafting such a requirement would be almost impossible, because the viral inactivation processes varied so greatly.

In drafting the amendments to the Order, the federal health officials ultimately settled on a compromise. The use of viral inactivation would not be mandatory, but to ensure that physicians and patients were informed of the inherent risks associated with the use of factor concentrates, the manufacturers would be required to state on the product label whether it had been subjected to viral inactivation procedures and, if so, by which process. This provision was to come into effect on 1 March 1985. The manufacturers were dissatisfied with this solution. On 20 December 1984, the general manager of Immuno wrote to the Federal Health Office to protest against the fact that the government had abandoned its earlier intention to revoke approval of non-inactivated factor concentrates and to impose requirements of viral inactivation. He was also critical of the fact that the Order applied only to factor VIII concentrate and not to factor IX concentrate and PPSB.

In late 1984 and early 1985, several articles appeared in the medical press endorsing the use of heat treatment methods. On 22 December 1984, an article was published in *The Lancet*, recommending the use of heat-treated factor VIII concentrate, and in January 1985, a study was published demonstrating that the AIDS virus was inactivated by heat treatment. In May 1985, the report of a study of 113 German hemophilia patients published in *The Lancet* showed that patients using only heat-treated concentrates did not become infected with the AIDS virus. The authors concluded that it seemed "quite reasonable to treat previously unexposed haemophiliacs with heat-treated concentrates only." German blood product manufacturers informed the Federal Health Office that, as of 1 October 1985, they would be distributing only factor VIII concentrate that had been heat treated. Heat-treated factor IX concentrate manufactured by Behringwerke was licensed by the Federal Health Office in January 1985.

At the end of 1988 the use of some form of viral inactivation method became mandatory. On 14 July 1988, the Federal Health Office wrote to the manufacturers, telling them that it would soon require the viral inactivation

of factor VIII concentrate. Regulations to this effect were subsequently enacted on 11 December 1988, effective immediately. These regulations were declared invalid by the Berlin Higher Administrative Court in July 1990, however, as being outside the jurisdiction of the federal government to make.

The Parliamentary Committee felt that it did not have the necessary information to make a finding on the issue of heat treatment; it commissioned a survey to determine when viral inactivation processes were introduced for the various factor concentrates. The results of this survey did not become available before the Parliamentary Committee concluded its work. Nevertheless, the Parliamentary Committee made the following comments. Although the Federal Health Office might be criticized for failing to require viral inactivation procedures until 1988, there were several mitigating factors that should be taken into consideration. First, manufacturers had a legal duty to market their factor concentrates in accordance with existing medical standards, including viral inactivation methods, and were required by law to ensure the quality, efficacy, and safety of the drug. Second, an informal survey of industry representatives conducted in September 1983 revealed that most manufacturers were already using some method to inactivate hepatitis viruses. Third, it was impossible to assess the efficacy of methods used to inactivate the AIDS virus until the end of 1984. Fourth, in its amended Order published in December 1984, the Federal Health Office required manufacturers to describe the inactivation method(s) used, and it could amend the Order to impose more stringent requirements at a later date if it felt they were necessary. Fifth, at the beginning of 1985, all manufacturers had tested their viral inactivation methods against HIV and, by 1 October 1985, had stopped producing non-heat-treated factor VIII concentrate. The Parliamentary Committee concluded that the Federal Health Office was simply attempting to establish a scientifically justified standard, based on the most current information available, which could eventually be applied to other blood products. It said that "it always takes a certain period of time before a new scientifically recognized standard can be made legally binding." The Parliamentary Committee also concluded that the federal government did not have the legislative authority to require blood product manufacturers to use viral inactivation methods in the production of factor concentrates.

In contrast, the Investigation Committee found it difficult to understand why the Federal Health Office omitted a requirement of viral inactivation from its December 1984 Order. The committee was also critical of the fact that the multi-stage plan did not address recalls of non-inactivated factor concentrates. It observed that blood product manufacturers were able to market both heat-treated and non-heat-treated factor concentrates simultaneously and, as a result, some manufacturers distributed non-heat-treated factor concentrates as late as 1986 and 1987.

Removing products from the market

As stated earlier, in the 1980s, legislative authority to order a recall of unsafe drugs rested with the states, although manufacturers had some legal obligation to do so. During this period, however, the states did not ever order a recall of factor VIII concentrate. The only recall of factor VIII concentrate was a voluntary recall by Immuno in early 1987 of its dry heat-treated factor concentrates, most of which had been produced in the first half of 1985 before the implementation of HIV testing.

The Parliamentary Committee acknowledged that the Federal Health Office had never ordered a recall of factor VIII concentrate, and offered several possible explanations for inaction. First, the Federal Health Office had no authority to order the recall of a drug, but could act only in an expert capacity when it was asked by a competent provincial authority for an opinion about an intended recall. Second, the Federal Health Office had on three separate occasions warned of the risk of contracting AIDS. In February 1983, it sent an information leaflet to physicians; in April 1983, it published an article in the *Federal Health Bulletin*; and in September 1983, it issued a press release. Third, the Federal Health Office's June 1984 Order required that product inserts for factor VIII concentrate caution users about the risk of AIDS transmission. Fourth, the Federal Health Office issued an Order on 20 February 1985 prohibiting the sale of factor VIII concentrate made from plasma not tested for the HIV antibody after 1 October 1985. The Order also said that blood product manufacturers were responsible for the safety of their factor concentrates; this responsibility included warning consumers of potential risks and recalling unsafe drugs.

The Investigation Committee found that there were no regulations in any of the multi-stage plans requiring the recall of non-heat-treated factor concentrates; that blood product manufacturers could offer both heat-treated and non-heat-treated factor concentrates simultaneously; and, as a result, that individual physicians were responsible for prescribing heat-treated factor concentrates. It also found that the supply of non-heat-treated factor concentrates was exhausted, causing unnecessary infections. Since it was well known that most hemophilia patients kept a store of factor concentrates with an expiry period of two years at home, the Investigation Committee found that "acceptance of this risk indicates negligent behaviour on the part of the attending physicians."

In 1987, Immuno recalled factor VIII concentrates that had been dry heat treated and manufactured from plasma not tested for the AIDS virus. The Investigation Committee endorsed this voluntary recall, stating that the company "took the only responsible action."

Surrogate testing for AIDS

The mandatory use of anti-HBc testing was first considered at the meeting of the Federal Health Office on 14 November 1983 as a preliminary method of screening donations for AIDS. Dr L'age-Stehr suggested that anti-HBc testing might be helpful in eliminating potentially contaminated donations, but the participants disagreed because of the prohibitive cost of testing and the resulting loss of many donations.

As a result of the discussions at that meeting, an Order published by the Federal Health Office in June 1984 provided that, effective 1 January 1985, blood centres would be required to test donations for either anti-HBc or ALT levels. On 26 June 1984, the Red Cross for North Rhine and Westphalia-Lippe brought a "petition for administrative review," alleging that the provisions were "incompetent and a threat to public health." It accordingly requested that the decision be set aside for "unlawful performance of duties." Specifically, the Red Cross argued that the Federal Health Office had failed to establish a justifiable suspicion, the prerequisite for federal government intervention. It stated that since surrogate testing was not required in any other jurisdiction, it had "no scientific validity"; and that if such testing had any merit, testing would have been required for stored blood as well as for clotting fractions. It also submitted that no risk-benefit analysis had been undertaken; that it would cause severe shortages (an estimated loss of 200,000 donations nationwide); and that the Red Cross medical directors were the only experts who could properly assess the risk of destroying the donations. Finally, the Red Cross estimated that such testing would cost more than DM 10 million annually (Can\$4,760,000).

Twenty-six other parties or petitioners, primarily manufacturers, joined the Red Cross in challenging the authority of the Federal Health Office to make regulations. The petitioners lodged complaints against the requirement of surrogate testing, and stated that anti-HBc testing would lead to a loss of neutralizing antibodies in the plasma pool and so would increase the risk of transmitting hepatitis. They also stated that ALT tests were unreliable. In letters to the petitioners, the Federal Health Office defended its position on surrogate testing, but indicated that, as a result of the petition for administrative review, the Order had not come into effect, and that "the reason for and against the disputed exclusion of blood and blood products testing positive for anti-HBc is again being examined."

The provisions of the amended Order published on 12 December 1984 by the Federal Health Office were significantly more lenient with respect to surrogate testing. Although the requirement for ALT testing was retained, anti-HBc testing was required only if HIV testing was unavailable. Moreover, the provisions were to come into effect on 1 July 1985, and not on 1 January 1985 as originally contemplated. By Order dated 20 February 1985, the date for implementation was extended to 1 October 1985.

Screening blood donations: HIV testing

In its final report, the Investigation Committee documented in some detail the unsuccessful efforts by Professor Gerhard Hunsmann of the Department for Virology and Immunology in Göttingen to develop a test to detect HIV antibody.

On 1 November 1984, Professor Hunsmann received a grant from the Federal Health Office to develop a test to detect antibodies to HIV. He also participated in a pilot study to evaluate the risk of transmitting HIV through blood transfusions in Germany. Using the test manufactured by the U.S. company Abbott Laboratories Ltd. (Abbott), donors were tested at major community and university blood banks in Berlin, Bremen, Bonn, Freiburg, Göttingen, and Tübingen. A total of 6,720 donors were tested, of whom 0.16 per cent were positive for the antibody on confirmatory testing. Professor Hunsmann wrote to federal health officials, expressing his concern about the rate of infection among German blood donors, and requested an additional grant of DM 250,000 (Can\$109,875) for further research to develop a test. On 3 December 1984, the Diagnostics Committee of the German Association for the Control of Virus Diseases rejected Professor Hunsmann's proposal because his test was not sufficiently sensitive or specific, and the number of false positive and false negative results would cause confusion. Instead, the committee decided that HIV testing should be limited to pilot studies performed in virological institutes.

On 12 December 1984, the Federal Health Office published amendments to the June 1984 Order. The amendments provided that, as of 1 July 1985, HIV testing of blood and plasma donations would be mandatory. However, until HIV testing was introduced, manufacturers and blood centres could test for anti-HBc. The manufacturers objected to this early date, and in February 1985, because no test had yet been approved in the United States and none was available in Germany, the date for the implementation of HIV testing was extended from 1 July 1985 to 1 October 1985. The manufacturers would be required to use the test as soon as it became available in Germany, and they would not be permitted to offer for sale any drugs manufactured from untested blood after 1 October 1985. The Federal Health Office also stated that any sale to patients or hospitals constituted a violation of the *Pharmaceutical Act*.

In February 1985, officials from Abbott presented their HIV test to members of the medical profession, including federal health officials. On 11 March 1985, Professor Hunsmann wrote to the Minister of Health a second time, requesting reconsideration of his proposal, but he received no reply. Blood banks in Germany eventually purchased test kits developed by Abbott.

In April 1985, the Federal Health Office published guidelines for the implementation of testing in the *Federal Health Bulletin*. These "Guidelines for Determining Blood Groups and Administering Blood Transfusion" required that all blood donations be tested for HIV as soon as possible, and no later than 1 October 1985. On 5 June 1985, the Abbott test was licensed for use in Germany, and as of 1 October 1985 all blood donations were tested for HIV.

The Investigation Committee considered that Professor Hunsmann's finding that 0.16 per cent of donations were positive for HIV should have been regarded as an important one, and it concluded that the Federal Health Office should have taken action immediately. Instead, the matter was not brought to the attention of the Minister of Health until April 1985. In evidence before the Investigation Committee, the Minister stated that he did not think that prompt acceptance of Professor Hunsmann's offer would have expedited the implementation of HIV testing because the manufacturers and the Red Cross would have insisted on an extension of the deadline imposed by the Federal Health Office. In fact, he continued, the delay was advantageous, given the potential for confusion surrounding false positive and false negative results. The Investigation Committee disagreed. It regarded the rejection of Professor Hunsmann's proposals as evidence that "rapid and proper consideration for safety of the blood supply was hampered by negligent or procrastinating processing by bureaucrats."

Infections caused by heat-treated factor VIII concentrate

In the spring of 1986, it became evident that patients who had been treated with heat-treated factor VIII concentrate were becoming infected with HIV. On 5 April, an article published in *The Lancet* described isolated cases of HIV infection in hemophiliacs in other countries who had been using dry heat-treated factor concentrates. The risks of dry heat treatment were outlined at a conference in May 1986. Professor Gurtler, a treating physician, gave a presentation entitled "Unexplained Seroconversions after Substitution with Heat-Inactivated Factor Concentrates" in which he spoke of the risks of dry heat treatment and said that "uncertainty persist[s] with respect to the possibility of HIV transmission." At a hemophilia symposium held in the autumn of 1986, it was reported that there had been seven cases of HIV infection in Munich after the conversion to dry heat-treated factor concentrates. The Federal Health Office was immediately informed of these seroconversions.

In response to these reports of HIV infection after the use of heat-treated factor concentrates, the Federal Health Office developed a multi-stage plan for heat-treated factor VIII concentrate on 13 October 1986. It requested from the manufacturers information about their donor-screening methods, tests performed, package inserts, and inactivation processes. It requested an assessment of the efficacy of the inactivation procedures used, and an opinion about the risk of HIV transmission from HIV-negative donations. In their responses, Behringwerke and Alpha stated that they used a wet heat-treatment method.

The next month, Dr Reinhard Kurth of the Paul Ehrlich Institute was given the task of assessing viral inactivation methods then being used by the manufacturers. He found that dry heat inactivation methods achieved a reduction of 4 logs, and concluded that "blood products available on the German market undergo inactivation processes which prevent the transmission of

HIV.” Dr Karl Stockhausen of the Federal Health Office reported that HIV was very heat sensitive. He stated that “it was not discernible whether there was any difference in efficacy with respect to virus inactivation between the individual processes,” and that “seroconversion cases offered no assistance in this regard.” In his opinion, there was no need for regulatory intervention. On 27 May 1987, the Federal Health Office wrote to all the participants in the multi-stage plan, saying that “[r]eports of individual cases of seroconversions in hemophilia patients who have received heat-treated factor products ... do not reveal any clues as to the possibility of insufficient efficacy of the heat inactivation process employed.” The Federal Health Office terminated the multi-stage plan for heat-treated factor VIII concentrate without making any recommendations.

Many persons working within the blood manufacturing industry were perplexed by the Federal Health Office’s assessment of the viral inactivation methods. On 1 July 1987, Dr Jürgen Schuster, the general manager of Immuno, wrote to Dr Manfred Steinbach, the director of the Department for Public Health in the federal Ministry of Health, to say that the findings caused specialists in the field to “shake their heads in disbelief.” He attached to his letter the proceedings of a round table held in May 1986 in which the participants discussed the “enormous differences in the inactivation processes.” He asked why there were no regulatory requirements for viral inactivation; why no minimum requirements respecting the efficacy of these processes had been established; and why no corresponding measures had been taken for factor IX concentrate, since the rates of HIV infection were comparable. In reply, Dr Steinbach asked Dr Schuster for more precise data on the efficacy of various heat inactivation processes. On 13 August 1987, Dr Schuster replied that at the end of the first multi-stage plan, the industry had offered to stop marketing non-heat-treated factor concentrates, but had received no response from the Federal Health Office. He also stated that Immuno had of its own accord changed from the dry heat process to wet heat inactivation for reasons of efficacy.

Again, on 11 December 1987, as part of the multi-stage plan for human proteins including albumin, the Federal Health Office assessed the inactivation processes used by manufacturers and concluded that “the manufacturing processes correspond[ed] to the current scientific state of the art,” and that they “present[ed] no risk of HIV transmission with a probability that borders on certainty.” As a result, no mandatory requirements for viral inactivation were introduced.

The Investigation Committee was puzzled by the benign conclusions of the participants in the multi-stage plan for two reasons. First, scientific evidence offered at the round table held in May 1986 revealed “enormous differences in the inactivation processes”; and, second, in November 1986, seven cases of seroconversion had been reported in Munich after the use of dry heat-treated factor concentrates.

Infections caused by PPSB

During the autumn of 1986 it was discovered that patients who had been treated with heat-treated PPSB were also becoming infected with HIV. In September 1986, Dr L'age-Stehr learned of a seroconversion in a non-hemophiliac, a fifty-nine-year-old woman in Mutlangen who had been treated with PPSB manufactured by Biotest under the tradename "Marcumar." On 9 October 1986, Dr L'age Stehr received the case report from a clinician at the University of Frankfurt on Main. It indicated that PPSB administered in August 1985 was the most likely cause of transmission. Until then, the Federal Health Office had not realized that factor concentrates were administered to non-hemophiliacs. Dr L'age-Stehr sent Dr Stockhausen a case report of another suspected HIV infection through PPSB that had occurred in August 1985, and made the point that the conditions for approval of all blood products should be reviewed, and that donor screening and inactivation processes should be required for all factor concentrates. On 2 February 1987, the Federal Health Office became aware of yet another seroconversion related to use of PPSB. Its health officials took no action, and in fact did not inform Dr L'age-Stehr about it.

On 10 February 1987, the Federal Health Office held a meeting to discuss the Robert Koch Institute's evaluation of heat treatment methods. At the meeting, Dr L'age-Stehr revealed that the Federal Health Office had received reports of five cases of HIV infection resulting from the use of factor IX concentrate, and of one seroconversion resulting from the use of PPSB. Finally, in June 1987, a case of seroconversion, from Behringwerke PPSB, was discovered in Frankfurt and was reported to federal health authorities. A report of these two "Frankfurt" seroconversion cases was subsequently published in *AIDS Forschung* in December 1988.

To address concerns about the infectivity of these factor concentrates, the Federal Health Office on 12 August 1987 announced the development of a multi-stage plan for factor concentrates other than factor VIII concentrate. On 23 September, Dr L'age-Stehr wrote to Dr Stockhausen of the Federal Health Office, and to the president of the Federal Health Office, asking that physicians and patients treated with PPSB be informed about the risks of non-heat-treated PPSB. On 7 October, she wrote to the president of the Federal Health Office, the legal section, and the heads of the Robert Koch Institute and the Pharmaceutical Institute to inform them that non-heat-treated PPSB was still on the market and to request that measures be introduced to protect patients.

Reports of seroconversions related to the use of PPSB continued to be received well into 1990. On 28 March and 2 May 1989, the German blood product manufacturer Biotest was informed by its American supplier of plasma that at least four donations made in January, destined for use in a batch of PPSB, came from donors who had since seroconverted. In spite of this knowledge, Biotest pooled the potentially contaminated donations in June 1989. The batch containing donations from donors then known to be HIV positive was

produced the next month and was marketed on 18 October 1989. In April 1990, it was learned that at least twelve seroconversions were linked to the same batch of PPSB, and that at least three non-hemophiliacs were among those persons infected. Although Biotest insisted that all donations used for this batch had tested HIV-antibody negative, it was proved by means of a p-24 antigen test for HIV that the batch was contaminated, and an examination of the viral inactivation process revealed that the cold sterilization process used “displayed an insufficient capacity whose limits may have been exceeded by a high virus load in the starting material.” Biotest then recalled the 2,363 ampoules of the product from the market (of which 1,853 had already been used), and the Federal Health Office revoked its regulatory approval of the product.

The Investigation Committee concluded that the discovery of the Mutlangen case should have caused federal health officials to review their policy with respect to viral inactivation and recall. It found that it was “incomprehensible ... why the investigation had not been pursued further,” and concluded that since it was probably PPSB manufactured by Behringwerke which had caused the seroconversion, the Federal Health Office had ample reason to suspect that the viral inactivation process was insufficient and should therefore have told the states to recall the old, questionable factor concentrates still on the market. It found that the Federal Health Office had failed to implement any tracing measures of persons directly infected by PPSB or secondarily infected. The Investigation Committee also concluded that Behringwerke should have recalled its dry heat-treated PPSB as early as 1985.

With regard to the seroconversion attributed to Biotest, the Investigation Committee concluded that the manufacturer should have immediately discarded the potentially contaminated donations in accordance with the legislation prohibiting the marketing of unsafe drugs. In defence of their actions, Biotest officials stated that they were not legally required to respond to “look-back” reports, reports identifying donors subsequently found to be HIV positive. Moreover, since Biotest employed an effective viral inactivation process, it was unnecessary to do so. The Investigation Committee did not agree, stating that “a donation must be discarded despite a negative HIV test if justified suspicion exists that it might nevertheless be infectious.” It also considered it “incompatible with the responsibilities of a drug company” to purchase from a supplier whose donor population had a high incidence of HIV infection.

Finally, the Investigation Committee questioned why the Paul Ehrlich Institute, which was aware that the degree of inactivation achieved by the Biotest process was less than that afforded by dry heat treatment, did not inform the Federal Health Office of this fact. After learning in November 1986 from Professor Kurth that the Biotest process resulted in insufficient levels of inactivation, the Investigation Committee was of the view that the Paul Ehrlich Institute should have made the Federal Health Office aware of the results and taken some action to prevent the later seroconversions.

Use of imports

On 23 June 1983, the Council of Europe published recommendations to prevent the spread of the AIDS infection. In part, it recommended that member nations discontinue the importation of American blood products and begin to become self-sufficient. As was stated earlier, because Germany relied heavily on blood products imported from the United States, the Food and Drug Administration contacted Federal Health Office officials to determine whether Germany would be imposing a ban on American imports, and was told that a complete import ban was not under consideration.

The issue of self-sufficiency was the subject of debate during the autumn of 1983. The suggestion of banning imports was discussed in a meeting in November 1983 organized by the Federal Health Office, but was rejected because there were insufficient supplies to meet the needs of hemophiliacs. The idea of reducing the use of American concentrates was also dismissed by representatives of the German Hemophilia Society. At meetings held on 6 December 1983 and 21 January 1984, the Federal Health Office discussed the issue of self-sufficiency with the Red Cross. Another meeting was held on 26 January 1984 to discuss the prospect of increasing the domestic production of factor VIII concentrate, but Red Cross officials stated that they were not prepared to respond to this request.

The Federal Health Office did not pursue the matter further. The Order issued in June 1984 contained no restrictions on the use of imported factor concentrates. Although the Order of June 1984 provided that manufacturers of blood products had to submit information about country of origin or manufacture, and prohibited the mixing of plasma from different countries, the provisions were deleted because of objections from the Red Cross and the blood product manufacturers that they were not necessary.

The Investigation Committee determined that the Federal Health Office had failed to encourage self-sufficiency, largely because of the Red Cross's resistance to discarding blood supplies and to donor screening.

Informing hemophiliacs of the risk

In December 1981, Dr Weise asked the president of the Federal Health Office for consent to establish an ad hoc commission to recommend quality requirements for manufacturers and to make recommendations about the use of factor concentrates. The commission, named the Commission on Standardizing the Use of Factor VIII and Factor IX Concentrates, was created in the spring of 1982 and met for the first time on 2 November 1982. The commission held four meetings during 1983 and 1984, and by June 1984 had prepared a memorandum entitled "Clinical Practice in Therapy of Hemophilia A and B – Indication in Therapy with Factor VIII and Factor IX Concentrates" that was published in the *Federal Health Bulletin* in June 1985. The article discussed the problem of transfusion hepatitis, but stated that the risk of transmitting the

AIDS virus through the use of clotting factor concentrates, “although possible according to the current state of knowledge ... is considered to be very low based on available data.” A change in therapy was therefore not recommended.

At the public meeting organized by the Federal Health Office on 14 November 1983, the exclusive use of cryoprecipitate was rejected, as was a ban of imported blood products. However, the Order of June 1984 stated that the use of concentrates should be limited to persons with blood coagulation factor VIII deficiencies. Many multi-stage plan participants objected to this provision on the basis that it interfered with freedom of treatment.

The Order of June 1984 also required the manufacturers to warn patients that factor concentrates “may cause infectious diseases through transmission of pathogens of hitherto unknown nature (for example, pathogens of non-A/non-B hepatitis and AIDS).” However, many blood product manufacturers objected to the publication of a possible link between the name of their factor concentrates and the transmission of AIDS, although they accepted the fact that there was a potential risk of contracting non-A, non-B hepatitis. In the amendments published by the Federal Health Office in December 1984, the required notice for product inserts was revised. These product inserts were now to state that “[t]he use of factor VIII preparations may cause infectious disease through the transmission of viruses, including viruses as yet unknown. This refers to non-A/non-B hepatitis and, more rarely, to the ‘acquired immune deficiency syndrome’ (AIDS).” This notice became mandatory on 1 March 1985.

In July 1988, manufacturers of factor concentrates were told that the Federal Health Office intended to have a regulation made to require that product inserts warn consumers about the possible transmission of HIV-2. The regulation was published on 11 December 1988, to take effect immediately.

The Parliamentary Committee found that irrespective of warning labels or package inserts, physicians owed a duty to their patients to inform them of the risks inherent in their treatment, and that “[e]ven lifesaving treatment like that administered to hemophiliacs requires legally effective patient consent.” However, the Parliamentary Committee was unable to assess whether physicians had in fact fulfilled this duty.

As stated earlier, a memorandum published by the Commission on Standardizing the Use of Factor VIII and Factor IX Concentrates in June 1985 stated that the risk of AIDS transmission was “possible,” but “very low based on available data,” and recommended no change in therapy. The authors of this memorandum subsequently acknowledged to the Investigation Committee that the statement was inaccurate, but was a reflection of the fact that the memorandum had been prepared a year earlier and had not been appropriately revised to reflect what was known in 1985. The Investigation Committee concluded that this oversight was “not in keeping with the mandate of the Federal Health Office, which was to protect the consumer and to provide safe drugs.”

Informing transfusion recipients of the risk

In recent years, several measures have been taken to find persons who may have become infected through blood and blood products. The Parliamentary Committee reported that the federal Minister of Health had asked the German Medical Association and the German Hospital Association to examine methods of tracing recipients of blood products. The Minister also stated that he planned to investigate the possibility of developing methods of tracing individual recipients of blood products sold before 1985. On 20 November 1992, the Federal Health Office issued a directive, requiring blood product manufacturers to minimize the risk of HIV contamination by excluding HIV-contaminated original material, whether or not an effective inactivation process had been used.

On 11 February 1993, the Federal Health Office informed multi-stage plan participants that efforts must be made to find persons already infected and stated that the cost of tracing was necessary to prevent further transmission. With respect to the infected Biotest batch of PPSB, the states were asked to find other affected individuals, to ensure that they were tested, and to report on the results. The Federal Health Office examined the feasibility of tracing all pre-1985 records on the basis of the experiences of one hospital in Siegen, and announced that amendments to the guidelines on look-back were also being contemplated. That autumn the federal government also advised anyone who had had major surgery in the past ten years to have an AIDS test. Finally, in November 1993, the Ministry of Health called for mass testing of all patients who had received transfusions or other blood products since the early 1980s.

In its report, the Investigation Committee found that more could have been done to find potentially HIV-infected persons. It found that it was not until February 1993 that the Federal Health Office informed participants of the multi-stage plan of the risks posed to patients treated with PPSB, and that the "transmission of HIV infection by blood and blood components, including blood coagulation factor concentrates that were marketed and used in the years up to 1985, is not completely improbable." It urged that "all possible efforts must be undertaken to identify those already infected," and that efforts would "require a review of patient files and, where necessary, notification of the affected patients."

Summary of findings and recommendations made by the Parliamentary and the Investigation committees

Interim and final reports of the Parliamentary Committee

The Parliamentary Committee made some suggestions for future actions to improve blood safety and it discussed the measures that, at the time, were under consideration. The measures included the quarantining for six months of plasma that had not been subjected to viral inactivation processes; p-24 antigen and polymerase chain reaction (PCR) testing for HIV; the

exclusion of imports from certain countries; and a reduction in the size of plasma pools. It also considered other long-term measures that were currently being examined:

- *Legislative amendments* The Parliamentary Committee said that the Federal Health Office did not, but should, have the legislative authority to order heat treatment. It stated that the *Pharmaceutical Act* might need to be amended to expand the powers of the Federal Health Office. The Parliamentary Committee was also of the opinion that the legislation might need to be amended to require physicians to report undesirable side-effects, and to expand the duty of manufacturers to report the side-effects of all drugs made from human blood and all sera and vaccines.
- *Tracing* The Parliamentary Committee concluded that physicians should record batch numbers in patient records and that a centralized, computerized link between factor concentrates, batch numbers, and patients was required. The federal Minister of Health asked the German Medical Association and the German Hospital Association to examine the problem.
- *Inspections* During the 1980s, blood product manufacturers were inspected every two years. The Parliamentary Committee recommended that the states intensify their efforts in monitoring the quality of blood products. The federal Minister of Health announced that there would be more frequent plant inspections and batch sampling. Under state regulations, drugs may not be imported unless they are accompanied by a certificate that their manufacturers have complied with the guidelines established by the World Health Organization and the Pharmaceutical Inspections Convention. At the request of the federal Minister, the participants at a special meeting of states held in January 1993 discussed methods by which states could better monitor the quality of blood products, but the meeting did not result in any agreement among the states. In May 1993, the federal Minister of Health again asked the states for their position on this issue, and was informed that local blood donor clinics would be monitored more closely and that blood products would be sampled and tested on a priority basis.
- *Use of blood and blood products* As a result of the work of the Parliamentary Committee, the federal Minister of Health proposed that the use of autologous donations be promoted and that the use of factor concentrates be reduced. The Federal Centre for Health Education was instructed to develop a plan to determine the measures that could be taken to assist blood centres, hospitals, and physicians in educating the public about autologous donations. To reduce the use of concentrates, a working group developed new treatment guidelines that were adopted at a meeting of the German Hemophilia Association in February 1993. The federal Minister for Health also asked the German Medical Association to revise its guidelines for treatment with blood and blood products.

- *Self-sufficiency* As stated earlier, approximately 60 per cent of the plasma used in Germany is imported. As a result of the Parliamentary Committee's report, a study of self-sufficiency was undertaken by the federal government and completed in September 1993. The federal Minister for Health later announced that he would invite all the participants in the blood system to establish a firm timetable for achieving self-sufficiency, and asked a group of experts to prepare a plan for doing so.
- *Working group on blood* In its reports, the Parliamentary Committee stated that the federal government intended to establish a working group consisting of representatives of the blood donor services, the blood transfusion services, the states, the Federal Health Office, the Paul Ehrlich Institute, and the pharmaceutical industry. The group would be asked to determine research requirements, evaluate test methods, select reference laboratories, examine the possibilities of establishing a comprehensive quality control system, organize information exchanges, and give expert opinions. The working group, named the Working Group on Blood (Arbeitskreis Blut), was established in September 1993 at the Robert Koch Institute. The first group sat until 1995; the current group, consisting of thirty members, will work until the end of 1998.

The Parliamentary Committee did not find any evidence of wrongdoing by the Federal Health Office, and could not therefore support a claim for compensation based on negligence. Although there had been requests for a compensation scheme similar to the one created in France, the Parliamentary Committee rejected this request, concluding that the facts and the law in the two countries were very different. However, in its final report, the Parliamentary Committee concluded that existing compensation payments were inadequate and should be increased. It therefore recommended that the federal and state governments, and the manufacturers, hospitals, and physicians involved, establish a fund of DM 400 million to DM 700 million (Can\$319,440,000 to \$559,020,000) to compensate persons directly and indirectly infected. The Parliamentary Committee also concluded that the German government should follow the example of France and publicly apologize to persons infected.

Interim report of the Investigation Committee

At the first meeting of the Investigation Committee on 11 November 1993, it was unanimously agreed that current issues should be examined as a first priority. Its interim report, published in January 1994, dealt exclusively with two issues: the improvement of the safety of the blood system and financial compensation for persons infected with HIV or AIDS.

To improve the safety of the blood supply, the Investigation Committee recommended that all regulations affecting the purity and safety of biological products be brought within one single statute – a “transfusion act.” To

protect against HIV transmission in the short term, it recommended that a manufacturing permit be required for collecting blood and plasma; that blood, blood products, vaccines, and sera be subjected to the same licensing requirements; that regulations to ensure traceable record keeping in the use of blood and blood products from donor to patient be introduced; that licensing authorities be empowered to issue immediate binding orders; that senior federal agencies responsible for blood and blood products be given authority to order a recall of suspect drugs (a power currently vested in states); that licensing authorities be given authority and responsibility for assessing viral inactivation methods and prescribing a specific level of inactivation; and, finally, that legislative amendments be enacted to require pharmaceutical manufacturers to report cases of HIV transmission and to require users (i.e., physicians and clinics) to report them. The Investigation Committee considered that three additional measures were essential for the safety of the system in the long term. They included the improvement of the reporting and risk management systems to remedy structural deficiencies; the establishment of a plasma donor system and a national plasmapheresis program within a specified period of time; and the creation of an independent federal institution with clear jurisdiction over licensing, quality control, and recalls.

The Investigation Committee also examined the adequacy of economic and social support given to persons infected with HIV from blood and blood products, and the appropriate level of, and eligibility for, financial compensation. As of the date of release of the interim report, 1,249 hemophiliacs had been compensated of a total of 1,346 reported claims. The committee concluded that financial compensation must be given to all persons infected, though it acknowledged that blood product manufacturers and insurers were not supportive of this recommendation, and that the attitude of the states had also not been very supportive. It said that in cases of unclear causation, consideration should be given to compensation similar to no-fault automobile insurance and collective self-insurance by drug manufacturers. However, to provide more immediate relief to persons affected, the Investigation Committee recommended that amendments be enacted to the *Pharmaceutical Act*. Specifically, it recommended that protection be extended to persons secondarily infected; that the rules of evidence be relaxed so that they conform with the standards of the European Union, which do not require persons infected to give evidence; that the maximum amounts awarded under strict liability be increased; and that claims for pain and suffering in compensation for non-pecuniary damages involving loss of life or severe health impairment be permitted.

Final report of the Investigation Committee

In its final report, published in October 1994, the Investigation Committee gave a detailed account of past events and made the following assessment of the performance of the Federal Health Office in preventing the transmission

of hepatitis B and HIV or AIDS. The Investigation Committee found that the Federal Health Office was informed of the risk of the transmission of hepatitis viruses through blood and blood products at the end of the 1960s and the beginning of the 1970s, and that blood product manufacturers were also aware that the transmission of hepatitis represented a serious problem in the use of clotting factors. Blood product manufacturers, the Federal Health Office, and physicians knew that, because 90 per cent of the plasma for the production of factor VIII concentrate was imported, there was an even greater risk of hepatitis infection. Virus-inactivated factor concentrates were introduced for PPSB in 1976 and for factor VIII in 1981. The introduction of virus-inactivated concentrates did not lead to an immediate switch to these factor concentrates, or to the withdrawal of non-heat-treated concentrates. Both heat-treated and non-heat-treated blood products were available on the market at the same time. The Investigation Committee concluded that while physicians treating hemophiliacs must also have known about the transmission of viral hepatitis agents, most of them did not treat patients with heat-treated factor concentrates until 1983–4. The Investigation Committee stated that the lack of communication between health authorities, manufacturers, and physicians with respect to hepatitis was “inadequate and must be considered an omission.”

As noted earlier, the Investigation Committee concluded that the actions by the Federal Health Office to reduce the risk of the transmission of AIDS by factor VIII concentrate were inadequate. It found that efforts by the Federal Health Office to investigate the first hemophilia case were met with resistance by treating physicians; that physicians denied the existence of AIDS in 1983; that the impetus for action came from without the Federal Health Office (from the U.S. Food and Drug Administration); that the Federal Health Office failed to acknowledge the risk associated with factor IX concentrate, PPSB, fibrinogen, and blood components, despite suggestions made by blood product manufacturers and persons working within the Federal Health Office, and therefore confined its early efforts to the risk associated with factor VIII concentrate; that the Federal Health Office failed to include a requirement in the December 1984 Order that blood products be virally inactivated despite repeated requests to do so by blood product manufacturers; that the federal and state governments did not order manufacturers to recall non-heat-treated factor concentrates; and that HIV-antibody testing may well have been delayed by the rejection of Professor Hunsmann’s proposals to develop a test.

As for efforts to reduce the risk of HIV transmission through factor IX concentrate and PPSB, the Investigation Committee concluded that “a chain of errors in judgment and omission had occurred at the Federal Health Office in the control of the risk of these infections.” First, the Federal Health Office erred in its assessment of the risk posed by blood and blood products. It failed to recognize that both patients with hemophilia A (treated with factor VIII

concentrate) and patients with hemophilia B (often treated with PPSB) were equally at risk of contracting AIDS. The Investigation Committee also found that federal health officials were not even aware that in some instances PPSB had been used to treat non-hemophiliacs. The Investigation Committee concluded that although the Federal Health Office was unable to state with accuracy what quantity of PPSB was used during the 1980s, it estimated that it may have been administered as often as 30,000 times a year. The Federal Health Office did not make any recommendations for therapy until 1988.

Second, the Federal Health Office erred in addressing the risks associated with the use of factor VIII concentrate and in ignoring the risks associated with the use of other blood products. The multi-stage plan addressed the risk of AIDS transmission through factor VIII concentrate, but failed to examine the risk to recipients of PPSB and factor IX concentrate. For example, although the amended Order published on 12 December 1984 respecting donor selection and testing implicitly applied to factor IX concentrate and PPSB, since these products were derived from the same source as factor VIII concentrate, other important provisions of the Order, such as the requirements that package inserts include a warnings about AIDS, did not.

Third, when confronted with the first confirmed case of transmission by PPSB involving a non-hemophiliac (the Mutlangen case) in September 1986, the Federal Health Office failed to act. The Mutlangen case was regarded by the Investigation Committee as a missed opportunity to extend the multi-stage plan to blood products other than factor VIII concentrate and to address the inadequacies of the plan. It stated:

The "Mutlangen" case was not taken as the cause for immediately establishing a connection with the multi-stage plan in force at that time, addressing the effectiveness of viral inactivation processes in factor VIII products, and to extend it to non-factor VIII products, or at least to react with a belated ruling by setting a firm deadline for all PPSB products for which no inactivation measures were required at all, or to advise the federal states to recall all the "old," questionable products still on the market. [Translation.]

The Federal Health Office did not, however, take this opportunity to review the adequacy of the multi-stage plan. Moreover, as a result of poor communication within the Federal Health Office, Dr L'age Stehr and Dr Koch were not informed of the second PPSB case reported in February 1987. Despite the similarities to the Mutlangen case, and repeated efforts by Dr L'age-Stehr to alert Federal Health Office officials to the absence of measures dealing with the transmission of AIDS through PPSB, the Federal Health Office again took no action.

Finally, the Federal Health Office failed to implement any measures to trace persons directly and indirectly infected by PPSB. The Investigation Committee found that the Mutlangen case did not prompt the Federal Health Office to find other patients exposed to the same risk or to take any measures to prevent possible secondary infections. The Federal Health Office did not inform the participants in the multi-stage plan of the risk incurred by recipients of PPSB and of the need for systematic tracing of all patients exposed to HIV before February 1993. In fact, the Investigation Committee learned through the course of its work that the Federal Health Office had deliberately given false information both to the media and to Parliament (Bundesrat) about the early PPSB cases.

In summary, the Investigation Committee concluded that not only the Federal Health Office but all parties – blood product manufacturers, physicians, blood donor services, hospitals, and federal states – had failed to safeguard the blood supply. It found that in 1983 there was sufficient experience with virus-inactivated Behringwerke factor concentrates, and sufficient information respecting the cause and transmissibility of AIDS through blood and blood products, to require the use of heat-treated concentrates exclusively after a transition period, and that many HIV infections could have been avoided. The Investigation Committee also concluded that infected persons were entitled to damages for pain and suffering. The Investigation Committee acknowledged, however, that a number of infected persons would be unable to make such claims, because proving causality was often an insurmountable problem, and many persons were unable to initiate legal proceedings owing to their limited life expectancy. The Investigation Committee did not consider that it would be appropriate to recommend that infected persons take legal action, and that to encourage a recourse to legal proceedings in these circumstances would be incompatible with the “principles of a social state.”

The Investigation Committee recommended that compensation should be granted in cases in which the causal link could be demonstrated between the transfusion of blood and blood products and subsequent HIV infection; that persons secondarily infected should be entitled to compensation; and that, after the death of persons infected, benefits should be paid to their dependants. It also recommended that one of the following compensation models should be adopted. Under the first proposed model, blood product manufacturers, the federal government, state governments, and physicians would provide for suitable compensation through the creation of a fund. Second, in the event that there was continued resistance to participation in a fund, a public corporation could be created. Blood product manufacturers and blood transfusion organizations would then contribute 60 per cent of the cost, federal governments, 20 per cent, state governments, 15 per cent, and physicians, 5 per cent. Third, the federal government could establish an item in its budget to provide for appropriate compensation. Infected persons would

then make their claims against other parties at fault in the amount allowed for under the budget, and the federal government would take legal proceedings against those parties to collect the compensation. If the benefits were not equal to the full amount of the appropriate compensation for damages for pain and suffering, persons infected and affected would continue to seek damages. The response of the federal government to these compensation proposals is discussed below.

Assistance to persons infected and affected

Insurance payments

Because section 84 of the *Pharmaceutical Act* provides for strict liability, a person who has suffered severe damage to his or her health, or serious disease after using a particular drug, is not required to prove negligence on the part of the manufacturer to obtain compensation. The affected person must only prove that he or she suffered harm as a result of using the product. The legislation also provides that payments are to be made solely for the purposes of compensating for loss of property and income, and not for physical injury or damage, for which proof of negligence is necessary. Payments made under the legislation cover HIV-related loss of income, treatment costs, increased personal needs, funeral expenses, and financial support of dependants. In most instances, insurers have only been required to make payment when applicants were suffering symptoms of the disease, but in the case of HIV infection, testing positive for the disease was sufficient to establish eligibility.

In 1986, the German Hemophilia Society approached blood product manufacturers to request compensation payments for hemophiliacs suffering from HIV or AIDS; for their HIV-infected wives and children; for hemophiliacs who had already died of AIDS; and for dependants of persons deceased. The next year, the society formed a special committee to conduct future negotiations. In the interim, pharmaceutical manufacturers had forwarded the matter to their insurers for settlement, and negotiations with the insurers were initiated in mid-1987. The insurers then established a coordinating committee and, in February 1988, payment options were discussed.

A payment plan developed by the coordinating committee came into effect at the end of 1987. Payments were made directly by the insurers of blood product manufacturers. If a patient had been treated with concentrates supplied by various blood product manufacturers, the insurer of the pharmaceutical manufacturer from which the patient had received the greatest amount of concentrates after 1 January 1979 was required to make payment.

All awards were lump-sum payments, limited to a maximum of DM 500,000 (Can\$388,500). Payments varied depending on the person's income, social and educational level, and family status. Hemophiliacs with HIV or AIDS received from DM 45,000 (Can\$34,965) to DM 350,000 (Can\$271,950), on average about DM 70,000 (Can\$54,390) to DM 80,000 (Can\$62,160); HIV-infected spouses received DM 25,000 (Can\$19,425);

students in high school or university and vocational trainees received a maximum of DM 80,000 (Can\$62,160); and for children under eighteen years, appropriate payments were calculated and approved by the court. Funeral expenses were reimbursed, and an allowance made for future funeral expenses of DM 7,500 (Can\$5,827). Where payment compensated loss of future income, the payment was not automatically tax exempt, although German taxation authorities were asked by the government to be lenient. All other payments were tax exempt and made in strict confidence, the name of the recipient being known only by the insurer.

As of December 1988, approximately 1,200 applications for payment had been received, and almost all applicants had received payment. As of that date, the total sum that had been paid out was DM 100 million (Can\$68,150,000).

Government assistance

In 1987, the German Hemophilia Society unsuccessfully sought additional financial assistance from the German government. Efforts to obtain financial assistance were resumed in late 1992 and were aided by the work of the Parliamentary Committee, whose report was made public in October 1993. As was stated earlier, the Parliamentary Committee concluded that compensation payments made by insurers were inadequate, and recommended that additional financial assistance be given. Shortly thereafter, the federal government announced that it would allocate DM 2 million (Can\$1,511,400) from the 1994 budget for such payments, and it asked blood product manufacturers, the states, the Red Cross, and insurers to contribute to a compensation fund.

In March 1995, the federal government announced that a formal compensation fund of DM 3 million (Can\$3,004,200) would be created, and legislation establishing the fund was enacted and proclaimed in force in July 1995. Under the *Act Concerning Humanitarian Assistance for Persons Infected with HIV Transmitted through Blood Products (HIV Assistance Act)*, the federal government contributed DM 100 million (Can\$100,140,000), the states, DM 50 million (Can\$50,070,000), and the Red Cross, DM 9.2 million (Can\$9,212,880). The *Act* stated that the blood product manufacturers Bayer AG, Immuno GmbH, Baxter Deutschland GmbH, Behringwerke AG, Armour Pharma GmbH, and Alpha Therapeutic GmbH must contribute the sum of DM 90.8 million (Can\$90,927,120) to the fund.

A public foundation, the Humanitarian Assistance for Persons Infected with HIV through Blood Products, was established in Bonn, and a council composed of representatives from the federal Ministry of Health, the German Parliament, the Red Cross, blood product manufacturers, and the German Hemophilia Society was created to administer the funds.

The following persons are entitled to claim benefits: persons directly infected with HIV or AIDS before 1 January 1988 as a result of blood products distributed in Germany; persons secondarily infected by such persons; and

non-infected spouses, partners, and children of infected persons. The awards vary significantly. HIV-infected persons are entitled to receive a monthly benefit of DM 1,500 (Can\$1,502), but persons with AIDS receive a payment of DM 3,000 (Can\$3,004) without regard to former income or financial circumstances. On the death of the infected person, his or her children are entitled to receive DM 1,000 (Can\$1,001) a month until the age of twenty-five; spouses also receive DM 1,000 a month for a period of five years. Benefits are retroactive to 1 January 1994, and are non-taxable. Finally, persons receiving benefits may not bring actions against the federal and state governments, the Red Cross, and donors. They are, however, entitled to take legal proceedings made against blood product manufacturers pursuant to section 16 of the *Pharmaceutical Act*.

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Japan

The blood system in the 1980s

During the 1980s, donations of blood and plasma were collected exclusively by the Japanese Red Cross Society (Red Cross). Although factor concentrates were manufactured in Japan by a number of private corporations, much of the factor concentrates used by Japanese hemophiliacs were imported from the United States. Donations of blood and plasma were voluntary, but patients receiving blood or blood products were charged a fee and were reimbursed by the government under the health insurance scheme. The Ministry of Health and Welfare regulated the blood system.

The Japanese Red Cross Society

Commercial blood banks, where donors were paid for making donations, began to operate in Japan in 1951. That same year, the Red Cross appointed a committee on blood transfusion and opened a blood bank at Tokyo Medical University, where persons could donate blood. By 1963 there were six public blood banks, eleven Red Cross blood banks, and thirty privately owned blood banks in Japan. However, in March 1964, when the U.S. ambassador to Japan was wounded by a terrorist and contracted hepatitis from a blood transfusion, the blood system in Japan came under great criticism. In response to this incident, the government made an order in August 1964 stating that “the State and regional public bodies shall promote blood donation, the Japanese Red Cross shall put into place a system for receiving donated blood, and all stored blood shall be donated blood.” In December 1964, the government renamed the blood banks “blood centres” to remove any commercial connotation. By 1973, no commercial blood banks remained in Japan, and by the mid-1980s, the Red Cross had sixty-nine blood centres, with 111 branches. The blood program of the Red Cross was managed by a director general, in consultation with the president of the Red Cross and the Ministry of Health and Welfare.

During the 1980s, the Red Cross did not collect enough plasma to meet the national demand. Although there were more than eight million individual blood donations by Japanese donors in 1984, making per capita donation

rates in Japan and the United States comparable, donors in Japan were giving only 200 millilitres of blood on each visit, half the volume given by donors in other countries. As a result, Japan depended on the United States for nearly 90 per cent of its plasma needs. This demand for plasma rose throughout the early 1980s, from 1.05 million litres in 1980 to 3.4 million litres in 1984.

Blood product manufacturers

During the early 1980s, approximately 90 per cent of the factor concentrates used by Japanese hemophiliacs were manufactured from American plasma. They came from two sources. First, Japanese corporations manufactured factor concentrates in Japan from plasma imported from the United States. These corporations, notably Green Cross, an affiliate of the Alpha Therapeutic Corporation (Alpha) that operated in the United States, and Chemo Sero Therapeutic Research Institute (Chemo Sero), supplied over 80 per cent of the factor concentrates used in Japan. Second, companies such as Alpha, Bayer Yakuhin Limited (Bayer), Baxter Limited (Baxter), Nippon Zoki Pharmaceutical Company (Nippon Zoki), and Immuno AG imported factor concentrate from the United States.

The role of government

In 1954, the national government made regulations that defined stored blood as a pharmaceutical product under the *Drugs, Cosmetics and Medical Instruments Act*. As a result, the government acts as the regulator, licensing the use of blood and blood products. This function is performed by the Blood Operations Policy Office of the Pharmaceutical Affairs Bureau in the Ministry of Health and Welfare (Ministry).

Decisions made by the government about blood policy are communicated to both the Red Cross and the pharmaceutical affairs divisions of the forty-eight prefectures. These prefectures are comparable to states or provinces and play an important role in safeguarding public health. In its role as policy maker, the Ministry has made several attempts to promote voluntary blood donation and to reduce the dependency on imported blood products. In 1975, the Blood Issues Research Group, the advisory body to the Minister of Health and Welfare, recommended that all blood products be manufactured from donated blood. In April 1986, the government issued guidelines intended to reduce the consumption of blood products and to promote self-sufficiency. By 1990, the government hoped to reduce the consumption of blood products by 70 to 80 per cent, and to have half this demand met from domestic supplies.

Because blood and blood products are classified as pharmaceuticals, health care facilities purchase blood products at a price established by the prefectures. The price is generally the same throughout the country, and payments made by health care facilities are used to finance the blood system.

The Japan Hemophilia Fraternal Association

The Japan Hemophilia Fraternal Association, a non-governmental national organization, was founded in 1967. In 1980, the Japanese government required all hemophiliacs receiving financial assistance from the government for the treatment of their illness to register with the association. In 1983, it had a membership of 1,500 families, and each prefecture had its own local association. During the early 1980s, the primary function of the Japan Hemophilia Fraternal Association was to lobby government to ensure that the treatment of hemophiliacs was covered by medical insurance. This coverage has since been achieved, and in recent years the goals of the association have been to promote the welfare of hemophiliacs and their families, to give support to hemophiliacs infected with HIV, and to promote research into gene therapy.

Prevalence of blood-related HIV or AIDS

In Japan, almost half of all persons infected with HIV or AIDS have been hemophiliacs. Of the 5,000 hemophiliacs in Japan, 2,000 have been infected with HIV or AIDS. According to the World Federation of Hemophilia, the majority are thought to have been infected during the years 1983 to 1985 by non-heat-treated factor concentrates imported from the United States. It is not known how many transfused patients have been infected.

Protecting the blood supply from HIV or AIDS

Investigating past events

Beginning in 1996, the Japanese government made attempts to understand how hemophiliacs became infected with HIV or AIDS. When a new Minister of Health, Naoto Kan, was appointed in January 1996, he ordered a search of government files and created a study group, the Project Team Studying HIV Infection from Blood Products (Project Team), to examine the role played by the Ministry in the infection of hemophiliacs. The Project Team examined what was known about AIDS in 1983; what measures were taken in the United States to reduce the risk of transmission through blood and blood products; when the first blood-related AIDS case emerged in Japan; and how the Ministry responded to the emergence of AIDS. It also looked at the introduction of heat-treated factor concentrate, specifically whether the Ministry had made efforts to import heat-treated factor concentrates in 1983; whether regulatory approval of heat-treated factor concentrates had been given in a timely way; and whether efforts had been made to recall non-heat-treated factor concentrates after heat-treated factor concentrates became available for distribution. The Project Team completed its report in March, and in the spring of 1996 the Minister asked a parliamentary committee, chaired by Sadao Wada, to gather submissions and hear evidence about the contamination of the blood supply. Finally, in June 1996, Mr Kan announced

the creation of an independent panel of experts from the National Institute for Research Advancement to investigate the matter further. The seven-member panel, chaired by Professor Isao Kuroda of Waseda University, is expected to submit its report by the end of 1997. The findings of the Project Team and the parliamentary committee are discussed below.

The emergence of HIV or AIDS

Precisely when the first AIDS cases in Japan were diagnosed and recognized is unclear from the literature. One source reports that “the earliest onset of the disease was observed in August, 1981.” Another source, a letter published in *The Lancet*, places the first HIV infection of Japanese patients in 1982. There is evidence to suggest, however, that the first AIDS case in Japan appeared in 1983. What is clear is that the Ministry received two reports of AIDS cases in March 1985, and that it recognized them as the first AIDS cases in Japan.

These first two official AIDS cases in Japan were in hemophilia patients. According to the April 1985 issue of *Taisha*, a Japanese medical journal, these cases were probably caused by factor concentrates imported from the United States. Although both cases were reported to the Ministry in March 1985, one of them involved a patient who had died in 1983. It became known as the “Teikyō University case.”

By the end of 1984, there were reports of “transfusion-mediated” HIV infection among chronic hemodialysis patients in Nagasaki. The report stated that “it seems likely that one unit of potentially infectious blood is sufficient for infection” with HIV, and predicted that there would be five new carriers of HIV in Nagasaki every day, or 2,000 per year, due to transfusion. It stated:

[B]lood transfusion is clearly one of the factors increasing the reservoir of virus carriers, who in turn can be sources of further infection. It seems desirable to include an appropriate screening measure to prevent unnecessary expansion of the fraction of HTLV carriers in the population, at least in highly endemic areas, such as Nagasaki.

Three months after the first official announcement in March 1985 of the first two AIDS cases, the Ministry reported five additional cases of AIDS. Three of the patients were hemophiliacs, the other two were homosexual men. Again, officials from the Ministry suspected that the source of infection in the hemophilia cases was imported factor concentrates. Dr Takeshi Abe, the head of the AIDS Research Group, reported that the causative agent of AIDS was found in factor VIII concentrate, most of which was imported from the United States, and concluded that Japanese hemophiliacs were therefore at “high risk for AIDS.” Later that year, Dr Abe and colleagues again reported that Japanese hemophiliacs with HIV or AIDS appeared to have contracted the disease from imported factor concentrates. They called

for a large-scale epidemiological survey, using hemophiliacs as a test population. They also called for the urgent preparation of virus-free factor concentrate – specifically, heat-treated factor VIII concentrate.

Whether the 1983 case ought to have been reported as an AIDS case has been a subject of much debate. Both the Project Team and the parliamentary committee learned that, in July 1983, Dr Thomas Spira of the U.S. Centers for Disease Control had told the AIDS Research Group, an advisory panel established by the Ministry, that, in his opinion, the Teikyō University case had indeed died of AIDS. However, the members of the group did not accept this diagnosis because they did not believe that the clinical evidence supported it. The patient had been treated with steroids, his CD4 count was not particularly low, and he had neither *Pneumocystis carinii* pneumonia nor Kaposi's sarcoma. In short, the case did not meet the definition of AIDS established by the U.S. Centers for Disease Control. Moreover, the weakening of his immune system could be attributed to steroid treatment. The AIDS Research Group regarded it merely as a “suspected” case of AIDS.

Response to the emergence of HIV or AIDS

The purpose of the AIDS Research Group was to conduct AIDS research, monitor research, inform the Ministry about new developments relating to HIV or AIDS, and coordinate the work of various organizations involved in the prevention of HIV or AIDS. Among these organizations were the Blood Products Division and the AIDS Patients and Virus Carriers Future Estimate Research Group within the Ministry, the AIDS Prevention Foundation, the Japan Public Health Association, the Japan Society for AIDS Education, the Tokyo Metropolitan Research Group on AIDS, and local public health departments.

The AIDS Research Group gave advice to the Ministry on whether to approve heat-treated factor concentrates, to restrict the use of imported factor concentrates, and to alter treatment regimes of hemophiliacs. In September 1983, the AIDS Research Group created a blood products subcommittee to examine the safety of blood and blood products.

In September 1984, an AIDS surveillance committee was established in the Health Protection and Medical Treatment Bureau of the Ministry. It was asked to undertake AIDS surveillance with the cooperation of the prefectures. In 1986, the Ministry established a system in which physicians could report cases of HIV and AIDS. Reporting was anonymous but, until 1989, not mandatory.

In 1986, the Ministry distributed pamphlets that reassured members of the public that if they lived a “normal” life they faced almost no risk of contracting AIDS. Prefectural and municipal health officials attended seminars about the disease, but ignorance was common and many persons still regarded AIDS as a “foreign disease.”

In 1987, the Japanese government introduced legislation aimed at educating the public and tightening public health measures to reduce the spread of AIDS.

Many persons felt, however, that the law unnecessarily infringed civil liberties. As originally drafted, the legislation authorized prefectural governors to order persons with HIV or AIDS to undergo medical tests or treatment. It also allowed authorities to prohibit the entry of aliens who had tested positive for AIDS antibodies. Physicians were required to report the age, sex, and source of infection of all patients found to be infected with HIV, and to tell patients or their guardians how to prevent the spread of the virus. Physicians were also required to report the name and address of any infected patient they believed might not heed their advice or might infect others. Infected persons had to follow their physicians' advice or face penalties. The law prohibited these persons from engaging in "acts which carry a high risk of infecting another person with the AIDS antigen," such as donating blood. Physicians and public officials who withheld information about infected persons were subject to a prison term of up to one year or a fine. Persons who either refused a governor's order to submit to a medical examination or who gave false answers to examination questions were subject to a fine.

Hemophiliacs opposed the legislation as discriminatory. Following intense lobbying, the legislation was modified and was enacted in February 1989 as the *AIDS Prevention Law*. It required physicians and clinics to report to the prefectural authorities any HIV carriers they detected.

The Project Team attempted to review the activities of the AIDS Research Group, but found that there were no records of the group's meetings. The Project Team did, however, interview former members of the group, and, in its report, concluded that during the early stages of the crisis there had been insufficient effort on the part of the Ministry both to gather information about infectious diseases and to inform the public.

Excluding persons at risk: Donor screening

In July 1983, after learning about donor-screening guidelines imposed on American blood product manufacturers by the Food and Drug Administration, the Ministry directed that imported plasma and factor concentrates be accompanied by certificates stating that they had not been collected from donors at high risk of contracting HIV or AIDS.

Little is known about when or how blood banks in Japan began to exclude donors at risk of contracting HIV or AIDS. In November 1983, the Ministry issued guidelines to blood centres, informing them of ways to exclude donors at risk of contracting HIV or AIDS. In April 1984, the Red Cross blood centres began "preparing a suitable method for screening donors" to reduce the risk of HIV transmission through transfusion. In October 1985, however, a month after a study by researchers at Jutendo University reported that five of 103 Japanese homosexual men tested positive for HIV, the Ministry directed the Red Cross to stop accepting blood from gay men.

Inactivating viruses in blood products

Offers of imported heat-treated factor concentrates

Officials from the U.S. fractionator Travenol Laboratories Inc. (Travenol) (later Baxter Healthcare Corporation) and its subsidiary corporation in Japan approached the Ministry in 1982 and 1983 with a proposal that Travenol be permitted to sell heat-treated factor VIII concentrate in Japan. At that time, a new product could receive regulatory approval without undergoing clinical trials if it could be classified as a “change to a manufacturing method having no effect on the effective ingredients.” The question was whether this characterization could be applied to heat-treated factor concentrates. Officials of the Ministry were initially willing to consider approving the Travenol proposal under this heading, but eventually decided that clinical trials were required.

It has also been reported that, in 1983, the AIDS Research Group considered importing heat-treated factor concentrates from the United States on an emergency basis, but ultimately rejected the idea. Although heat-treated factor concentrates had been approved by the Food and Drug Administration in the United States, the Ministry mistrusted the reliability of the tests and feared that the concentrates might produce unwanted side-effects. Officials were particularly concerned about the problem of inhibitors. Dr Abe took the position that the Ministry should not import emergency supplies of heat-treated factor concentrates, and his view was adopted by the Ministry.

Use of non-heat-treated factor concentrates

Because Japan relied heavily on imports from the United States for its blood product needs, the history of the approval of heat-treated factor concentrates in Japan is inextricably connected to the history of imports of blood products.

In August 1983, when reports from the United States showed that AIDS could be contracted from contaminated factor concentrates, the Japan Hemophilia Fraternal Association demanded that the Ministry prohibit the import of non-heat-treated factor concentrates from the United States. However, the government continued to permit the import of non-heat-treated factor concentrates, with the stipulation that they be accompanied by a certificate that they did not contain plasma from donors at high risk of contracting HIV or AIDS.

The use of imported non-heat-treated factor concentrates increased in 1984 and peaked in 1985. By 1985, almost 90 per cent of imported factor concentrates used in Japan came from the United States. That year, in an effort to reduce Japan’s dependence on imports of factor concentrates, the Red Cross decided to resume production of blood products from blood donated in Japan. The Ministry proposed that donors donate 400 millilitres instead of 200 millilitres on each visit, that plasmapheresis be more widely used, and that physicians avoid unnecessary waste of plasma. It expected that, over a five-year period, this policy would decrease Japan’s dependence on imported blood by 50 per cent.

Efforts to reduce the reliance on imported factor concentrates had little impact on consumption during 1985 and 1986. Despite efforts by Japanese blood product manufacturers to produce domestic factor concentrates, in 1985 American blood product manufacturers sold even higher quantities of non-heat-treated factor concentrates in Japan. In part, this increase was due to the fact that, by late 1984, American blood product manufacturers had ceased selling non-heat-treated factor concentrates in the United States and offered them to their Japanese subsidiaries.

Conversion to heat-treated factor concentrates

Clinical trials of heat-treated factor concentrates began in early 1984 in Japan, but heat-treated factor concentrates were not approved for use until the summer of August 1985. Before that date, blood product manufacturers continued to distribute non-heat-treated factor concentrates without warning labels about the risk of AIDS, and the Ministry recommended that physicians continue to prescribe their use. As a result, many Japanese hemophiliacs continued to use non-heat-treated factor concentrates in 1986 and were told by their physicians it was safe to do so.

The Project Team's conclusions

The manner in which officials in the Ministry responded to Travenol's offer to supply heat-treated factor concentrates to the Japanese market was examined by the Project Team in 1996. It found that decisions whether to use heat-treated factor concentrate were not made exclusively on the basis of scientific and medical evidence.

Although Dr Abe denied ever having been asked to consider importing heat-treated factor concentrates from the United States on an emergency basis, documents released in 1996 revealed that the idea was considered and rejected by a subcommittee of the AIDS Research Group in September 1983. One such Ministry document, entitled "The handling of factor concentrates as it relates to AIDS," was prepared in mid-1983 and had been circulated to the AIDS Research Group. It contained a number of statements that revealed to the Project Team that the decision whether to approve the Travenol request was at least in part influenced by commercial and political concerns. This connection was denied by Ministry officials, who told the Project Team they had not been influenced by such factors; rather, the AIDS Working Group had simply had reservations about the safety and effectiveness of heat-treated factor concentrates.

Removing products from the market

Until 1986, the Ministry was content to leave the decision to withdraw non-heat-treated factor concentrates to the blood product manufacturers. In a 1987 survey, Green Cross reported to the Ministry that it had completed its recall of non-heat-treated factor VIII concentrate by 31 October 1985, and

non-heat-treated factor IX concentrate by 31 May 1986. However, when the Ministry inspected the facilities of Green Cross in 1996, pursuant to the provisions of the *Drugs, Cosmetics and Medical Instruments Act*, it discovered that Green Cross had been distributing non-heat-treated factor concentrates as late as December 1986, and that it did not recall these products until 1988. In August 1996, a spokesman for Green Cross stated: "We had no choice but to ship non heat-treated factor concentrates because it was hard for us to meet the demand for heat-treated factor concentrates ... The Ministry did not ask us to recall the non heat-treated factor concentrates."

In August 1996, the former president of Green Cross stated that the corporation could not have produced enough heat-treated factor concentrate in 1986 to meet the demand if non-heat-treated factor concentrate had been withdrawn from the market. He also said that in 1986 he was not aware that Green Cross was continuing to supply non-heat-treated factor concentrate.

The Project Team was informed that Ministry officials feared that a withdrawal of non-heat-treated products might have jeopardized supply, would have interfered with the treatment of patients, and was unnecessary since the Food and Drug Administration in the United States had not recalled non-heat-treated products.

Surrogate testing for AIDS

No surrogate testing for AIDS was performed in Japan.

Screening blood donations: HIV testing

As of May 1985, the Ministry had no plans to screen imported plasma for AIDS. In November 1985, the Ministry concluded that there was no need for mandatory AIDS screening of blood donors. The estimated cost of testing was thought to be prohibitively high. Instead, "voluntary" testing for high-risk groups such as homosexual men and drug addicts would be paid for under the health insurance system.

In February 1986, in response to increased media coverage and public concern, the Ministry and the Red Cross announced that they would begin screening blood donors in Tokyo and Osaka using the ELISA test. Japan's Science and Technology Agency awarded an emergency grant of 40 million yen (Can\$304,320) to two research teams at the Ministry's Health and Medical Affairs Bureau and the National Institute of Health to develop more reliable AIDS tests.

From February 1985 to February 1986, the Red Cross tested the blood of one million donors in Tokyo and Osaka, representing more than 10 per cent of the ten million expected donations. Testing of donors in the Tokyo area revealed only three seropositive males among 80,000 blood units. In an economic analysis of the benefits of donor screening for HIV published in 1987, the authors concluded that such screening, if implemented throughout Japan, would not be cost effective unless intangible benefits such as the elimination

of fear among transfusion recipients were taken into account. They recommended donor screening in larger metropolitan areas such as Tokyo and Osaka if the incidence of HIV reached levels found in the United States.

Informing hemophiliacs of the risk

As a rule, the Ministry relied on physicians to inform their patients about the risks associated with a particular treatment, rather than launching a public information campaign or making direct contact with patients. The former head of the Biological Products Section said in 1996: "I have no clear recollection of our issuing a policy as a section on providing information to the media ... For patients, I think the principle was that the physicians caring for them would provide information as it became necessary, and the Ministry did not consider providing information to all patients through direct channels."

At a meeting in March 1983, members of the AIDS Research Group discussed reintroducing the use of cryoprecipitate as a treatment for hemophilia. It considered a formal recommendation to the Ministry that hemophiliacs be placed on cryoprecipitate rather than non-heat-treated factor concentrates, but decided that hemophiliacs should continue to be treated with non-heat-treated factor concentrates.

Patients were rarely told the results of HIV testing. For example, in 1984, Dr Abe had blood samples from forty-eight of his own patients sent to Dr Robert Gallo's laboratory in the United States to determine whether any were infected with HIV. The results, which Dr Abe received in late 1984, showed that twenty-three of them were infected. None were informed of the results.

Until the late 1980s, most physicians treating hemophiliacs maintained a similar policy of not disclosing HIV test results. At a meeting of hemophiliacs in October 1985, Dr Abe stated: "Please don't ask your physicians about HIV test results. Trust your physicians. I'm sure they will provide the best treatment for you." In a survey of hemophiliacs conducted in 1988, most said they had had an HIV test, but a third of them had not been notified of the results.

The reason for this failure to notify patients of test results is complex. The nature of the medical profession in Japan is more hierarchical than it is in Europe and North America, and the relationship between patients and physicians may be characterized as paternalistic. The paternalism is more pronounced in rural communities, where maintaining good relations with a physician usually means not challenging him or her, and not asking questions. Patients were expected to trust their physicians implicitly. It is also possible that many physicians treating hemophiliacs may have recommended treatment with factor concentrates, and were perhaps reluctant to inform patients of the consequences of their own treatment choices. Finally, in a culture that has been slow to accept persons with HIV or AIDS, patients may not wish to know the results of HIV tests out of fear of being ostracized. Hemophiliacs

known to be infected have suffered from discrimination and, in some instances, have been refused treatment at hospitals, dismissed from their employment, or denied the right to attend school.

Informing transfusion recipients of the risk

In early 1996, the Ministry ordered manufacturers that distributed blood products in Japan to produce a list of medical institutions that received blood products in the 1980s that might have been contaminated with HIV. The purpose of this request was to identify 300 or more non-hemophiliacs who might have been exposed to the virus through the use of blood products. This measure reflected a recognition that the focus to date on hemophiliac patients had led officials to overlook the plight of non-hemophiliacs.

In August 1996, the Ministry released the names of 500 to 600 hospitals that might have administered non-heat-treated factor concentrates to non-hemophiliac patients, in the hope that patients would come forward to be tested. Previous efforts were hampered because many hospitals had routinely destroyed patient records.

The results of government investigations

Soon after establishing the study group in January 1996, Mr Kan, the Minister of Health, ordered a thorough search of government files. He made public those documents that related to the infection of persons through blood and blood products. The documents were found, despite assertions by previous officials, both in court and in Parliament, either that they did not exist or that they had been lost. The documents revealed that officials responsible for monitoring the emerging AIDS epidemic in the Ministry were aware as early as 1983 that the agent responsible for AIDS was likely transmissible through blood.

At a press conference at the Ministry in February 1996, Mr Kan accepted responsibility on behalf of the government and issued a formal apology to all persons who had been infected through blood products. "On behalf of the Ministry of Health and Welfare," he stated, "I apologize from the bottom of my heart for the heavy damage inflicted on many innocent people." Although this statement was regarded in Japan as the first official acknowledgement of governmental responsibility, a similar apology had been made by the previous Minister of Health in October 1995: "We would like to sincerely apologize to the families of those who have died and those still fighting the disease. We cannot deny that delayed government measures led to the tragic increase of victims."

Mr Kan announced that he would also reduce his salary by 20 per cent for two months as a gesture of remorse for the past conduct of Ministry officials. He added that Ministry officials would be the subject of disciplinary action. The findings of the investigations resulted in the dismissal of two senior officials in the Ministry. The first, a manager of the blood products

division, was dismissed because he had displayed “insufficient recognition of risk in regard to unheated blood preparations,” and he was later charged with professional negligence. The second, the chief of the Pharmaceutical Affairs Bureau, was dismissed for failing to disclose documents showing that the Ministry was aware of the risk posed by non-heat-treated factor concentrates as early as 1983.

In its report released in March 1996, the Project Team acknowledged that during the early stages of the crisis there had been insufficient efforts on the part of the Ministry both to gather information on infectious diseases and to inform the public. It found that policy decisions were made without adequate information, that too much reliance was placed on the opinion of experts, and that there was a lack of transparency in decision making. It concluded that Ministry officials should have been more active in giving information to hospitals and physicians; that choices about treatment should have been made by physicians and patients, and not by Ministry officials; and that, in future, efforts should be made to obtain informed consent of patients. Finally, it stated that the tasks of surveillance and regulation of blood and blood products should have been undertaken by separate government organizations. It accordingly recommended that a new advisory body be established in the Ministry to develop the means for surveillance of infectious diseases, and that better efforts be made to create linkages with other countries, particularly the United States.

As a result of findings made in the Project Team’s report, the Tokyo Public Prosecutor’s Office began a criminal investigation into the actions of some of the Ministry officials and Green Cross executives. When criminal investigations were concluded in September 1996, Ministry officials Dr Abe and Dr Akihito Matsumura were charged with professional negligence, as were Green Cross executives Renzo Matsushita, Tadakazu Suyama, and Takehiko Kawano. Trials of the five began in the spring of 1997.

Assistance to persons infected and affected

Government assistance

Until the late 1980s, persons who tested positive for HIV infection but who were not yet symptomatic were not entitled to full national health coverage. The Ministry responded by making treatment and counselling services available throughout Japan to asymptomatic HIV carriers. The Japan Hemophilia Fraternal Association was not satisfied with these measures, however, and demanded more complete treatment and compensation for victims and their families. In April 1988, the Ministry announced the establishment of a relief scheme for hemophiliacs.

The Yuai Welfare Foundation was established by the government in December 1988 and began operating in January 1989. The board of directors of the foundation comprised government officials, representatives of blood product

manufacturers, the major medical associations, and the blood-banking program. A medical council provided expert advice. The foundation received 30 million yen from the government. Each year after 1990, the government increased the budget to account for the increasing number of patients with hemophilia and AIDS.

Additional funds were collected from the pharmaceutical corporations that had sold imported factor concentrates in Japan, and these funds were deposited with the Yuai Welfare Foundation (or Fund). The foundation also made a financial contribution to the Adverse Drug Reaction Research Promotion program, which sponsored measures aimed at preventing AIDS. Counselling services for HIV-infected hemophiliacs, operated by the AIDS Prevention Foundation, were established in thirteen locations throughout Japan with funds from the national government. The Task Force on the Prevention of AIDS in HIV-infected Hemophiliacs was established with U.S.\$2.14 million in research funds, and, in addition to the task implied in its title, it investigated new treatments for those who developed AIDS.

Early in 1993, the Ministry announced that it would begin making regular payments to hemophiliacs who were infected with HIV. The decision was made after a group of eighty-six hemophiliacs filed a class action contending that the spread of HIV among Japanese hemophiliacs was due to gross negligence on the part of the Ministry. The Ministry had already decided to pay each infected hemophiliac the sum of 30,000 yen monthly (about Can\$280), and it earmarked a total of 500 million yen (Can\$5,221,000) in the current year's fiscal budget to meet payments. The plaintiffs had sought about 1.3 billion yen (Can\$13 million) in compensation.

The 1993 financial assistance plan was initially in the form of lump sums. The first amount of compensation was decided on in 1989, but it was regularly increased, beginning in 1990. As of 1 April 1993, the financial assistance given to hemophiliacs was as follows:

- a monthly medical care allowance of U.S.\$318 to patients with hemophilia who had been hospitalized for eight days or longer per month due to an AIDS-related illness;
- a monthly special allowance to all HIV-infected patients with hemophilia who eventually developed AIDS, consisting of
 - U.S.\$2,328 per month to those who were over eighteen, or U.S.\$947 per month for minors;
 - a monthly bereaved family pension of U.S.\$1,575 for ten years, if the deceased person was the primary family wage earner;
 - a lump sum of U.S.\$63,257, paid in the event of death of a person other than the main family wage earner; and
 - a lump sum of U.S.\$1,352 to cover funeral expenses.

Decisions about the awards were made by the Committee on Damage and Injury Caused by HIV Infection by Use of Blood Products, a committee created by the Pharmaceutical Affairs Bureau of the Ministry and composed of medical specialists.

In April 1993, the scheme was expanded to cover the health costs of asymptomatic HIV-infected patients with hemophilia whose immune systems were failing and whose CD4 cell counts were below 500. These patients received a monthly allowance of U.S.\$314. All patients falling under this category were obliged to report their health status and to undergo clinical examinations at regular intervals. All payments were tax free.

The financial assistance plan put in place in 1989 covered those who had contracted HIV infection through factor concentrates as well as their families. If an infected hemophiliac transmitted the infection to his spouse, however, this newly infected person would receive only the financial assistance to which she was entitled as a family member, and not as a person infected with HIV. As of October 1993, it was estimated that several dozen persons fell into this category. By this time, the medical costs of HIV-positive hemophiliacs were being paid by the pharmaceutical corporations that had sold the contaminated factor concentrates, but the costs incurred by their infected spouses – up to 60,000 yen a month – were not covered. The government amended its program in April 1994 and began making direct payments of 33,000 yen per month to spouses infected through sexual contact with hemophiliacs who had contracted the virus through factor concentrates.

Settlement of civil actions

Civil actions were brought by hemophiliacs and their families in May 1989. Two plaintiffs brought an action in Osaka District Court against the Ministry, Green Cross, and Baxter, alleging that their infection with HIV was the result of the negligence of the government and the blood product manufacturers for failing to screen imported factor concentrates. In July 1989, another seven hemophiliacs brought legal proceedings against the government and five corporations: Green Cross, Bayer, Baxter, Nippon Zoki, and Chemo Sero.

In early 1993, an additional forty-seven Japanese hemophiliacs who tested positive for HIV sued the Japanese government and five blood product manufacturers for negligence. Another forty-five hemophiliacs in the Kansai area of western Japan brought similar actions. They charged that the corporations were negligent in continuing to sell non-heat-treated factor concentrates for several years after safety procedures were developed. The plaintiffs also claimed that the government was negligent for not suspending sales of non-heat-treated factor concentrates until 1985.

In October 1995, the Tokyo and Osaka District Court ruled that the government and five pharmaceutical corporations were jointly responsible for the tragedy. The court urged the defendants to reach an out-of-court settlement with the plaintiffs, proposing that they pay U.S.\$450,000 to each of the

219 plaintiffs. The court's proposed settlement did not, however, include a formal acknowledgement of responsibility by any of the defendants. In early March 1996, the parties moved closer to a settlement when the court made a new compromise proposal. It called upon the government and the five corporations to accept responsibility, and recommended that the government establish a comprehensive program of compensation, medical treatment, AIDS research, and education. The proposed compensation plan consisted of a lump-sum payment of U.S.\$430,000 to each plaintiff, as well as a monthly payment of U.S.\$1,400 to each patient who subsequently developed AIDS.

In mid-March 1996, before a final settlement was reached, senior executives of Green Cross made a public apology for their role in the tragedy. They knelt and pressed their foreheads to the floor before several hemophiliac victims and their families in a televised news conference. The other four corporations issued written apologies, but did not accept responsibility.

A final settlement was announced on 29 March 1996. Mr Kan played an instrumental role in securing the agreement of blood product manufacturers. He met first with the president of Baxter in early 1996, and later secured agreement from Bayer and three Japanese corporations: Green Cross, Chemo Sero, and Nippon. These corporations – in particular, Baxter and Bayer – were reluctant to admit any form of responsibility out of fear that such admissions would be used against them in civil actions by plaintiffs in other countries.

The settlement included a formal government apology, approximately U.S.\$430,000 paid to each victim, and compensation for future medical expenses. The government agreed to cover 44 per cent of the cost of the settlement, with the corporations paying the other 56 per cent. The corporations' payments were made to the Yuai Welfare Foundation, which would then make payments directly to the plaintiffs. A representative of Baxter said that the corporation "deeply regret[s] that the earlier versions of the therapies that were designed to save lives unknowingly carried the virus that causes AIDS." He also stated that the corporation had tried to provide its heat-treated concentrates for almost two and a half years before the Ministry approved it.

In May 1996, another eighty-seven hemophiliacs brought legal proceedings against the government and the five corporations, seeking a settlement similar to that announced in March. By June 1996, it was estimated that approximately 750 hemophiliacs had brought actions and that about 1,000 others were in a position to do so. A government-appointed research team set up to investigate the conduct of the medical profession towards persons infected with HIV found that some physicians were not cooperating with patients who sought compensation, and would, for example, refuse to fill out forms required by the court because they disagreed with the compensation scheme. The research team called upon the profession to be supportive of and cooperative with these patients.

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The Netherlands

The blood system in the 1980s

In the Netherlands, blood and plasma were collected primarily by the Netherlands Red Cross (Red Cross). This system is still in place today. Donors are voluntary and unpaid. Red Cross blood banks and the Central Laboratory of the Netherlands Red Cross are also fractionators, preparing and supplying blood products for the domestic market.

The Netherlands Red Cross blood transfusion service

During the 1980s, the blood transfusion service consisted of a national advisory body called the Central Medical Blood Transfusion Committee, twenty-two regional blood banks, and the Central Laboratory of the Netherlands Red Cross (Red Cross Central Laboratory).

The function of the Central Medical Blood Transfusion Committee, founded in 1939, was to establish blood transfusion policy during the 1980s. It was composed of a chair appointed by the Red Cross, an independent treasurer, prominent local physicians, directors of the Red Cross Central Laboratory, and a member of the Dutch Association of Hemophilia Patients. The Central Medical Blood Transfusion Committee advised the Minister of Welfare, Health and Cultural Affairs about the administration of blood transfusion legislation; informed the Minister of applied scientific research being conducted in the field of blood transfusion; gave the Minister yearly estimates of the need for blood and blood products; and made regulations for the recruitment of donors as well as guidelines for the collection of blood. It was assisted by two permanent committees, the medical advisory committee and the logistics advisory committee. The latter gave annual estimates of both the domestic requirements and the supply of blood and blood products, and recommended how the needs could be met.

In February 1989, the Central Medical Blood Transfusion Committee was replaced by the Netherlands Red Cross Blood Transfusion Council, a group composed of representatives of organizations having an interest in blood and blood products. By law, it is required to have on its board two members

from both the Netherlands Red Cross and the federation of Red Cross blood banks, and one member representing each of the following: the Red Cross Central Laboratory, donors, patients, doctors, hospitals, health insurance associations, and health insurance firms.

The first Red Cross blood bank was founded in Rotterdam in 1930 and had thirty-four registered donors. Several other blood centres were later established, and during World War II the number increased dramatically. By 1940, the Red Cross was operating fifty-one centres with 42,000 donors. By 1973, it had 110 local centres. Existing blood centres were then consolidated into a smaller number of regional blood banks, which were made responsible not only for recruiting and collecting blood but also for its processing. Between 1973 and 1984, the Red Cross established twenty-two regional blood banks.

In the Netherlands, blood banks were, and continue to be, operated by local branches of the Red Cross and by hospitals in the area. They are joined in a federation that allows them a high degree of individual freedom. Each blood bank has its own region, with boundaries that often correspond to those of the local health district, and each has a contract with hospitals in its region to be the sole supplier of blood products. Individual blood banks are required to maintain an adequate supply for their region and to perform a broad range of tasks beyond the recruitment of donors and the collection of blood and plasma. They must prepare red cell and platelet concentrates, leukocyte-depleted red cell concentrates, and heat-treated cryoprecipitate; store and distribute blood products to hospitals; test for blood groups; and send plasma to the Red Cross Central Laboratory. A few blood banks also manufacture factor VIII concentrate. Blood banks and the Red Cross Central Laboratory also carry out developmental research in the field of blood transfusion to ensure that blood products meet current regulatory standards; as a result, some of the larger blood banks are involved in research in such fields as immunohematology, clotting, transmissible diseases, and protein chemistry.

Red Cross blood banks have always been reimbursed for their services and products by hospitals. The National Health Care Fees Association, under the terms of the *Health Care Fees Act*, has established nationwide standard fees for the different blood products based on their costs. Charges for the blood banks' fixed costs are prorated according to the number of beds in each member hospital.

The Red Cross Central Laboratory is a non-profit organization jointly administered by the Government of the Netherlands, the Netherlands Red Cross, and the Municipality of Amsterdam. It has three branches. The product branch manufactures blood products and diagnostic tests. Because both the Red Cross Central Laboratory and the blood banks must collect enough plasma to meet the demand for blood products, this branch may also collect blood in county districts. The diagnostic branch performs diagnostic research in the fields of immunology and blood transfusion, acts as a national reference centre, and maintains a national and international service for the storage

and supply of red cells of unusual blood groups. The research and education branch carries out basic and applied research in immunology and is actively involved in the teaching of transfusion medicine and immunology. In 1977, because of its knowledge and experience in the field of plasma proteins and blood grouping reagents, the Red Cross Central Laboratory was designated as a World Health Organization International Laboratory for Biological Standards, with special reference to human blood products.

The Red Cross receives an average of fifty-one blood donations per thousand of population annually. The Netherlands is self-sufficient in whole blood, red blood cells, fresh frozen plasma, and platelets, but not in factor VIII concentrate and specific immunoglobulins such as anti-rhesus (D) and anti-tetanus. Some products must therefore be imported. Netherlands officials hope to achieve self-sufficiency within a few years. When there are shortages of plasma, the Red Cross Central Laboratory obtains supplies derived from voluntary unpaid blood donations in other European countries.

The role of government

The Ministry of Welfare, Health and Sport (formerly the Ministry of Welfare, Health and Cultural Affairs) regulates blood and blood products and “is ultimately responsible for the safety of the blood system.” Within the Ministry, the Drug Inspectorate has routinely inspected blood banks and the Red Cross Central Laboratory for compliance with good manufacturing practices developed by the Netherlands Red Cross Blood Transfusion Council, based on guidelines of the European Commission. The licensing of blood products was carried out by a national commission entrusted with the control of plasma products. Since May 1993, this task has been given to the Drug Evaluation Board.

The collection, preparation, and supply of blood and blood products are governed by the *Blood Transfusion Act*, which, although enacted in 1988, did not come into force fully until 1993. Before then, these matters were governed by the less comprehensive *Human Blood Act* of 1961. Under that *Act*, only the Red Cross could collect human blood destined to be pooled for blood products; those blood products could be prepared only at the facilities of the Red Cross Central Laboratory; and blood and blood products could be imported and exported only in accordance with rules made by the Minister. Section 14 of the *Act* authorized the Minister to make additional regulations pertaining to the preparation, storage, and quality of blood and blood products. Using that power, new regulations were made in January 1988 for the preparation of factor VIII concentrate. The *Human Blood Act* was repealed in August 1994.

The current *Blood Transfusion Act*, in accordance with European guidelines for blood transfusion, requires the use exclusively of voluntary, unpaid donations, prohibits any profit from the purchase and sale of blood and blood

products, and requires the Netherlands to supply all the blood and blood products it needs, subject to special exemptions. Only Red Cross blood banks and the Red Cross Central Laboratory may collect blood and manufacture blood products, subject to restrictions imposed by their respective licences. The number and location of blood banks are determined by the Minister, in consultation with the Blood Transfusion Council. Every blood bank must meet regulatory requirements to receive a licence. Factor concentrates must be registered with the Drug Evaluation Board. Violation of any of the provisions of the *Act* is a criminal offence, punishable by a sentence of six months in jail or a fine.

Under section 29 of the *Act*, the Minister may make regulations for the collection of blood; the manufacture of blood products; the storage, packaging, labelling, transport, and delivery of blood and blood products; and the distribution, processing, and storage of blood and blood products in hospitals. In accordance with guidelines issued by the Council of the European Communities, the government of the Netherlands introduced new regulations in 1993. These regulations require that blood banks test every donation for certain infectious agents, including HIV and the viruses of hepatitis B and C; that hospitals maintain records of the identity of both the donor and the recipient; that batch numbers and patient names be recorded; that the records be kept for a period of ten years; and that every batch of blood products be inspected. The importation of blood and blood products requires a special permit from the Minister of Welfare, Health and Sport. Permits are granted only when they can be shown to be necessary to ensure an adequate supply of a particular product for medical purposes. The Netherlands imports plasma and plasma products from members of the European Community and the European Free Trade Area, but not from the United States. The export of blood and blood products is prohibited by law, with specific exemptions. Products may be made available to patients outside the country in an emergency. Plasma products may also be prepared at the request of a foreign institution and exported to it.

Under the *Health Act*, enacted in 1965, the Government Health Authority enforces public health laws and regulations. It also makes recommendations and gives information about public health issues to both the Minister and the director general of public health. The promotion of health care is the shared function of two agencies: the National Public Health Council and the Health Council. The former gives advice about the quality and suitability of health care and fosters cooperation among the agencies active in public health; and the latter keeps ministers informed about health issues. Certain officials of the Ministry of Health, Welfare and Sport are by law members of both councils: the director general of public health, the chief officers of the Government Health Authority, and the director general and general manager of the National Institute of Public Health and Environmental Protection.

The Dutch Association of Hemophilia Patients

The Dutch Association of Hemophilia Patients, formed in 1971, is an advocacy group composed of hemophiliacs and persons with related hereditary blood coagulation disorders. Of the approximately 1,300 hemophiliacs in the Netherlands, at least 850 are members. The association works to ensure high standards of medical treatment and blood transfusion. It gives information to members through a quarterly newsletter, *Faktor*, and through books, brochures, and videotapes; and it represents the interests of hemophiliacs internationally. It has both regional and local working groups.

Prevalence of blood-related HIV or AIDS

According to the European Centre for the Epidemiological Monitoring of AIDS, as of 31 December 1996 there were sixty-two hemophiliacs in the Netherlands with AIDS (1.5 per cent of all AIDS cases), and thirty-nine transfusion recipients with AIDS (0.9 per cent of all AIDS cases). A study by the Netherlands government completed in July 1995 reported that approximately 150 transfused patients and 170 hemophiliacs (13 per cent of Dutch hemophiliacs) were infected with HIV between 1979 and 1985. Although it is impossible to state accurately the number of HIV infections attributed to specific factor concentrates, the Dutch Association of Hemophilia Patients estimates that half the cases were caused by factor concentrates that had not been heat treated to inactivate HIV and were imported from the United States between 1979 and 1984; the other half were caused by Dutch blood products that had not been heat treated and were administered between 1981 and 1985.

Protecting the blood supply from HIV or AIDS

Inquiry by the national ombudsman

In December 1992, the Dutch Association of Hemophilia Patients asked the Ministry of Welfare, Health and Cultural Affairs to establish an independent inquiry into the infection of hemophiliacs with HIV. The Minister replied that he did not have the authority to create a board of inquiry with power to examine fully the actions of the producers of blood products, hospitals, and attending physicians, but that an inquiry into the state's role could be undertaken by the national ombudsman. In December 1993, the association formally requested the ombudsman to examine the role of government, and in particular that of the Ministry of Welfare, Health and Cultural Affairs, in preventing AIDS infection among hemophilia patients and recipients of blood transfusions.

Under the *National Ombudsman's Act*, the inquiry was limited to an examination of the role of the Ministry, the Health Services and Health Protection Directorates, and the Government Health Authority. Government councils and commissions, such as the National Public Health Council and the Health Council, were not subject to scrutiny because they did not fall under direct supervision of the Minister. For the same reason, the actions of producers,

physicians, and hospitals could not be examined except to assess the role of the government. During the investigation, both the Dutch Association of Hemophilia Patients and the Minister were given the opportunity to put forward their positions on relevant issues and to respond to statements made by others. The ombudsman was assisted by an independent expert, and sought additional information from the Red Cross Central Laboratory, the Groningen-Drenthe Blood Bank, and the Dutch Association of Hemophilia Treating Physicians. The ombudsman's report was made public in July 1995.

The report addressed five issues identified by the Dutch Association of Hemophilia Patients. These issues were that the Ministry had neglected to gather timely information in the field with respect to HIV infections and to formulate a policy based on the information; failed to prohibit the import of non-heat-treated U.S. blood products in late 1982 and early 1983 when it should have assumed that these products were most likely infected with the causative agent of AIDS; neglected to issue timely orders requiring Dutch producers to change to heat-treated products; failed to withdraw heat-treated products manufactured by the Armour Pharmaceutical Company (Armour) after published reports in early 1986 linked Armour products and HIV infection; and failed to provide timely information about the risk of transmission of AIDS to physicians, hemophilia patients, and donors. The ombudsman's findings are described later in this chapter.

The emergence of HIV or AIDS

The first cases of AIDS in the Netherlands appeared among sexually active homosexuals in the autumn of 1981. In 1982, there were five cases of AIDS, all homosexuals "with contacts in major American cities." In the next four years, the number of cases of AIDS increased steadily: there were nineteen in 1983; thirty-one in 1984; sixty-seven in 1985; and 136 in 1986.

Although the number of AIDS cases increased substantially, not one had been reported among hemophilia patients by late 1984. Dutch hemophiliacs were, however, developing antibodies to HIV during the early years of the 1980s. One study, conducted from 1983 to 1985, found that 27 per cent of hemophiliacs treated with domestic non-heat-treated concentrates had developed antibodies. Another study, conducted between 1983 and 1986, found that twenty out of 157 patients studied (12.7 per cent) had seroconverted, or become positive for the HIV antibody. The authors of the second study estimated that eighteen of the seroconversions were related to the use of non-heat-treated products; only one had occurred with the exclusive use of cryoprecipitate. A third study, completed in 1986, found that, although no cases of hemophilia-related AIDS had been reported, thirty-six of the 217 participating patients tested positive for the HIV antibody. It was not until 1987 that AIDS was reported among hemophiliacs. Three patients were diagnosed that year, five in 1988, and six in 1989.

Response to the emergence of HIV or AIDS

The fact that there were few cases of AIDS in the Netherlands during the early 1980s did not deter public officials from recognizing its potential impact. Beginning in 1983, the chief public health officer sent circulars to physicians about HIV or AIDS and helped finance efforts by the Dutch Association of Hemophilia Patients to inform its members about the risk of transmission.

In November 1983, after informal consultations with the Red Cross Central Laboratory, blood banks, the Central Medical Blood Transfusion Committee, public health authorities, and homosexual organizations, the Ministry established a National AIDS Coordination Team. In April 1985, the director general of public health created an Intradepartmental AIDS Consultation Group to facilitate the development of a cohesive intradepartmental policy, taking into account the medical, psychosocial, and social aspects of AIDS. Subsequently, a number of governmental bodies and committees were established, including the National Commission for AIDS Control, the permanent committee on AIDS of the Health Council, the AIDS Research Program Coordination Committee of the Health Research Council, and AIDS organizations established to deal with regional policy.

Public health officials in the Netherlands considered and rejected the mandatory reporting of cases when AIDS first appeared in the country. Public health officials feared that, because the disease was occurring predominantly among male homosexuals, mandatory reporting might cause additional stigmatization and discrimination of homosexuals, pose an ethical dilemma for physicians and other health professionals, and ultimately lead to under-reporting. It was also argued that, because the disease is difficult to diagnose during the long period in which patients may show various symptoms but have not yet developed full-blown AIDS, it would be difficult to report cases with any accuracy. Dutch authorities thus adopted, and have since maintained, a system of voluntary, anonymous reporting of AIDS. There has never been any legal requirement to report cases to public health authorities.

Physicians voluntarily file anonymous reports with the main Public Health Inspectorate. They are asked to complete a brief questionnaire about the presenting disease, the date of diagnosis, and the patient's age, sex, and risk group. With that information, a separate working group at the Inspectorate determines whether the case should be classified as AIDS on the basis of the criteria established by the Centers for Disease Control and Prevention in Atlanta, Georgia. If it is so classified, the attending physician is told, and the physician may then ask the patient to allow his or her identity to be disclosed so that all relevant data may be passed on to the blood banks, the Red Cross Central Laboratory, and the Public Health Inspectorate.

This policy of voluntary reporting was introduced in September 1982 in a circular from the chief public health officer to health care professionals asking them to report patients with AIDS symptoms, though it did not name the disease. The Health Council endorsed the approach in a report it released

in March 1985. The report stated that physicians should ask patients with symptoms of AIDS whether they had donated blood or sperm in the previous five years. If any had done so, physicians were told to seek the patient's consent to disclose his or her identity to public health officials, who would in turn inform blood and sperm banks.

Excluding persons at risk: Donor screening

Because of the debate then under way in the United States about the possible transmission of AIDS through blood and blood products, the Red Cross Central Laboratory held a meeting on 30 January 1983 to discuss the possibility of excluding male homosexuals from the donor pool. Representatives of blood banks and of homosexual and hemophilia organizations attended, along with public health officials from Amsterdam and Rotterdam. During the meeting, representatives of homosexual organizations objected to such a policy as discriminatory and said it would be ineffective because many homosexual donors would lack the courage or the willingness to so identify themselves. Consequently, blood banks decided to postpone any decision about the exclusion of homosexuals. The participants agreed that the first step was to examine ways in which donors at risk could be educated about AIDS.

The task of coordinating this effort was given to Dr Roel Coutinho, who, as head of the Department of Infectious Diseases of the Municipal Health Service in Amsterdam, had worked closely with the gay community. Over the next few months, he organized a number of meetings between representatives of homosexual organizations, public health authorities, the blood banks, and the Dutch Association of Hemophilia Patients. By the end of April 1983, all parties had agreed to a compromise. Male homosexual donors would not be barred from donating; instead, blood banks and homosexual organizations would launch an information campaign to promote voluntary self-exclusion by gay men with multiple partners. The campaign plan was drawn up in May 1983 by the Health Information and Training Bureau of Amsterdam and a prominent gay organization.

On 27 April 1983, the president of the Central Medical Blood Transfusion Committee wrote to the Red Cross Central Laboratory and the blood banks to say that, in future, potential donors must be told which groups were at greatest risk of contracting AIDS; any donors who identified themselves as members of a group at risk must be encouraged to refrain voluntarily from donating. Groups at risk were persons with symptoms of AIDS, homosexual men with "many and frequently changing [sexual] contacts," persons originating in Haiti, intravenous drug abusers, and the sexual partners of persons at risk. Persons with signs of AIDS were to be rejected, and employees of the blood banks were to be trained to recognize those signs. A brochure containing information about the risk of contracting AIDS, the letter said, would be available to donors and homosexual men in the near future.

That brochure was released in June 1983, the same month that the Council of Europe recommended the use of donor leaflets. The brochure was paid for by the Ministry and prepared by the Health Information and Training Bureau, the Central Medical Blood Transfusion Committee, and a prominent homosexual organization. It advised members of high-risk groups to “seriously consider not donating blood for the time being” and recommended that homosexual men reduce the risk of infection by limiting the number of their anonymous sexual partners. Copies were distributed in bars frequented by homosexuals throughout the country, information on AIDS was published in the Dutch gay media, and discussion groups were organized.

Later, printed information – posters, leaflets, booklets, and postcards – was distributed in Amsterdam at gay meeting places and in literature circulated in the gay community. Donor notices were regularly revised to incorporate information from the Centers for Disease Control and Prevention in the United States along with the standards set by the American Association of Blood Banks. In mid-1984, for example, the high-risk categories were revised to include persons with “multiple sex partners in the last year.”

The Dutch Association of Hemophilia Patients had criticized the Ministry for failing to conduct donor awareness campaigns. The ombudsman, however, concurred with the Ministry’s view that the blood banks were ultimately responsible for this activity. He concluded that the Ministry had acted appropriately by supporting and funding efforts to persuade persons at high risk to refrain voluntarily from giving blood.

Inactivating viruses in blood products

In February 1983, Dutch physicians and the Dutch Association of Hemophilia Patients learned from Travenol Laboratories Inc. (Travenol) that it had recently developed a heat treatment process that reduced the risk of transmission of hepatitis non-A, non-B viruses. Although Travenol warned that it could not extrapolate the data to other viruses, it hoped that the process would be of some use in preventing the transmission of HIV. The next month, Travenol was granted approval from the U.S. Food and Drug Administration to distribute heat-treated factor VIII concentrate under the tradename Hemofil-T, and in late April or early May 1983 it began to make the product available to Dutch treating physicians. The product came with the caveat that it was still unclear whether heat treatment prevented the transmission of AIDS, since the causative agent of that disease had not yet been identified. Travenol was formally licensed to import Hemofil-T into the Netherlands on 12 August 1983 on the condition that it supply data within a year about the product’s effect on AIDS. Its licence to import non-heat-treated concentrates, issued in 1980, was revoked.

In the spring of 1984, another importer of blood products, Tramedico B.V. Weesp (Tramedico), was granted a licence to import heat-treated factor VIII concentrate. Several other manufacturers were licensed in 1986 to import

heat-treated products – Hoechst Holland NV in Amsterdam to import the German product Haemate-P, Bayer Nederland BV in Mijdrecht to import Koate HT, and Tramedico to import H.T. Factorate produced by the U.S. fractionator Armour Pharmaceutical Company (Armour). In February 1987, Travenol received a licence to import heat-treated factor IX concentrate.

During 1983 and 1984, the Red Cross Central Laboratory carried out its own research and development of heat treatment for factor concentrates. In June 1983, several staff members visited the Scottish National Blood Transfusion Service to learn about its work in using a wet heat-treatment method, but discovered that significant losses of factor VIII occurred during this process. The Red Cross Central Laboratory then began negotiating with Travenol for the use of its heat treatment process. Negotiations were suspended, pending the receipt of further data, when Travenol's process was found to be not entirely effective in eliminating hepatitis non-A, non-B viruses. The negotiations resumed in April 1984 and, later that year, a patent licence agreement was signed by the parties, and a sublicense was granted to the Red Cross Central Laboratory at no charge. The agreement was announced in December 1984 in a letter to treating physicians. In the same letter, the Red Cross Central Laboratory said it had implemented a modified production process so that clinical research into Dutch heat-treated factor VIII concentrate could be conducted as soon as possible. The Red Cross Central Laboratory and Baxter Travenol agreed that "if there is a shortage of Factor VIII concentrate that cannot be met by calling on similar producers of Red Cross affiliated organizations, the CLB [Red Cross Central Laboratory], when desirable and permissible, may also distribute Factor VIII concentrate manufactured by Baxter Travenol in the Netherlands." The Red Cross Central Laboratory had also begun to develop processes for the heat treatment of factor concentrates used in treating type B hemophilia.

In November 1984, the Dutch Association of Hemophilia Patients urged the Minister to investigate whether fractionating centres abroad could be used to heat treat Dutch products as an interim measure. At the end of March 1985, it distributed a brochure entitled *Hemophilia and AIDS: 45 Questions and Answers*. The document included the following statement about the relative safety of domestic non-heat-treated factor VIII concentrate and imported heat-treated factor concentrates:

The answer to this question cannot at this time be definitive because data from comparative studies are not known, the heating conditions which various manufacturers are using are different, and it is not clear if LAV/HTLV-III [HIV] is always inactivated. As the number of carriers of LAV/HTLV-III in Dutch blood donors is lower than, for example, in paid plasma donors in the U.S. it is to be expected that the source material (plasma) in the Netherlands carries a smaller risk of contamination. This

may change over time. When cryoprecipitate is used, the recipients are exposed to a considerably smaller number of different donors than when factor VIII concentrates are used. [Translation.]

In January 1985, the Red Cross Central Laboratory submitted a protocol for heat-treated factor VIII concentrate to the Dutch Blood Products Committee and began to develop a heat-treated cryoprecipitate. Domestic heat-treated factor VIII concentrate was successfully administered without side-effects to Dutch hemophiliacs in April 1985, and, in June, the Red Cross Central Laboratory announced that, as of 3 June 1985, it would start delivery of heat-treated factor VIII concentrate. It warned, however, that "although heat treating reduces the risk of transmitting AIDS, it does not eliminate it entirely." Hospitals were told that they could return all stocks of non-heat-treated product to the Red Cross Central Laboratory in exchange for heat-treated products. After June 1985, all factor VIII concentrate distributed by the Red Cross Central Laboratory was heat treated. Heat treatment of cryoprecipitate began in December 1985.

At the end of June 1985, the Red Cross Central Laboratory began clinical trials of heat-treated factor IX concentrate, and soon afterwards announced that it would begin supplying that product on 22 July 1985. In September, it announced that patients would have until 15 October to return non-heat-treated factor VIII and factor IX products to have them heat treated, and in November it announced that heat-treated cryoprecipitate would be available at the beginning of December. Non-heat-treated stock produced after 1 June 1985 would be exchanged for heat-treated products until the beginning of February 1986 at no charge.

The regional blood banks did not adopt heat treatment methods at the same time as the Red Cross Central Laboratory, and were not required to do so until 1988. A survey in November 1987 found that although most blood banks were supplying heat-treated products, some were instead relying on the quarantine method, in which plasma was stored for a period equivalent to the window period (that is, the period after infection before HIV antibody is detectable) and donors were retested for the HIV antibody. At the beginning of 1986, representatives from the Red Cross Central Laboratory and the blood banks, and some treating physicians, met to develop standards for the production of factor VIII concentrate. Regulations drafted in June 1986 required the use of viral inactivation processes in the production of factor VIII concentrate and cryoprecipitate to produce a demonstrated inactivation of at least 10 logs. The regulations were to come into force in June 1987, but implementation was postponed until 1 January 1988. They did not apply to factor IX concentrate and PPSB (prothrombin complex) because these products were produced only by the Red Cross Central Laboratory and were used infrequently.

The delay in requiring the use of heat inactivation processes was the subject of an investigation by the ombudsman, who found that the Ministry had been negligent. He concluded that by the beginning of 1985 there were many good reasons, including the forthcoming introduction of a diagnostic test for the HIV antibody and a heat treatment process, to question whether it was still appropriate to treat hemophiliacs with blood products that had not been heat treated. The U.S. Centers for Disease Control had recommended the use of heat-treated preparations in November 1984, and by the end of 1984 there were already indications that it was not certain that the plasma from Dutch donors was free of HIV contamination. The ombudsman found that there had been no discussion or consideration of the possibility of changing to heat-treated products from the United States, nor was there any suggestion that blood bank officials had paid attention to the warning signs. In his view, given the seriousness of HIV infection, “[t]he government should have taken the lead ... to eliminate all risk by forbidding the use of unheated blood products ... This did not happen and wrongly so.” He found that in failing to take any action with respect to the continued use of non-heat-treated products, the Ministry did not adequately fulfil its duty to take measures to promote public health.

Surrogate testing for AIDS

No surrogate testing for AIDS was undertaken in the Netherlands.

Screening blood donations: HIV testing

In the summer of 1984, U.S. manufacturers began developing commercial kits that could test for HIV antibody, and in November of that year the Dutch Association of Hemophilia Patients recommended that all donor blood be tested as soon as possible. No AIDS cases had yet been reported among Dutch hemophiliacs. The recommendation was sent to the Minister on 10 December, and on 8 January 1985 the chief public health officer sent a circular to health care professionals, blood banks, and hospital boards, stating that diagnostic kits would soon be evaluated by the National Institute of Public Health and Environmental Protection and the Red Cross Central Laboratory. On 1 February 1985, the Minister sent a letter to the Dutch Association of Hemophilia Patients informing it that the Central Medical Blood Transfusion Committee had recommended testing for HIV antibody and that a decision would be made when the test kits had been evaluated. On 27 March, the committee asked the Minister to give blood banks additional money for the testing. A new guideline was drafted that provided for an increase in blood bank budgets, and on that basis blood banks began to buy equipment and reagents and to train employees. On 1 April 1985, the test kit manufactured by Abbott Laboratories Ltd. became commercially available in the Netherlands.

The Central Medical Blood Transfusion Committee had established a study group to examine some of the practical implications of testing donors. The results of its deliberations were summarized in three reports, dated 14 December 1984, and 22 March and 24 May 1985.

In the first report, the committee said it would establish a committee of experts, with representatives of the blood banks and the Red Cross Central Laboratory, that would evaluate the commercially available test kits. The Red Cross Central Laboratory and the National Institute of Public Health and Environmental Protection would be reference laboratories in the evaluation and would conduct confirmatory testing. The report contained four recommendations. The first recommendation was that test results should be considered confidential and that special precautions should be taken because the results might indicate a donor's sexual preferences; the second was that, as a temporary measure, donors should be told their test results only on request, pending a final decision about notification after all blood transfusion organizations had been consulted; the third was that alternative testing sites should be established to discourage homosexual men from registering as donors only to learn their HIV status; and the fourth was that education campaigns should be introduced to explain the meaning of a positive test.

The second report dealt specifically with the implementation of HIV-antibody testing in blood banks. It made the following recommendations:

- every blood donation should be screened;
- blood units that tested positive for antibodies should not be used for transfusions and the donor in question should be rejected permanently;
- before the general introduction of testing, the general public and donors in particular should be told about the character of the test and the related consequences for the donor; and
- following an introductory period, the Red Cross Central Laboratory and blood banks should introduce the tests simultaneously.

During the introductory period, the study group expected that test kits would be evaluated, beginning at the end of March 1985; screening tests would be confirmed using the western blot technique; blood bank budgets would be expanded to cover the cost of screening; provision would be made for psychosocial assistance to donors who tested positive; and alternative test sites would be created.

By the end of April 1985, the Red Cross Central Laboratory had begun testing all blood units collected by its mobile units. On 2 May 1985, the Central Medical Blood Transfusion Committee instructed the Red Cross Central Laboratory and the blood banks to test every blood donation for HIV antibody beginning 1 June 1985 and to discard any donation found to

be positive. On 20 May 1985, the Central Health Care Cost Agency authorized an increase in blood budgets to cover the cost of the AIDS test, and this increase was approved by the Minister on 12 July.

A third report on testing was released by the Central Medical Blood Transfusion Committee on 24 May 1985. This report dealt extensively with the issues of notification and alternative test sites. It explored the relative merits of pursuing three options when a donation tested positive. These options were never informing the donor, telling the donor only at his or her own request, and always informing the donor. It recommended that donors testing positive for the AIDS virus be notified only after a six-month phase-in period of testing. Positive test results were to be conveyed to a donor in a personal conversation, and additional information was to be provided in a brochure. The blood bank would be held responsible for ensuring that a seropositive donor be given the names of physicians and other professionals who could be of help. The blood bank would also send the patient's general practitioner the test result; an information booklet for seropositive persons; and further information about the symptoms, diagnostics, and therapy of AIDS and its precursor, the AIDS-related complex.

The report recommended that twenty alternative test sites, where non-donors could be tested at their own request, should be created within six months by the existing Area Health Authorities and the Industrial Health Service. The sites, it said, should be readily accessible, open at convenient hours, and as close as possible to the nearest blood bank; tests should be inexpensive and should require no doctor's referral; and there should be opportunities for confidential conversation. Three public health authorities (Amsterdam, Rotterdam, and Arnhem) were designated as alternative test sites and began operations in October 1985. That month other public health authorities were instructed by the Minister to await the availability of a reliable confirmatory test before offering this service.

On 13 December 1985, the Central Medical Blood Transfusion Committee announced that, as of the first quarter of 1986, all donors who tested positive for HIV antibody had to be told of their test results, and it gave specific instructions about the method of notification. They were that it was the physician who ordered the test who was to inform the donor of a positive result; that the information should be conveyed in both a personal interview and in writing; that the donor should be referred for further help and support to another physician; that the blood bank should have a list of physicians in the region for those donors who did not want to use their family physician; and that a positive test result should never be sent to a donor's general practitioner without his or her consent. Blood banks later adopted a policy of informing all potential donors about blood screening and the possible consequences of a positive test outcome.

The Red Cross Central Laboratory began confirmatory testing, using the western blot technique, in January 1986. Regulations requiring the testing of donations for HIV antibody were made on 14 December 1987, to become effective on 1 January 1988.

Use of imports

The use of imported (primarily U.S.) blood products was not as extensive in the Netherlands as in some other European countries. It is estimated that half of HIV infections among hemophiliacs in the Netherlands were connected with imported concentrates, both non-heat treated and heat treated. The use of these products was examined by the ombudsman.

The Dutch Association of Hemophilia Patients had, in 1979, urged the government, the Red Cross Central Laboratory, and the blood banks to develop and implement as soon as possible a plan for self-sufficiency in blood and blood products. In the interim, non-heat-treated concentrates were imported regularly during the early 1980s. Tramedico was licensed to import non-heat-treated factor VIII concentrate produced by Armour in 1979, and in 1981 Travenol was also licensed to import its own products.

In February 1983, the daily newspaper *Trouw* reported that the government planned to ban the importation of foreign concentrates to prevent the spread of AIDS. The suggestion of banning imports had come from the director of the National Institute of Public Health. In response, both the Dutch Association of Hemophilia Patients and the Dutch Association of Hemophilia Treating Physicians asked to be consulted before any decision was made. The Central Medical Blood Transfusion Committee wrote to the Minister, arguing that foreign concentrates had played a pioneering role in the treatment of hemophilia and that it was unwise to erect a permanent barrier against products that might some day be free of AIDS. It proposed that the Medical Inspectorate instead draw the attention of treating physicians to the possible risks associated with imported concentrates, but leave open the question of advising against its use pending further research.

In May 1983, the public health officer for drugs in North Holland sent a report to the chief public health officer for drugs about a study that the Red Cross Central Laboratory had done on hemophilia patients who had received various blood products. Among those receiving only cryoprecipitate, 73 per cent had normal T-4 ratios; among those receiving imported factor VIII concentrate, 29 per cent had normal levels. The officer recommended that the government consider banning imports of factor VIII concentrate and examine the possibility of producing factor VIII concentrate from a pool of no more than four donors.

The ombudsman found that by 1983 it had become clear that the risk of HIV infection was higher with factor VIII concentrate than with cryoprecipitate. He stated that the combination in the United States of relatively widespread

AIDS and plasma from paid donors increased the probability that non-heat-treated American factor VIII concentrate posed a greater threat of infection than non-heat-treated Dutch products. The ombudsman found that the Ministry's decision to continue to permit the use of imported products was understandable for several reasons. There was much uncertainty at the time whether AIDS was a viral disease that could be transmitted by blood products; it was not until late 1984 that the U.S. Centers for Disease Control recommended the use of heat-treated concentrates; and, when the Ministry did seek to prohibit the importation of American factor VIII concentrate, the Dutch Association of Hemophilia Patients campaigned actively against such an action.

The ombudsman also investigated the facts relating to the HIV infections caused by Armour's heat-treated factor VIII concentrate. In March 1984, regulatory officials had advised the Minister to grant Tramedico, Armour's agent in the Netherlands, permission to import heat-treated products in the belief that it was reasonable to assume that heat treatment would reduce viral activity. Ministerial approval was not granted until July 1986, but in the interim Tramedico imported Armour's heat-treated factor VIII concentrate, H.T. Factorate, on the authority of its 1979 permit for the non-heat-treated product. In late 1985 and early 1986, cases of seroconversion were reported among patients using H.T. Factorate in the United States, the United Kingdom, and the Netherlands. The Dutch case was discovered in early 1986 by the University Medical Centre in Amsterdam, reported in *The Lancet* in April, and presented at the International AIDS Conference in Paris in June of that year. In December 1987, the U.S. Food and Drug Administration announced that Armour had voluntarily recalled 208 batches of H.T. Factorate as a result of seroconversions reported in Canada. The Minister was unaware of any problems associated with Armour's products, however, until the Central Medical Blood Transfusion Committee wrote to her on 20 January 1988 about the Canadian cases and asked her to find out whether similar products had been imported into the Netherlands, and, if so, to have them recalled without delay. The letter was signed by the president of the Dutch Association of Hemophilia Patients and the president of the Dutch Association of Hemophilia Treating Physicians.

Regulatory officials also received a copy of the letter sent by the deputy secretary of public health, and, in an emergency meeting on 19 February 1988, they decided it was no longer defensible to import H.T. Factorate. They stated that Tramedico should undertake a recall immediately. On 22 February, Tramedico agreed to recall products from blood banks and patients' homes. On 2 March, however, regulatory officials concluded that Tramedico's recall had been only a limited one, since it was impossible to verify what supplies patients still had in their homes. On 9 March, the chief medical officer informed the Dutch Association of Hemophilia Patients and the Dutch Association of Hemophilia Treating Physicians of the recall, and they in turn told their

members. On 14 March, the chief medical officer instructed Tramedico immediately to inform patients who might still have Armour concentrates in their homes about the risks of using them.

The ombudsman stated that the Ministry's responsibilities in public health required it to follow developments in the field and to acquire and interpret current scientific knowledge. The fact that the Ministry had been unaware of reports of seroconversion after the use of H.T. Factorate was a grave omission; had the Ministry been aware of those reports earlier, it would have investigated whether the product was still distributed in the Netherlands and, if it was, whether there was any reason to withdraw it from the market. The ombudsman was also critical of the fact that Armour's heat-treated product had been distributed for several years without an import licence, and concluded that the Ministry erred, given its duty to control the import of blood products.

Informing hemophiliacs of the risk

Use of factor concentrates

Treating physicians and the Dutch Association of Hemophilia Patients worked together to educate patients with hemophilia about AIDS. Physicians at treatment centres recommended a number of changes in the treatment of hemophilia patients, organized meetings with their patients to discuss treatment options, and discussed the risk of AIDS with patients individually. The association participated in discussions about treatment and wrote regularly about AIDS in its publications.

Concern about the risk to hemophiliacs began in late December 1982 when a staff member of the Red Cross Central Laboratory received a copy of an article published in the *New England Journal of Medicine* describing abnormal T-cell ratios in hemophiliacs treated with factor VIII concentrate. Officials from the laboratory immediately held a meeting with hemophiliacs and their physicians to discuss the need for a similar comparative study of Dutch hemophiliacs treated with cryoprecipitate, domestic factor VIII concentrate, and imported factor VIII concentrate. Health authorities were at the same time told of the potential risk posed to hemophilia patients. Treating physicians, the Red Cross Central Laboratory, the Dutch Association of Hemophilia Patients, and the National Institute for Public Health and Environmental Protection subsequently agreed on guidelines for modifying hemophilia therapy to reduce the risk of HIV infection. They advised hemophilia patients and their physicians to

- use cryoprecipitate wherever possible;
- treat new patients and children under the age of four with cryoprecipitate exclusively;
- treat patients with moderately severe or mild type A hemophilia with DDAVP (desmopressin, a chemical that can be used to increase the level of circulating factor VIII) or, if necessary, cryoprecipitate;

- use domestically produced factor VIII concentrates when concentrates are necessary;
- use imported factor VIII concentrates only for patients with severe allergic or hemolytic reactions to the Dutch products; and
- treat type B hemophiliacs with domestically produced factor IX products.

These guidelines were published in the *Dutch Journal of Medicine (Nederlands Tijdschrift voor Geneeskunde)* in May 1983.

On 27 February 1983, the Dutch Association of Hemophilia Patients wrote to its members to alert them to a possible connection between factor concentrates and AIDS. The letter summarized the spread of the disease in the United States, reported that the incubation period was believed to be from six months to two years, and stated that it was highly likely that American hemophiliacs had been infected by factor concentrates made from plasma from infected donors. It said that the association's board had held intensive consultations with treating physicians, the Red Cross Central Laboratory, public health authorities, and other agencies to determine how the risk of infection could be reduced and that, as a preliminary measure, guidelines for treatment had been issued. It also said that it might be necessary to limit the use of concentrates manufactured in the Netherlands. In the issue of its newsletter, *Faktor*, of March 1983, the association again outlined the steps that had been taken to minimize the risk of the transmission of AIDS among hemophiliacs. The association had issued guidelines for temporarily limiting the use of imported concentrates; had been involved in consultation about a possible change from the use of concentrates to cryoprecipitate; had sent a telexed message to the Minister of Welfare, Health and Cultural Affairs, stating that any decision to revoke existing import permits must be based exclusively on scientific grounds; and had held talks with the Ministry about AIDS in late March.

In April 1983, the director general of the National Institute of Public Health and Environmental Protection wrote to the Minister of Health to say that experts generally agreed that U.S. factor concentrates should not be used. He recommended that the use of imported factor VIII concentrate made from plasma from paid donors should be prohibited until further notice. Physicians of hemophiliacs who had signed a consent were exempt. He reported that the United States had approved a process of heat treating factor VIII concentrate to inactivate the HIV virus, but that the resulting product was more expensive than concentrates that had not been heat treated; he suggested that heat-treated factor VIII concentrate be used only if the patient signed a consent, pending approval of heat-treated factor concentrates in the Netherlands.

That month, treating physicians attended a one-day symposium on AIDS organized by the Red Cross Central Laboratory. During this much-publicized meeting, preliminary results were presented from the first study of T-cell ratios in Dutch hemophiliacs. The study found that the ratios in patients

treated with imported factor VIII concentrate were often abnormal. There was also a discussion of measures soon to be implemented in the United States to prevent the transmission of AIDS.

In June 1983, the recommendations for the treatment of hemophilia patients made earlier that year were published in the *Dutch Journal of Medicine*. The authors said that AIDS was “presumably transmitted by transfusion,” citing as evidence the death of an American infant from AIDS after receiving a blood transfusion; that the likelihood of infection was directly related to the number of donors the patient was exposed to through treatment; that patients treated with cryoprecipitate were exposed to the plasma of twelve to sixteen persons with every treatment, while those using factor concentrates were exposed to plasma from a pool of 2,000 to 3,000 persons; and that the risk increased with the use of foreign concentrates obtained from purchased plasma. By this time only five cases of AIDS had been reported in the Netherlands, all homosexual men with contacts in the United States.

The ombudsman considered whether the government should have done more to discourage the use of imported, non-heat-treated concentrates. He found that the Ministry had participated actively in the search for solutions to this issue and, as early as January 1983, had discussed the possibility of prohibiting imports of factor VIII concentrate. It had also discussed with the Red Cross Central Laboratory ways of increasing domestic output in order to reduce reliance on imports. Because “the front-line personnel” (blood banks and treating physicians) had assumed responsibility, and physicians and their patients were advised in time to change to Dutch coagulation products, he concluded that the Ministry did not have sufficient reason to take the lead in the matter.

Extent of HIV infection

Treating physicians and the Red Cross Central Laboratory studied the extent to which Dutch hemophiliacs developed antibodies to HIV during the early and mid-1980s. Between 1982 and 1985 one physician, Dr Cees Breederveld, undertook a long-term study of hemophiliacs who were using a variety of products. His first results, in April 1983, showed that hemophilia patients were being infected by Dutch and U.S. concentrates that had not been heat treated. He forwarded this information to government officials the same month. In January 1985, using a non-licensed experimental technique, the Red Cross Central Laboratory conducted a seroprevalence study using blood collected from Dutch hemophilia patients in 1983 and 1984. It found that fourteen of forty patients (35 per cent) treated with imported factor VIII concentrate tested positive for HIV antibody, compared with only two of twenty patients (10 per cent) who had received a combination of Dutch concentrates and cryoprecipitate, and two of fifty-six patients (3.6 per cent) who had received only cryoprecipitate.

No similar studies were undertaken by the government. The ombudsman found that the government was reluctant to carry out surveillance studies of hemophiliacs because, given the small number of patients involved, the value of the research would be limited and the anonymity of the participants could not be ensured. The ombudsman did not agree with the Dutch Association of Hemophilia Patients that the Ministry had been negligent in failing to conduct studies of HIV infection among hemophiliacs. He rejected the Minister's arguments that surveillance studies would be "invalid." But, he said, since scientific research into public health is not the exclusive responsibility of government, the government could decide not to conduct its own studies, particularly when the research had already been undertaken by others and the findings had been made known to Ministry officials.

The ombudsman concluded that there were "no situations during the period concerned where the government failed to take its own initiative to provide information to physicians and other health-care professionals." He agreed with the Ministry's position that the primary duty to inform patients lay with physicians and other health care professionals. He found that by making a financial contribution to the Dutch Association of Hemophilia Patients specifically for an exchange of information, the Ministry had contributed indirectly to the communication of information to hemophiliacs and had "sufficiently assumed its responsibility to inform."

Informing transfusion recipients of the risk

In early 1984, the Red Cross Central Laboratory asked the Health Council to inform it of all newly diagnosed AIDS patients who had donated blood or plasma, and the donation number, so it could trace any unused blood products derived from the contaminated donation. Government health officials rejected that request because they regarded tracing as a governmental obligation.

In June 1985, the Central Medical Blood Transfusion Committee issued a statement that the tracing of HIV-contaminated blood was, as a general rule, inadvisable because the significance of a positive test result was not clear and the reporting of such a result could cause unnecessary alarm. Two years later, the committee reversed its stand and decided that, in cooperation with the Ministry of Welfare, Health and Cultural Affairs, it would try to trace recipients of blood products prepared from blood that was possibly contaminated with HIV. The reason for this change in policy was that tests for HIV antibody had proved reliable, and the risk of infection through blood transfusion was considered minimal as a result of the screening.

The recommended procedures for notification were outlined in a guideline of the Central Medical Blood Transfusion Committee dated 19 December 1986. The committee stated that a blood bank physician who supplied a product that might be HIV contaminated should trace both the recipient and his or her attending physician, but should inform only the latter. It would be the task of the attending physician to judge whether the recipient should be informed.

If the physician decided to tell the recipient, he or she would then contact the recipient, or in cases where the recipient was a child, his or her parents or guardians. In most cases, the recipient's blood would be tested for the HIV antibody and the results reported to the blood bank.

Findings of the ombudsman

The ombudsman first examined the role of the government to determine the appropriate standard of conduct to which public authorities should be held. He found that although the government was responsible for promoting public health, it was not directly concerned with the medical treatment of individual patients and generally confined its activity to monitoring physicians' practices in treatment. He found also that the government's role in public health was "largely determined by the structure of professionals, institutes, and producers, and in particular the duties and responsibilities of the players concerned," and that "the government and certain other players shared the responsibility for the health of hemophiliac patients." However, "when situations arise for which treating physicians may not yet have a suitable solution, the government may have reason to play a more active role in order to promote public health" and, when faced with a serious threat to public health, the government had the "exclusive responsibility to ensure that other parties would react appropriately, and in a timely manner." The ombudsman concluded that AIDS could be characterized as such a threat, and it was therefore appropriate that the Ministry take an active role in monitoring developments.

The ombudsman considered whether the government's actions might have been influenced by any extraordinary mitigating circumstances, and he found three: the lack of domestic self-sufficiency in plasma during the period under study; a lack of uniformity among blood banks that was "unsatisfactory for attaining the desired coherence and cooperation"; and complaints of discrimination from gay organizations when homosexual men were faced with possible exclusion from donating blood in 1983. He also underscored the importance of interpreting events in light of the knowledge available to health officials during the early years of the emergence of AIDS:

Hindsight is always 20/20 ... the seriousness and the scope of AIDS are now far more obvious than they were at the time ... This assessment concerns ... a government that had to decide when which risks were still or no longer acceptable and which measures were available to eliminate or at least reduce certain risks. The assessment must be based on knowledge that can reasonably be assumed to have been available to the government at the time. [Translation.]

The ombudsman concluded that, as a general rule, measures taken by the government should complement those of the front-line personnel working in the field. In view of the unique threat posed to public health by AIDS,

however, he stated that government intervention in the absence of actions by those in the field was not only appropriate but required. In such circumstances, “in addition to the proper use of specific instruments intended exclusively for the government in this area, it is also the government’s responsibility to take active measures whenever the front line personnel fail to do so.” He also stated that, although the actors in the front line had indeed been active (and in many instances to such an extent that active intervention by government would have been redundant), the Ministry had not always provided direction in circumstances in which it would have been appropriate for it to take the lead:

Considering the seriousness of the AIDS contamination, the situation called for the government’s alertness, especially in the light of the prevailing uncertainty and the fast-paced development of medical science. On the basis of the inquiry, we must conclude that the government has not complied with these requirements in every respect. With regard to some of the points raised by the [Dutch Association of Hemophilia Patients], it would appear that the government was running after the facts/developments and/or was not sufficiently informed about the state of things or remained passive. [Translation.]

The ombudsman accordingly considered the conduct of the Ministry improper in the following respects: the absence of any initiative in late 1984 or early 1985 to reduce the risk of infection resulting from the use of domestic non-heat-treated blood concentrates; the failure to require Dutch blood banks and manufacturers to heat treat blood concentrates until January 1988; and the failure to recall Armour factor VIII concentrate before the beginning of 1988.

He declined to comment on any possible causal link between the shortcomings of the Ministry and HIV infection or to discuss the question of compensation, because these issues lay outside his terms of reference:

An extremely important point to examine is if, and to what extent, there is a causal connection between the shortcomings of the Netherlands government in the period until 1 January 1988, as highlighted by the National Ombudsman in the course of this inquiry, and specific cases of HIV contamination of hemophiliac patients in that same period. This question must be answered on a case-by-case basis. However, it falls outside the scope of this inquiry as a result of the Petitioner’s [the Dutch Association of Hemophilia Patients’] application, and it cannot consequently be answered by the National Ombudsman. Therefore, the National Ombudsman is not in a position to determine if, based on some concrete cases of HIV contamination of hemophiliac patients through the use of blood products, there can be any question of a causal connection, nor can it determine if there are grounds to find the government at fault in this

regard, in the sense that there would be grounds for compensation. A question of a different kind – not to be answered here – would be, regardless of the answer to the question of a possible liability of the government to provide compensation in individual cases of HIV contamination, to determine whether financial compensation of any kind should be provided to hemophiliac patients. [Translation.]

With respect to this question of liability and financial compensation, he concluded that he could not provide any guidance except to offer an accurate reconstruction of events. The decisions required political judgment and should more properly have been referred to the legislature for consideration.

Assistance to persons infected and affected

The Dutch Association of Hemophilia Patients had established a fund to provide financial assistance to its members before 1980. Since the appearance of AIDS, a significant number of contributions have been made to the fund. In 1988, the association received a government grant of U.S.\$55,000 for its AIDS-related activities. A private foundation, the Stichting Hemofilie, was established with this money. The Stichting Hemofilie makes payments to hemophiliacs with HIV or AIDS and their families when financial support cannot be obtained from regular social security programs.

Because Dutch insurers were reluctant to insure people believed to be at risk of HIV infection, the association approached the government for life insurance and home mortgage insurance, to a maximum of Dfl. 200,000 (Can\$125,000), for any patient with hemophilia who could not otherwise obtain such insurance. In 1992, the Minister for Welfare, Health and Cultural Affairs gave Dfl. 5 million (Can\$3.4 million) to the Dutch Red Cross Contingency Fund to implement an agreement between the Dutch Red Cross and the Dutch Association of Life Insurers. Under that agreement, HIV-infected hemophiliacs are eligible for life insurance benefits of Dfl. 200,000. In February 1994, the Minister committed an additional Dfl. 4.5 million (Can\$3.3 million) for hemophiliacs who had been infected with HIV before 1986 and who had been diagnosed with AIDS. The Dutch Association of Life Insurers also offered to introduce an insurance plan specifically for hemophiliacs under which they would pay regular monthly contributions to a special fund, and surviving family members would receive benefits based on contribution levels. The negotiations leading to the establishment of that fund in 1992 involved the Dutch Red Cross, the Ministries of Finance and Legal Affairs, the Dutch AIDS-Fonds, the Stichting Hemofilie, the Dutch Association of Life Insurers, and the Association of Accident and Sickness Cost Insurers.

In July 1995, the Minister of Health said that the government accepted the ombudsman's conclusion that it had been partially responsible for the infection of hemophiliacs and would compensate all who had become infected with HIV. Each person is expected to receive the equivalent of Can\$175,000.

There have not yet been any successful civil actions for damages. In December 1992, the Dutch Association of Hemophilia Patients brought an action against the government, producers of blood products, hospitals, and physicians, but the action was barred by the statute of limitations. Another action, launched against a hospital by a plaintiff who had received non-heat-treated Armour blood products in June 1983, was dismissed by the Amsterdam District Court in July 1992 because the plaintiff was unable to prove that he was infected in June 1983.

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The United Kingdom

The blood system in the 1980s

During the early 1980s, there were two separate blood transfusion services in the United Kingdom – the National Blood Transfusion Service, serving England and Wales, and the Scottish National Blood Transfusion Service, serving Scotland and Northern Ireland. Most of this chapter is based on information from the former organization, but reference will be made to the latter as often as possible. These two services were managed separately, but in a similar manner. Traditionally there has been close cooperation between them and they have had common policies on many issues. In the United Kingdom, no pharmaceutical corporations have ever operated commercial blood banks; moreover, both of the transfusion services have always collected blood and plasma exclusively from voluntary unpaid donors. Since 1987, the system in England and Wales has undergone many changes, the most notable being the creation of the National Blood Authority in April 1993.

The National Blood Transfusion Service and the Scottish National Blood Transfusion Service

The first civilian blood bank was established in Ipswich in 1938 and, after the outbreak of World War II the next year, five large transfusion centres opened to supply blood and plasma for both civilian and military casualties. Only voluntary unpaid donors were recruited. In 1940, eight regional transfusion centres were opened as part of the Emergency Medical Service, and, at the conclusion of the war, the Emergency Medical Service and the army transfusion service were amalgamated to form the National Blood Transfusion Service in England and Wales. The Scottish National Blood Transfusion Service was created in 1941. In 1948, with the enactment of the *National Health Service Act*, the National Blood Transfusion Service and the Scottish National Blood Transfusion Service became part of, and were funded by, the National Health Service, and were administered by regional hospital boards.

The collection of blood in the United Kingdom is carried out by regional transfusion centres. During the 1980s there were thirteen centres in England and Wales, and five in Scotland. Each of these centres was responsible for

meeting the transfusion requirements of hospitals in its region. Although the centres performed different functions depending on the demands of their regional health authorities, they were all responsible for recruiting donors and collecting blood donations, implementing screening tests, processing whole blood into various blood components for delivery to the hospitals in their localities, supplying fresh frozen plasma for fractionation, distributing plasma to hospitals, and providing blood-grouping services and medical advice about transfusion.

Regional transfusion centres operated under the authority of regional health authorities, which, until 1974, were known as regional hospital boards. The regional transfusion director of each centre was accountable to either the regional medical officer or another senior health manager for the region. Despite this formal reporting arrangement, regional transfusion centres enjoyed a great degree of autonomy.

The British government has long been committed to the principle of self-sufficiency, yet the National Blood Transfusion Service was unable to achieve this goal during the 1980s. It did not import source plasma, but in the early 1980s it did import almost 80 per cent of the blood products used by hemophiliacs. Although the demand for blood products escalated dramatically, the National Blood Transfusion Service was able to increase its supply steadily and, by the end of the 1980s, only 20 per cent of factor VIII concentrate used by hemophiliacs was derived from foreign commercial sources. The Scottish National Blood Transfusion Service had more success in achieving self-sufficiency. Since the early 1980s, it has consistently been able to produce all the blood and plasma needed by patients, and almost all the requirements for blood products.

The Blood Products Laboratory and the Protein Fractionation Centre

During the 1980s, blood products in the United Kingdom were manufactured at two fractionation plants: the Blood Products Laboratory in England, known after the mid-1980s as the Bio-Products Laboratory, and the Protein Fractionation Centre in Scotland. Both of these fractionation plants were funded by the National Health Service. Apart from a small amount of plasma for therapeutic use in hospitals, the plasma recovered from whole blood or donated by plasma donors was sent to the Blood Products Laboratory or the Protein Fractionation Centre for fractionation into a range of blood products for use mainly by the National Health Service; surplus products were exported.

In an effort to achieve self-sufficiency in blood products, the Blood Products Laboratory constructed a new and larger plasma fractionation plant at Elstree in Hertfordshire in April 1988. The plant was built with a capacity to produce 100 million units of factor VIII concentrate and sufficient amounts of albumin and other plasma products to treat all patients in England and Wales.

The role of government

The Medicines Control Agency was the governmental body that regulated the supply of blood and blood products in the United Kingdom. In accordance with the *Medicines Act 1968*, the agency inspected every transfusion centre as a condition of licensing. In addition, quality assurance employees from blood transfusion centres conducted annual peer review audits of each centre and sent their reports to the national quality assurance manager. All regional transfusion centres in the United Kingdom were also required to adhere to guidelines issued by the Department of Health (or the Department of Health and Social Security, as it was known before 1988). These guidelines were prepared by representatives of the U.K. Blood Transfusion Service in liaison with the National Institute for Biological Standards and Control. In recent years, the guidelines have been revised to take into account recommendations made by the World Health Organization, the U.S. Food and Drug Administration, and the American Association of Blood Banks.

Blood products and fractionation premises are licensed under the *Medicines Act 1968* and in accordance with standards set by the Council of the European Communities. All licensing and inspection are still conducted by the Medicines Control Agency. In addition to satisfying the standard licensing requirements, manufacturers must ensure that the processes used in the preparation of blood products are properly validated, that batch-to-batch consistency is maintained, that the absence of viral contamination is guaranteed (to the extent that technology permits), and that records are properly maintained.

There are no import restrictions in the United Kingdom, although licensed products must be manufactured in accordance with the directives and guidelines for good manufacturing practices used in the European Community. Factor concentrates and albumin are not exported, although there are no restrictions on the export of these products.

Two departmental bodies were important during the 1980s in the study and surveillance of AIDS. The Public Health Laboratory Service played a major role in the scientific study of HIV and AIDS, investigating antibodies and developing an efficient means of testing, while the Communicable Disease Surveillance Centre, in collaboration with the Communicable Diseases and Environmental Health (Scotland) Unit, was responsible for monitoring the prevalence of diseases and for conducting surveillance. In addition, the Public Health Laboratory Service published a bulletin entitled the *Communicable Disease Report*.

The Haemophilia Society

The Haemophilia Society was established in 1950 to represent the interests of persons with hemophilia or related bleeding disorders in the United Kingdom. It has a national office and more than twenty local organizations, which are

responsible for fundraising, social activities, and mutual help. The society was one of the six founding members of the World Federation of Hemophilia in 1963.

The goal of the Haemophilia Society is to “improve the quality of life for people with hemophilia (and related disorders) and their families.” It attempts to do so by providing financial assistance to hemophiliacs and their families, promoting high standards of treatment, lobbying government, publishing information, and providing financial support for research.

At the national level, there are two governing bodies, the executive committee and the council. The executive committee is the policy- and decision-making body, while the council is a consultative body composed of representatives of each local organization. The society also has several committees and advisory bodies, including the policy and development committee, the member services committee, the resources committee, the friends group, and the medical advisory panel. Operating and research funds come from membership fees, fundraising activities, local group contributions, donations, government grants, and income from trusts and foundations.

Hemophilia treatment centres

During the 1980s, hemophiliacs in the United Kingdom received treatment and blood products exclusively at hemophilia treatment centres. There were 110 treatment centres in the United Kingdom, most of them small, in addition to a national treatment centre in Oxford. The physicians in charge of these hemophilia treatment centres were members of the U.K. Haemophilia Centre Directors Organisation.

Prevalence of blood-related HIV or AIDS

In December 1991, approximately 5,000 hemophiliac patients in the United Kingdom were tested for HIV. Of those, 1,227, or 24.5 per cent, tested HIV positive. The source of HIV infection is thought to be both domestic factor concentrates from the National Blood Transfusion Service and non-heat-treated factor concentrates imported from the United States before December 1984.

The World Federation of Hemophilia reported in 1992 that, by December 1991 in the United Kingdom, there were 290 cases of AIDS among hemophiliacs, or 3 per cent of the total hemophiliac population, and that 23.6 per cent of hemophiliacs were HIV positive. Between 1991 and 1996, the number of hemophiliacs with AIDS doubled. By 31 December 1996, the European Centre for the Epidemiological Monitoring of AIDS reported that there were 584 cases of AIDS among hemophiliacs in the United Kingdom.

According to data compiled by the European Centre for the Epidemiological Monitoring of AIDS, by the end of December 1996 there were 114 cases of transfusion-related AIDS in the United Kingdom, less than 1 per cent of all AIDS cases. Figures on the prevalence of HIV infection among transfused patients were not available.

Protecting the blood supply from HIV or AIDS

Parliamentary study

In November 1985, the House of Commons requested that its Social Services Committee briefly review the measures taken in the United Kingdom to reduce the transmission of HIV through blood and blood products. In May 1987, eighteen months after it began its task, the Social Services Committee issued its report on AIDS. In essence, it endorsed the actions taken by the National Blood Transfusion Service in safeguarding the blood supply. "We commend the way in which the Blood Transfusion Service has responded to the challenge of AIDS, protecting donor and recipient alike," the committee stated, "and urge a constant review of policy and procedures to maintain that high standard."

The emergence of HIV or AIDS

The first AIDS case in the United Kingdom was reported in *The Lancet* in December 1981. The deceased patient was a forty-nine-year-old male homosexual who had suffered from *Pneumocystis carinii* pneumonia and cytomegalovirus. He had resided in London, but had travelled to the United States annually. By July 1983, only fourteen cases of AIDS had been reported in the United Kingdom, but the numbers soon increased: by May 1984, there were forty-seven reported cases; by July 1984, fifty-four cases; and by the end of October 1985, the number had risen to 241 cases.

In the spring of 1983, reports of possible British cases of the transmission of AIDS through blood began to appear in medical and scientific journals. By August 1983, the Communicable Disease Surveillance Centre had received the first report of AIDS in a hemophiliac, a patient from Wales who had received factor VIII concentrate imported from the United States. The authors of this report concluded that, given the number of persons receiving treatment for hemophilia, "the risk from blood products imported into Britain seems at present very small." By the end of October 1983, another case of AIDS had been reported in a hemophiliac who had been treated with imported factor concentrates.

In November 1983, *The Lancet* reported the first fatal case of AIDS in a hemophiliac. Again, the patient, who lived in Bristol, had been treated intensively with imported American factor VIII concentrate. His physicians concluded: "It seems highly probable that the development of AIDS was related to this treatment. This case provides further evidence for a link between exposure to blood products and AIDS." An article in *The Lancet* in December 1983 confirmed that this case indeed fell within the definition of AIDS formulated by the U.S. Centers for Disease Control.

By the end of 1984, three cases of AIDS acquired through blood products had been reported, and, according to one study of 184 hemophiliacs using pooled factor products, 39 per cent were positive for HIV antibody. At the end

of June 1985, there were five cases of hemophiliacs with AIDS, and 44 per cent of hemophilia A patients and 6 per cent of hemophilia B patients were HIV positive. By October 1985, among the 241 reported cases of AIDS, four were transfusion related (two of them had been transfused outside the country) and eight were in hemophiliacs. By February 1986, there were five cases of AIDS in persons who had received blood transfusions, two of whom had been transfused overseas. At the end of May 1986, the number of hemophilic AIDS cases had increased to seventeen, and there were six cases of transfused patients with AIDS.

Response to the emergence of HIV or AIDS

The first surveillance program to monitor cases of Kaposi's sarcoma and opportunistic infections was established by the Communicable Disease Surveillance Centre, in collaboration with the Communicable Diseases (Scotland) Unit, in September 1982. The centre received reports from three sources. The Office of Population Census and Surveys agreed to send it copies of death certificates mentioning Kaposi's sarcoma or AIDS; microbiologists were asked to report opportunistic infections noted on routine laboratory report forms; and venereologists and dermatologists were asked to report AIDS cases voluntarily. In March 1983, the centre decided to extend its surveillance program by requesting physicians in all branches of medicine to report AIDS cases on a confidential basis and to give information about its modes of transmission, clinical features, and demographics. In addition, the centre received any reports of opportunistic infections sent to the National Health Service. This information was compared with the voluntary reports received from the physicians. Directors of hemophilia treatment centres reported AIDS in hemophilia patients to their national centre in Oxford, which relayed the data to the Communicable Disease Surveillance Centre. Surveillance of HIV infection began in late 1984, through voluntary confidential reports from microbiologists in laboratories where HIV tests were carried out.

AIDS has never been a statutorily notifiable disease in the United Kingdom. When cases of AIDS first emerged, public health experts were of the opinion that to include AIDS as a notifiable disease under the public health legislation was inappropriate because of its modes of transmission and its long incubation period. They also thought that mandatory reporting would discourage persons at risk from seeking testing and counselling. In 1987, however, the *AIDS (Control) Act* was passed, requiring district health authorities, regional health authorities, and health boards in England and Wales to report to the Secretary of State for Health the number of persons with HIV or AIDS, the number of persons known to have died from AIDS, and the number of blood donors testing positive for HIV.

Excluding persons at risk: Donor screening

In the autumn of 1983, the National Blood Transfusion Service issued guidelines for the voluntary exclusion of donors at high risk of contracting AIDS. It also began a health education campaign to inform the public about the risks of transmission.

The first educational leaflet, entitled *AIDS and How It Concerns Blood Donors*, was published in September 1983. Persons in high-risk groups were asked not to donate. High-risk categories were defined as homosexual men who had many different partners; male and female drug addicts who used injections; and sexual contacts of persons suffering from AIDS. Patients with AIDS, the leaflet explained, seemed more likely to have suffered at some time from diseases such as hepatitis B, syphilis, or other sexually transmitted diseases, and AIDS had been discovered in a number of immigrants to the United States from Haiti. The leaflet also mentioned that a few cases of AIDS had been reported in the United Kingdom, although not in the same numbers as in the United States. In announcing the publication of the leaflet, the Minister for Health informed the public that “[i]t has been suggested that AIDS may be transmitted in blood or blood products. There is no conclusive proof that this is so.” Regional transfusion directors were allowed to use their discretion in distributing the leaflet. As a result, some regional transfusion centres included the leaflet in letters to individual donors reminding them to donate, some handed it to donors when they arrived at the centre, and others made it available at the centre, to be picked up as donors wished.

In September 1984, the Department of Health and Social Security announced that it was considering reissuing the leaflet about AIDS and blood donation, and in January 1985 a second pamphlet for donors, *AIDS: Important New Advice for Blood Donors*, was published. It asked persons in the high-risk categories of contracting AIDS to refrain from donating and listed these groups as practising homosexual and bisexual men, male and female drug abusers who injected drugs, and sexual contacts of persons in these groups. The pamphlet said that AIDS had occurred in a small number of hemophiliac patients who had been treated with blood products. It added that persons who had lived in Haiti or Central Africa, particularly Zaire and Chad, might be at risk of acquiring AIDS. Stronger measures were now taken to ensure that prospective donors actually read the leaflet. Regional health authorities were sent a circular, informing them that it was “essential that the revised leaflet be brought to the attention of each donor *on an individual basis*,” and that simply displaying the leaflet was not sufficient. It stated that “[d]isplays of leaflets, whilst continuing to be useful, will not meet these new distribution requirements.” Regional health authorities also were directed to send the revised leaflets to persons who had received the earlier version and to destroy all remaining copies of the 1983 edition.

On 30 August 1985, the Department of Health and Social Security sent a letter to all regional transfusion directors announcing that the leaflet would be revised for a third time to coincide with the introduction of HIV testing of donations, which was expected to start in October 1985. Entitled *AIDS: Important Information for Blood Donors*, and dated September 1985, the leaflet identified the following groups as most at risk: homosexual or bisexual men, male and female drug abusers who injected drugs, hemophiliacs who had been treated with blood products, and sexual contacts of persons in these groups. The leaflet also informed donors that, if they consented, their donations would be tested for the antibody to the AIDS virus. Donors were cautioned that despite testing, persons in risk groups must refrain from donating blood. In a separate letter dated 24 September 1985, the general managers of regional health authorities were asked to ensure that "individual distribution arrangements detailed ... for the January 1985 leaflet ... are again applied to the September 1985 leaflet."

The AIDS leaflet was revised a fourth time in September 1986. Entitled *AIDS: What You Must Know before You Give Blood*, the leaflet stated that the following persons were at risk of contracting AIDS: men who had had sex with another man since 1978; male and female drug abusers who had injected drugs at any time since 1978; hemophiliacs who had received non-heat-treated factor concentrates at any time since 1978; people who had lived in or visited Africa south of the Sahara at any time since 1978 and had had sex with men or women living there; and sexual partners of persons in these groups, whether the relationship had been a single contact or a long-term association.

In July 1987, a fifth edition of the leaflet, entitled *AIDS: Think before You Give Blood*, was released. After the publication of a news report that seven female prostitutes had tested positive for HIV in 1986, prostitutes were added to the list of groups at high risk of contracting AIDS. The groups at risk included men and women who knew they were infected with the AIDS virus or who had AIDS; men who had had sex with men at any time since 1977; men and women who had injected themselves with drugs at any time since 1977; men and women who had had sex at any time since 1977 with men or women living in African countries, other than those on the Mediterranean; men and women who had had sex with anyone in these groups; sexual partners of hemophiliacs; and men and women who were prostitutes. On 11 August 1987, the Department of Health and Social Security wrote to all regional general managers informing them of the leaflet and reaffirming the continued need for donor screening. It was imperative, the department stressed, that donors be warned individually of the groups at risk, since the screening test could not identify anyone infected with HIV during the window period (that is, the period after infection before HIV antibody is detectable). Regional general managers were asked to ensure that the leaflet was sent to all donors before every donation.

Despite this emphasis on donor screening, the National Blood Transfusion Service did not require prospective donors to make a written or oral declaration that they were not at risk of contracting AIDS. In October 1985, however, after the introduction of HIV testing, they were asked to sign a form acknowledging that they had read the leaflet and were aware that their blood would be tested for HIV.

Because of the high prevalence of HIV or AIDS in the North London region, the regional transfusion centre in Edgware implemented a means for confidential unit exclusion by blood donors. This method of exclusion permitted donors to inform the centre in confidence on a questionnaire that they were in a high-risk group; there was no interview and no one to ask awkward questions. Donors were asked to indicate that they had read the notice listing the groups at risk of contracting AIDS. They were then asked to indicate whether, should they be in a high-risk group, they wished to donate on the understanding that the blood would be used for research purposes only. The questionnaire was introduced in July 1984 after the region's medical director learned of the screening method at an AIDS conference in the United States. Use of the confidential unit exclusion method resulted in a deferment rate among men of 1 to 2 per cent.

Inactivating viruses in blood products

In September 1983, a memorandum was circulated to all hemophilia centre directors informing them of the types of heat-treated factor VIII concentrate that would be available for clinical trials in 1983–4. This document was revised and circulated to directors again on 29 March 1984. At this early stage, the chairman of the Haemophilia Centre Directors Organisation reported that there were eight different products in preparation or available for trial, though Hemofil-T, manufactured by Travenol Laboratories Inc., was the only product for which clinical trials had been completed. Other heat-treated factor concentrates available for trial included those manufactured by foreign fractionators Armour Pharmaceutical Company (Armour), Miles Laboratories Inc., Alpha Therapeutic Corporation, Behringwerke AG, and the National Health Service. Also available were National Health Service factor VIII concentrate, prepared from donations made by specially selected donors who were monitored for abnormal liver function and hepatitis. It was also noted that, with the exclusion of National Health Service products, all other factor concentrates were produced from plasma imported from the United States and carried “a putative risk of transmission of AIDS.”

On 19 November 1984, the Blood Products Laboratory announced that, by April 1985, it would begin heat treating factor concentrates to 60°C for thirty minutes. Shortly before this announcement, it was learned that a second British hemophiliac had died from AIDS.

The *AIDS Advisory Document* issued by the hemophilia centre directors in January 1985 reported that although HIV was inactivated by dry heat at 68°C for twenty-four hours, it was “unlikely” that the process completely inactivated non-A, non-B hepatitis. The Blood Products Laboratory would have a capacity to dry heat 30 per cent of its factor VIII concentrate, beginning on 30 January 1985, and the remaining 70 per cent two months later, when two more ovens would be installed to supplement the existing one. By 30 January, a limited supply of heat-treated British factor VIII concentrate from the Blood Products Laboratory would also be available. Preference would be given to patients not previously exposed to concentrates and to patients willing to participate in clinical trials. In addition, the Scottish National Blood Transfusion Service would begin heat treating factor VIII concentrate at the Protein Fractionation Centre for use in Scotland and Northern Ireland. Finally, the *Document* stated that the Blood Products Laboratory could not “take back for reissue unused unheated concentrate,” and that blood transfusion centres should not order more than they needed because this increased demand would have prejudiced supplies of heat-treated products later in the year.

In January 1985, the Department of Health and Social Security confirmed that the Blood Products Laboratory at Elstree had begun the process of heat treatment and that routine heat treatment of all factor VIII concentrate was expected to start in April. In June, however, a substantial number of hemophilia centres were still using non-heat-treated domestic factor VIII concentrate; domestic heat-treated domestic factor IX concentrate was not yet available. One reason for the continued use of non-heat-treated factor IX concentrate might have been that the heat-treated variety had to be purchased from foreign commercial sources, whereas the domestic non-heat-treated variety was supplied free of charge by the Blood Products Laboratory.

On 15 August 1985, the deputy chief medical officer of the Department of Health and Social Security wrote to all hemophilia centre directors to tell them that the Blood Products Laboratory had been heat treating factor VIII concentrate since April and to give them current information about the availability of these concentrates. The letter stated that only limited supplies had been available in the past and, although production levels had increased, it was still necessary to import heat-treated factor concentrates.

Heat-treated factor IX concentrate was not made available until the early autumn of 1985. Even then the Blood Products Laboratory and the Scottish National Blood Transfusion Service were not convinced by the existing data, and they undertook additional studies to ensure that the product was safe.

Removing products from the market

In December 1984, a batch of factor VIII concentrate was withdrawn by the Blood Products Laboratory when it was discovered that one of the donors who had supplied plasma for it had been admitted to hospital with AIDS.

At least thirty-eight hemophiliacs had already received factor concentrates from this batch.

By July 1985, two cases of seroconversion had been associated with the use of H.T. Factorate, a heat-treated factor VIII concentrate manufactured by Armour. A third seroconversion case was reported in October 1985. At an AIDS conference held in February 1986, Dr Peter Jones, a British physician who treated hemophilia patients, reported these and other seroconversion cases related to the use of imported heat-treated factor concentrates. Shortly thereafter, the Department of Health and Social Security questioned Armour about the efficacy of its heat-treatment methods, and in March 1986 departmental staff met with Armour officials to review the data on inactivating viruses. In late September 1986, two more seroconversion cases were reported in persons who had been treated with H.T. Factorate. On 6 October, Department of Health and Social Security staff again met with Armour officials. At this meeting, it was agreed that Armour would voluntarily withdraw all H.T. Factorate from the U.K. market. The company also agreed to relinquish its product licences for all factor VIII concentrate products.

Surrogate testing for AIDS

No surrogate testing for AIDS was undertaken in the United Kingdom.

Screening blood donations: HIV testing

On 27 June 1985, the Minister of Health announced that, within the next four to five months, an AIDS test would be introduced to screen blood donations. At this time, no decisions about the choice of test kits had been made, although £57,000 had been allocated for the evaluation of the kits. The announcement also confirmed that alternative test sites would eventually be created.

On 1 August 1985, the Department of Health and Social Security informed health officials that the first stage of the evaluation of test kits had been completed by the Public Health Laboratory Service. The results of that evaluation had been reviewed by a panel of experts, and manufacturers were asked to comment. The test kits evaluated were manufactured by Abbott Laboratories Ltd., Electro-Nucleonics Inc., Organon Teknika Ltd., Ortho Diagnostic Systems Ltd., and Wellcome Diagnostics. The Department of Health and Social Security concluded that the Organon, Ortho, and Wellcome test kits delivered a clear distinction between positive and negative results, a low rate of false positives, and reliable results with heat-treated factor concentrates, and would therefore be suitable for use in diagnostic laboratories. It also stated that the Organon and Wellcome tests appeared to be "particularly suitable" for use in blood transfusion centres. Finally, it announced that the second stage of evaluations would assess the performance of these two kits in the large-scale screening of blood donations.

A letter was also sent on 1 August to the regional transfusion directors to inform them about recent developments with regard to HIV testing. They were told that the first phase of evaluation had been completed and that the

second phase was currently under way in North London and in Manchester. Because this second phase would not be completed for another two to three months, however, and the directors themselves had agreed that routine screening of donations should be introduced simultaneously throughout the country, the letter told the directors not to wait until the final evaluation report was available before making preparations for routine screening. Rather, they should prepare for the introduction of routine screening, using either the Organon or the Wellcome kits on a provisional basis. They were urged to ask their regional health authorities for the necessary funding, to make practical arrangements for laboratory space and the training of employees, and to ensure that both they and their staff became acquainted with the two tests. Finally, the directors were asked to inform the Department of Health and Social Security of any difficulties in meeting the tentative deadline for the introduction of the test, scheduled for 14 October.

The evaluations were completed in September 1985. On 1 October, all physicians received a letter from the Department of Health and Social Security informing them that testing in blood transfusion centres would begin in mid-October. They were told that alternative test sites would be available at health clinics and that test results must be treated as confidential. Enclosed with the letter was a booklet containing detailed information about both testing procedures and counselling for persons found to be HIV positive. The cost of HIV testing was estimated to be £3 to £4 million (Can\$5.8 to Can\$7.8 million) nationally, and would be paid by the regional health authorities.

On 14 October 1985, the Minister of Health announced that the National Blood Transfusion Service had begun routine screening of blood donations, using either the Organon or the Wellcome test. The Minister stressed that persons in risk groups should not use the National Blood Transfusion Service to have their blood tested, but should go instead to the sexually transmitted disease clinics or should ask their physicians for advice.

Blood donations testing positive for HIV were not used for transfusion. Confirmatory tests were performed, and a sample from the donation was also sent to the virus reference laboratory of the Public Health Laboratory Service. If the test was positive, the transfusion centre director contacted the donor and asked him or her to visit the regional transfusion centre to discuss the test results. These donors were interviewed and informed of the significance of the test results by medical staff of the National Blood Transfusion Service who had been trained in counselling. A further sample of blood was taken to confirm the results of the test performed on the person's donation, and this sample was then tested at the virus reference laboratory. The donor was asked to consult a physician, who, with the donor's consent, was informed of the test results.

Although HIV-antibody testing of donors was officially introduced in all blood transfusion centres in October 1985, some hospital departments collecting blood donations did not begin testing until several months later. On 20 January 1986, the Department of Health and Social Security wrote to the

regional general managers to inform them that a number of the hospitals had not yet introduced routine HIV testing and to request that they be reported to the department.

As for alternative test sites, on 30 July 1985 a letter was sent to all regional general managers asking them to provide facilities for organ and semen donors and for hemophiliacs. They were informed that the Public Health Laboratory Service would conduct the testing, but that they must be responsible for taking blood samples and counselling for persons with positive test results. Regional managers were asked to select two persons from their district health authorities to attend a course on AIDS counselling to be held in the autumn. Finally, the letter stressed the importance of publicizing the testing facilities and of working closely with the family practitioner committees to ensure that general practitioners become familiar with these local arrangements. On 23 September, the Department of Health and Social Security wrote to all district medical officers to inform them that testing for HIV would begin in mid-October and to ensure that alternative test sites would be available to all physicians. It was suggested that alternative test sites be established at sexually transmitted disease clinics and other locations. District medical officers were also asked to consider ways in which the information about these locations could be communicated to general practitioners who might be approached by their patients about the test.

Informing hemophiliacs of the risk

On 4 May 1983, a notice was issued by the chairman of the Haemophilia Society in response to “unduly alarmist reports on AIDS which appeared in the press.” The chairman said that “[t]he cause of AIDS is quite unknown and it has not been proven to result from transmission of a specific infective agent in blood products.” He went on to say that the number of infected American hemophiliacs was small, and that there had been no reported cases of AIDS in the United Kingdom or in Germany, a large importer of American factor concentrates. He also stated that the factor concentrates prepared from British plasma were not necessarily safer than those prepared in the United States, but said that “whilst it would be wrong to be complacent, it would equally be counter-productive to alter our treatment programmes radically.”

On 13 May 1983, a meeting of the hemophilia centre directors was held to discuss AIDS and hemophilia. At this date, the directors were aware of one possible case of AIDS in a hemophiliac. They recommended treatment with desmopressin (a product commonly known as DDAVP that was used to promote factor VIII activity) for mildly affected patients with hemophilia A or von Willebrand’s disease and for minor lesions. They agreed that supplies of National Health Service concentrates should be reserved for the treatment of children and mildly affected patients or for patients who had not yet been exposed to imported concentrates, as was already the practice in some areas. As far as other patients were concerned, the directors stated that there was

not yet enough evidence to justify restricting the use of imported concentrates in view of the immense benefits of therapy. Since the risks of using factor IX concentrate were lower than those of using factor VIII concentrate, the directors said that it would be logical to continue using National Health Service factor IX concentrate.

An article published in the *British Medical Journal* in December 1983 about the risk of harm from imported commercial concentrates contended that donor screening alone would not eliminate the risk of the transmission of AIDS or of non-A, non-B hepatitis. The authors of the article acknowledged that most hemophiliacs had reverted to routine treatment programs because of the prevailing view that the risk of hemorrhage outweighed the risk of contracting AIDS or hepatitis, but concluded:

For the moment ... it seems sensible to treat very young severely affected children with cryoprecipitate rather than concentrates. Alternative methods of raising factor VIII activity with desmopressin (DDAVP), danazol or perhaps the new porcine material should be used in mildly affected haemophiliacs, people with von Willebrand's disease, and carriers of these disorders.

At their meeting of 13 May 1983, the hemophilia centre directors also discussed the proposed trials of heat-treated factor VIII concentrate, which had originally been developed to reduce the risk of transmitting hepatitis. They concluded that there was "no evidence that the processes involved in the manufacture of these inactivate any other hypothetical viruses," but they agreed that formal clinical trials should be undertaken.

An editorial in the December 1984 issue of *The Lancet*, in which the risk of AIDS to hemophiliacs was assessed, suggested that heat-treated products should be used, even though their ability to inactivate HIV or non-A, non-B hepatitis had not yet been demonstrated. The author argued that "the serious nature of AIDS justifies a pragmatic approach, and it is reasonable to switch to heat-treated factor VIII concentrates for haemophilia A." Although the editorial stated that "all blood products must be reassessed," it concluded with the statement, "[W]e must not forget that by far the commonest cause of haemophilic death is bleeding."

On 9 January 1985, the U.K. Haemophilia Centre Directors Organisation issued an *AIDS Advisory Document*. The document stated that there had been 102 reported cases of AIDS in the United Kingdom, three of which were among hemophiliacs. It summarized donor-screening measures taken by the National Blood Transfusion Service, and reviewed the blood products that offered the best protection against the transmission of AIDS. The safest products were said to be heat-treated domestic concentrates, followed by single-donor cryoprecipitate, heat-treated imported concentrates, non-heat-treated domestic concentrates, and, finally, non-heat-treated imported

concentrates, which were “almost certain to be contaminated.” The document stated that concentrates were still needed because bleeding was the most common cause of disability and death among hemophiliacs, but it made a number of recommendations with respect to methods of treatment. It recommended that persons with mild hemophilia A and von Willebrand’s disease use desmopressin if possible; that children and hemophilia A patients not yet exposed to factor concentrate use cryoprecipitate or heat-treated National Health Service factor VIII concentrate; that severe and moderate hemophiliacs previously treated with factor VIII concentrate use heat-treated National Health Service factor VIII concentrate or heat-treated American commercial concentrates; that patients with mild hemophilia B use fresh frozen plasma or National Health Service factor IX concentrate; that patients with hemophilia B who had never before been exposed to factor concentrates use fresh frozen plasma or National Health Service factor IX concentrate; and that patients with severe and moderate hemophilia B previously exposed to factor IX concentrate continue to use National Health Service factor IX concentrate. Finally, it stated:

In general heated concentrate appears to be the recommendation of virologists consulted but individual [Haemophilia Centre] Directors may wish to make up their own minds. This is particularly true of unheated NHS [National Health Service] material. The evidence that heated U.S. factor VIII is safer than unheated NHS is debatable and some Directors may wish to continue using unheated NHS material until all supplies are heated. This is valid for carefully selected patients but must be on individual decision based on the assumption that some batches of NHS materials will be contaminated with HTLV-III [HIV]. The argument that HTLV-III positive patients have already been infected and could receive unheated American material is probably scientifically true but this material would pose an additional risk to staff and families and its continued use would pose logistic problems.

On 9 February 1985, the chairman of the U.K. Haemophilia Centre Directors Organisation wrote to *The Lancet* in response to an article about the possible side-effects of heat-treated products. In his letter, the chairman took issue with the arguments for the continued use of non-heat-treated factor VIII concentrate and stated:

Although American concentrates pose the most risk, untreated factor VIII concentrates of any type must be considered potentially to be infected with HTLV-III [HIV] ... A hierarchical assignment of risks from single donor cryoprecipitate and various heated concentrates together with different patient characteristics such as age, previous treatment, and HTLV-III serology should be made before each lesion is treated. The use of coagulation

factor concentrates in the UK is still increasing by arithmetic progression. It may be wise, now, to take stock of the situation so that treatment intensity at least levels out until the possible risks can be more rationally assessed.

The chairman addressed this issue again in an article published in the *British Medical Journal* in June 1985. In reporting on the use of non-heat-treated products in hemophilia treatment centres, he and his co-authors stated, “[t]he safety of cryoprecipitate and unheated UK blood products with regard to HTLV-III [HIV] infection can therefore no longer be assumed ... we no longer consider that the use of cryoprecipitate or other non-heat treated concentrates is justified.”

With regard to HIV testing, in December 1984, hemophilia treatment centre directors decided that all hemophilia patients should be tested. Those testing positive for the virus “should be informed, reassured, and counselled regarding transmission to spouses, etc., including the possible use of barrier contraception.”

Informing transfusion recipients of the risk

In the mid-1980s, hemophilia A and B patients who had been treated with factor VIII or factor IX concentrates before the introduction of methods to inactivate viruses in blood products were tested for HIV unless the treating physician believed there was good reason not to do so. It was also standard practice to identify and test all recipients of recalled blood and blood products.

A process to identify recipients at risk retrospectively was introduced in 1985, along with the implementation of the testing program for all blood donations. In addition, physicians and counsellors were encouraged to ask persons who were diagnosed as HIV positive whether they had ever donated blood. If so, the transfusion service was notified, and efforts were made to trace the infected person’s donation to the recipient or recipients. Because the practice was voluntary, however, it was not as effective as it could be. As Dr Hewitt, the medical director of the North London Blood Bank, explained:

The difficulty transfusion services face in the tracing of ex-donors infected with HIV is avoidable. If all HIV counselling and testing services were to ask individuals found to be infected with HIV if they have ever donated blood those answering in the affirmative could be requested to provide the date and location of the last donation. If those details are passed on to the blood transfusion service, with the individual’s consent, the fate of his or her donations could be traced and any infected recipients identified. In the UK such questioning is not routine. Furthermore, even when the blood transfusion staff strongly suspect that an ex-donor is HIV infected they cannot confirm this because the reporting ... is confidential.

There is a strong probability, therefore, that some recipients who were infected before 1985 were not identified. Nevertheless, between October 1985 and October 1993, the voluntary questioning method was successful in identifying 255 HIV-positive persons who had been blood donors.

Assistance to persons infected and affected

Government assistance

Government financial help for HIV-infected hemophiliacs in the United Kingdom has totalled over £76 million (Can\$162 million). The money has been allocated to a charitable trust, and includes payments to each infected hemophiliac, payments to settle litigation against the government, and financial assistance for those infected through blood transfusions and organ transplants.

In June 1987, the Haemophilia Society began to lobby members of parliament by sending them letters from HIV-infected hemophiliacs and their families along with leaflets describing the financial hardships endured by persons infected. In this way, the Haemophilia Society obtained the support of more than 200 MPs.

In October 1987, the society made a submission to the Department of Health and Social Security outlining the financial, social, and family burdens imposed by HIV or AIDS. It asked the government to establish a special fund of £90 to £100 million (Can\$196 to Can\$218 million) to help support insurance premiums for homeowners; to provide, on the death of a hemophilic head of a family, a weekly, non-means-tested hardship allowance for the widow until her death, for the children until they reach the age of nineteen years, and for elderly dependent parents until their death; to pay a disability allowance that would be retroactive to the presumed time of seroconversion and that would be high enough to cover the costs related to HIV or AIDS; and to underwrite a mortgage protection scheme to ensure that the family home was secure in the event of the death of the breadwinner.

In response, the government made a grant of £10 million in November 1987 for HIV-infected hemophiliacs. The grant was expressly described as an *ex gratia* payment to give financial assistance, and not compensation. The government also agreed to establish a special trust in accordance with the proposals of the Haemophilia Society. The Macfarlane Trust, named in honour of the late Professor R.G. Macfarlane, a pioneer in hemophilia care, was established in March 1988. The trust made an *ex gratia* payment of £20,000 (Can\$46,000) to each of the 1,200 hemophilia patients with HIV or AIDS, and additional payments to cover special needs, such as winter heating and clothing. Legislation was enacted to ensure that these payments were tax free and would not be considered when determining eligibility for social security benefits.

In December 1989, to enable the trust to make *ex gratia* payments to all HIV-infected hemophiliacs, the government made a second grant of £24 million (Can\$44 million). By the end of 1990 nearly all HIV-infected patients with

hemophilia had received a lump-sum *ex gratia* payment of £20,000 (Can\$37,000). The government again emphasized that the additional payment must not be construed as compensation for negligence, nor should the government be viewed as endorsing the principle of no-fault compensation.

The British government initially refused to extend compensation to persons infected through blood transfusions, but in early 1992, efforts by members of this group to lobby the government proved successful. On 17 February 1992, the Secretary of State for Health announced that the special payments available to persons with hemophilia and HIV were to be extended to those infected with HIV as a result of blood transfusion or tissue transfer. The details of this award were announced on 27 April 1992. These persons were entitled to payments of £41,500 to £80,500 (Can\$87,000 to Can\$168,000), depending on family circumstances. Infected spouses, partners, and children were also eligible for payments. The program applied to patients treated in England, Wales, and Northern Ireland, and a similar scheme was established in Scotland. To ensure that those who were eligible for awards were identified, the chief medical officer wrote to all National Health Service consultants and general practitioners to ask for assistance. The National Blood Transfusion Service also asked regional transfusion directors to check their records to determine whether donors found to be HIV positive had previously donated, and, if so, who had been the recipients of that blood or plasma.

Settlement of civil actions

Despite the efforts of the government to give some form of financial assistance to recipients of infected blood products, in April 1989 a number of hemophiliacs brought a civil action against the Department of Health, the Medicines Licensing Authority, the Committee on Safety of Medicines, the Blood Products Laboratory, and the regional health authorities. Physicians were not named as parties to the action, but were asked to testify in support of the government. Litigants were given until 2 February 1990 to join the class action. By October 1990, a total of 962 HIV-infected patients with hemophilia and their families had become parties to the action.

The plaintiffs based their claims on two main arguments. They alleged that the Department of Health and regional health authorities were negligent and in breach of their statutory duty by failing to produce sufficient factor concentrates in Britain to meet the needs of hemophiliacs and relying on imported factor concentrates, and by continuing to use non-heat-treated factor concentrates after the heat-treated factor concentrates became available.

They alleged that the Department of Health and Social Security should have known of the risks of concentrates obtained from the United States, sought alternative sources of supply, and taken steps to eliminate or reduce that risk by heat treating concentrates as early as possible. They claimed that the failure to achieve self-sufficiency, and the reliance on imported blood

products, caused many hemophiliacs to become infected. They also submitted that the Department of Health and Social Security did not make efforts to seek safer blood products from sources outside the United States, not even from the Protein Fractionation Centre in Scotland, and that hemophiliacs were not told of the risks of continuing to use imported products.

As for the second argument, the plaintiffs alleged that the defendants had failed to exclude high-risk donors properly, to encourage the use of safer treatment methods, and to implement surrogate testing. In particular, they questioned the length of time it took to introduce heat-treated products. Even though the Blood Products Laboratory began heat treating in January 1985, heat-treated products were not universally available until June. Consequently, non-heat-treated National Health Service factor concentrates and U.S. heat-treated factor concentrates continued to be distributed during this period.

On 20 July 1990, counsel for the government gave opposing counsel a list of 600 documents relating to policy decisions about the safety of the blood supply during the period 1972 to 1986, in respect of which public interest immunity was claimed. The plaintiffs then made an application seeking disclosure of these documents. The High Court ruled that not all the documents were protected by public interest immunity, and ordered that the Haemophilia Society be given production of specific classes of documents. The production did not extend to documents pertaining to self-sufficiency, allocation of resources, expansion of the Blood Products Laboratory, reorganization of the National Blood Transfusion Service, and heat treatment of blood products. The order was appealed.

In the Court of Appeal, the government argued that the documents should not be disclosed for two reasons. First, the case had no merit; and, second, confidentiality was required to safeguard the kind of full, free, and uninhibited discussions that were integral to the policy process. On 20 September 1990, the Court of Appeal rejected the government's arguments and ordered the Department of Health to make production of a broader class of documents. For the court, Lord Justice Gibson held that the hemophiliacs' right to proper presentation of their case overrode the right to public interest immunity, and that the plaintiffs had "a good arguable claim in law based upon common law negligence." He said that it was very likely that the documents in question would contain material that would lend substantial weight to their claim:

The plaintiffs need the documents for the proper presentation of their case in order for them to obtain the necessary expert evidence directed to the explanations for that failure which the documents will reveal. It seems to me to be necessary for the fair and proper disposal of the case that there should be known to both sides the actual grounds for the various decisions which led to the continued use of imported and other blood products capable of infecting a patient with HIV.

Lord Justice Gibson accordingly held that all documents relating to self-sufficiency, allocation of resources, the Blood Products Laboratory, the National Blood Transfusion Service, donor screening, testing, heat treatment, and steps to minimize hepatitis infection must be produced.

After the Court of Appeal's decision, with the trial scheduled to begin in March 1991, Mr Justice Ognall urged the parties to settle, stating that the government had a "moral duty" to the hemophiliacs. Regional health authorities then met with the Secretary of State for Health to present their arguments in favour of settlement, going so far as to threaten that they would settle on their own, independently of the Department of Health. They argued that legal costs were escalating and that physicians were spending too much time preparing their case instead of caring for patients. The chief medical officer also urged the Department of Health to settle the matter out of court.

Finally, in December 1990, the government acquiesced, on the condition that the action be discontinued. In addition to a settlement of £42 million (Can\$94 million), the government agreed to pay for the plaintiffs' reasonable legal costs, and specified that the settlement applied to non-litigants. Prime Minister John Major announced on 11 December 1990 that the government would pay the settlement moneys into a new special fund created within the Macfarlane Trust which, inclusive of legal costs, exceeded £50 million (Can\$112 million). The fund was formally established in May 1991 as the Macfarlane (Special Payments) (No. 2) Trust, with the £42 million (Can\$83 million) capital grant from the government.

Payments from the fund were made only on the express authorization of the Department of Health. They were all made anonymously, using a code so that the recipient's name could not be disclosed. As of 31 March 1991, 1,226 persons were registered with the fund and, on average, each had received a lump-sum payment of £35,000 (Can\$74,000). Payments were allocated on the basis of the family status of the applicant on the day before the announcement of the settlement:

infant	£ 21,500 (Can\$45,400)
single adult	£ 23,500 (Can\$49,600)
married without children	£ 32,000 (Can\$67,600)
married or single with dependent children	£ 60,500 (Can\$127,700)
infected intimate	£ 23,500 (Can\$49,600)
close relative or intimate not infected	£ 2,000 (Can\$4,200)

These payments were in addition to the *ex gratia* payment of £20,000 (Can\$43,800) that had already been made in 1988. Again, all payments were tax free and would not be taken into consideration when determining eligibility for social security or other benefits. Recipients were required to sign a statement waiving any right to bring a civil action against the National Blood Transfusion Service or the Department of Health and Social Security for their HIV infection.

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Comparative Tables

Table 1
The emergence of AIDS

Country	First reported case of AIDS	AIDS made reportable to public health authorities ¹	First reported cases of AIDS from use of blood and blood products	
			AIDS in a hemophiliac	Transfusion-transmitted HIV or AIDS
Australia Population: 18 million ²	April 1983 ³	May 1983– August 1984 ⁴	May 1985	July 1984
Canada Population: 28.8 million ⁵	March 1982	1983–1987 ⁶	March 1983	May 1985 ⁷
France Population: 58 million	August 1981	June 1986	June 1983	May 1983
Germany Population: 81.7 million	November 1982	September 1987	April 1983	Unknown
Japan Population: 125 million	July 1983 ⁸	February 1989	July 1983 ⁹	Late 1984
Netherlands Population: 15.5 million	Autumn 1981	Never	1987	Unknown
United Kingdom Population: 58.6 million	December 1981	Never	August 1983	Unknown ¹⁰
United States Population: 263 million	June 1981	May 1983	July 1982	December 1982

Table 1 (cont'd)

Notes

-
- 1 Refers to mandatory reporting only, and does not include any earlier efforts to promote voluntary reporting.
 - 2 Population numbers obtained from *Information Please Almanac, 1996* (New York: Houghton Mifflin, 1996).
 - 3 This case was diagnosed in December 1982.
 - 4 Victoria – May 1983; Queensland, South Australia, and the Northern Territory – July 1983; Tasmania – August 1983; Western Australia and the Australian Capital Territory – September 1983; and New South Wales – August 1984.
 - 5 Statistics Canada, 1996 Census.
 - 6 Alberta, British Columbia, and Ontario – 1983; New Brunswick and Saskatchewan – 1984; Nova Scotia and Prince Edward Island – 1985; Quebec – 1986; Manitoba and Newfoundland – 1987.
 - 7 The first known case occurred in September 1984 but was not officially reported.
 - 8 The person with AIDS was a hemophilia patient, known as the “Teikyō University case.”
 - 9 The Japanese government did not officially recognize the Teikyō case as one of AIDS until March 1985.
 - 10 Although it is not known when the first case of transfusion-related AIDS appeared, by October 1985 there were four such cases.

Table 2
Donor screening

Country	Introduction of donor screening			
	Official public statement by blood transfusion service or government asking persons at risk of contracting AIDS and those with symptoms of AIDS not to donate	Information about risk groups and symptoms of AIDS given to prospective donors at blood donor clinics	Donors may call the blood donor clinic after donating to request that their donations not be used for transfusion (call-back)	Donors may sign a form before donating, asking that their donations not be used for transfusion (confidential unit exclusion, or CUE)
Australia Population: 18 million ¹	June 1983 ²	June 1983 ³	Unknown	Unknown
Canada Population: 28.8 million ⁴	March 1983	May 1984	November 1986	Autumn 1988 ⁵
France Population: 58 million	Unknown	May–June 1983	Unknown	Unknown
Germany Population: 81.7 million	June 1983 ⁶ September 1983 ⁷	June 1983	Unknown	Unknown
Japan Population: 125 million	November 1983	Unknown	Unknown	Unknown
Netherlands Population: 15.5 million	Unknown	June 1983	Unknown	Unknown
United Kingdom Population: 58.6 million	September 1983	September 1983	Unknown	July 1984 ⁸
United States – Voluntary sector	January 1983	January to March 1983	February 1984 ⁹	February 1983 ¹⁰
United States – Commercial sector	January 1983	December 1982 ¹¹ to March 1983	January 1984	January 1984

Table 2 (cont'd)

Notes

- 1 Population numbers obtained from *Information Please Almanac, 1996* (New York: Houghton Mifflin, 1996).
- 2 The blood transfusion service in New South Wales had already done so in April 1983.
- 3 As directed by the national Australian Red Cross Society.
- 4 Statistics Canada, 1996 Census.
- 5 Available in Toronto in autumn 1985.
- 6 Statement made by the German Red Cross.
- 7 Statement made by the Federal Health Office.
- 8 Used at the North London Blood Centre.
- 9 Introduced by the Greater New York Blood Program.
- 10 Introduced by the American Red Cross at all its blood centres.
- 11 Introduced by Alpha Therapeutic Corporation.

Table 3
Introduction of heat-treated factor concentrates

Country	Introduction of heat-treated factor concentrates		
	Partial use of heat-treated factor concentrates	Full conversion to use of heat-treated factor concentrates	Required by regulator
Australia Population: 18 million ¹	February 1985	Unknown	Unknown
Canada Population: 28.8 million ²	May 1985	July 1985	November 1984
France Population: 58 million	June 1985 ³	October 1985	October 1985
Germany Population: 81.7 million	1981 to 1983 ⁴	October 1985	December 1988 ⁵
Japan Population: 125 million	Summer 1985	mid-1986	Unknown
Netherlands Population: 15.5 million	April–May 1983 ⁶	Unknown	January 1988
United Kingdom Population: 58.6 million	April 1985 ⁷	Summer 1985	Unknown
United States Population: 263 million	Spring 1983	1985	1989

Notes

- 1 Population numbers obtained from *Information Please Almanac, 1996* (New York: Houghton Mifflin, 1996).
- 2 Statistics Canada, 1996 Census.
- 3 The first domestic heat-treated products were manufactured and distributed by the Lille centre in February 1985, but national distribution of heat-treated products did not begin until June 1985.
- 4 Introduction of Behring hepatitis-safe (HS) factor VIII.
- 5 These regulations were subsequently declared invalid.
- 6 Imported heat-treated factor concentrates manufactured by Travenol; domestic heat-treated factor concentrates were first distributed by the Netherlands Red Cross in June 1985.
- 7 Introduction of domestic heat-treated factor VIII concentrate. It is not known when imported products were made available to patients.

Table 4
Screening blood donations

Country	Use of surrogate tests for AIDS		Introduction of HIV-antibody testing	
	ALT testing	Hepatitis B core testing	At all collection centres	Required by the regulator
Australia Population: 18 million ¹	Unknown	October 1984 ²	May 1985	Unknown
Canada Population: 28.8 million ³	Not used	Not used	November 1985	Never
France Population: 58 million	Not used	Not used	August 1985	August 1985
Germany Population: 81.7 million	1984 ⁴	1985 ⁵	October 1985	October 1985
Japan Population: 125 million	Not used	Not used	Spring 1986	Unknown
Netherlands Population: 15.5 million	Not used	Not used	June 1985	January 1988
United Kingdom Population: 58.6 million	Not used	Not used	October 1985	Unknown
United States Population: 263 million	Not used	Spring 1984 ⁶	May 1985	February 1988

Notes

- 1 Population numbers obtained from *Information Please Almanac, 1996* (New York: Houghton Mifflin, 1996).
- 2 Used only by the New South Wales blood transfusion service.
- 3 Statistics Canada, 1996 Census.
- 4 Testing required by orders of the Federal Health Office dated June 1984 and December 1984.
- 5 Required by orders of the Federal Health Office dated December 1984 and February 1985. Testing might have been in use before this date.
- 6 Used at several blood banks in California and by Cutter Laboratories Inc.

Table 5
Financial assistance

Country	Establishment of a government fund to give financial assistance to persons with blood-related HIV or AIDS
Australia Population: 18 million ¹	November 1989
Canada Population: 28.8 million ²	December 1989 ³
France Population: 58 million	July 1989
Germany Population: 81.7 million	July 1995
Japan Population: 125 million	December 1988
Netherlands Population: 15.5 million	July 1995 ⁴
United Kingdom Population: 58.6 million	March 1988 ⁵
United States Population: 263 million	Never

Notes

- 1 Population numbers obtained from *Information Please Almanac, 1996* (New York: Houghton Mifflin, 1996).
- 2 Statistics Canada, 1996 Census.
- 3 Nova Scotia: May 1993; Quebec: June 1993; Provincial/Territorial Agreement: September 1993.
- 4 The government of the Netherlands had made financial contributions to existing funds before this date.
- 5 Financial assistance was first awarded in November 1987, but the Macfarlane Trust was not established until March 1988.

PART V

Safety of Plasma Derivatives

Safety of Plasma Derivatives: The Role of Regulation

In the Interim Report, I said that Canada's blood supply was not less safe than that of other developed nations. I added, however, that there is no justification for complacency. Blood is a biological substance and can never be absolutely safe. My analysis in the Interim Report was based on a review of the types of hazards that pose a risk to the recipients of blood and blood components and on an assessment of the safety and organization of the blood supply system in Canada. The recommendations in the Interim Report are reproduced in Appendix H of this Report. The safety of plasma derivatives for which blood is the starting material was not the subject of my review. As I said in the Interim Report:

I have not yet investigated fractionation processes or products in detail. As a result, I have insufficient information about the specific risks associated with the use of plasma derivatives and the effectiveness of the strategies currently used to reduce those risks.

A general discussion of plasma derivatives, the risks associated with their use, and the measures taken to reduce those risks is followed by a brief review of changes to the legislation governing the regulation of plasma derivatives and the reorganization of the federal directorate that enforces this legislation. Finally, there is an assessment of the role and performance of the federal government in ensuring that the blood products distributed in Canada are not unsafe.

Plasma and plasma derivatives

Plasma is the liquid component of blood. "Plasma derivatives," sometimes referred to as "blood products" or "blood derivatives," is a term used to describe the biologically active proteins that are separated from plasma for use in treating human illnesses and diseases. Plasma derivatives include coagulation factors, such as factor VIII and factor IX, which are essential for persons with bleeding disorders such as hemophilia; albumin, the most abundant protein

in plasma, used to help maintain a balance of fluids in persons suffering from shock or acute loss of blood volume; specific immune globulins, used to treat persons thought to be in imminent danger of contracting certain diseases such as rabies or tetanus; non-specific immune globulins, used to protect persons with impaired immune functions; and certain other proteins that are used to treat persons with deficiencies of those proteins.

Plasma separated from a donated unit of whole blood is called “recovered plasma.” Plasma collected by a process called plasmapheresis is called “source plasma.” Plasma collected for the purpose of manufacturing plasma derivatives is frozen as soon as possible, stored, and transported to a pharmaceutical manufacturer for fractionation. At the fractionator’s plant, plasma from thousands of donations is mixed together, or “pooled.” The proteins are then separated and purified to produce the desired plasma derivatives.

Factors affecting the safety of plasma derivatives

The risks affecting the safety of plasma derivatives come from two sources: plasma, the starting material; and the process of manufacture. The risks associated with the starting material are the same as those associated with other blood components. These risks were discussed in the Interim Report. Because plasma is usually frozen immediately after it is collected, contaminating microorganisms do not have the same opportunity to multiply or form toxins as they do in blood and its cellular components. Unlike the case with components, there are no serious risks of immunological reactions from plasma.

The many differences between the processing of plasma derivatives and the processing of blood components affect both the magnitude and the type of risks associated with the use of plasma derivatives. The size of the plasma pool affects the magnitude of the risks. The large pools used to manufacture plasma derivatives afford economies of scale and ensure a wide range of antibodies in the non-specific immune globulin preparations made from the plasma. They also allow both the manufacturer and the regulator to test samples of the final product to determine the biological activity, the purity, and – to some extent – the safety of all the vials produced from the batch. The greater the number of donations in the pool, however, the greater is the risk that one donation was from an infected donor. Because a donor infected with a blood-borne infectious disease agent usually has hundreds of millions of microorganisms in his or her blood, the number of microorganisms present in each donation – even after being diluted by thousands of other donations in the pooling process – is usually sufficient to contaminate all of the thousands of vials of products derived from the pool to contain infectious microorganisms.

The measures used in the manufacturing process to reduce the risk of contamination can themselves introduce new risks. For example, the processing may alter the purity, potency, or structure of the product in such a way that it could cause an immune reaction in or be toxic to a recipient. Immune

reactions to altered human proteins are rarely life-threatening, but they may make any further treatment with the protein ineffective. The manufacturing process can remove some microorganisms and inactivate others.

The health of a recipient and the number of treatments received are other factors that determine whether the person will suffer an adverse health effect from a plasma derivative. Recipients of plasma derivatives often have chronic conditions that, over a lifetime, expose them to products that have been derived from hundreds of thousands of donors. These persons face a much greater risk of exposure to hazards than do recipients of blood components. Many recipients of plasma derivatives have suppressed immune responses arising from their medical conditions, making their vulnerability especially high.

Measures to reduce the risks

The current measures used to protect the safety of source plasma are very similar to the measures used to protect the safety of blood donations and, therefore, that of recovered plasma. Every blood and plasma donor fills out a questionnaire and is asked orally about his or her medical history, travel, and behaviour to determine the probability of the existence of an infectious disease. A sample from every donation is tested for indicators of some infectious disease agents. However, the tests that are used have a small margin of error and lack sensitivity in the early stages of an infection because there is a delay, called the “window period,” between the time a person is infected and the time the indicators of infection can be detected.

After the plasma is pooled, samples of the pool are tested using a highly sensitive method – polymerase chain reaction – to detect the presence of fragments of HIV or the hepatitis C virus. Several of the steps in the fractionation and purification processes inactivate or remove, or reduce in number, those microorganisms that may have contaminated the starting plasma. Bacteria and larger microorganisms, such as the parasites that cause Chagas’ disease, are removed by filtration. Viruses cannot be so removed, but other measures are taken during the fractionation or purification process to reduce the probability that the final product will contain certain viruses. The measures most commonly used were introduced in the 1980s and involve treatment either with heat or with a combination of solvents and detergents. The solvent-detergent treatment inactivates viruses that have a lipid envelope, but is ineffective for hepatitis A virus, parvovirus B19, and other viruses that do not have that kind of envelope. Many, but not all, manufacturers now use both heat and solvent-detergent treatments to decrease the risk of contamination of the final product.

Many other means of reducing the risks of contamination are being explored, including reducing the number of donations that are pooled, and treating the products with high-temperature terminal dry-heat sterilization, which uses temperatures of 80° to 100°C, “nanofiltration,” and chromatography. Nanofiltration involves especially fine filters that remove viruses without

affecting the biological activity or structure of the product. Chromatography is a process in which the plasma fraction is passed through columns of beads or resins that are coated with chemicals that attract and bind specific proteins. In this way, proteins may be separated by size, by electric charge, or by their binding to a particular antibody. Because only some proteins, depending on their size or antigenic structure, are collected by this process, it is highly unlikely that contaminating microorganisms will separate with the product.

Another safeguard that is used by at least one manufacturer and is being explored by others is the storage of the frozen plasma for at least three months before processing begins. The delay makes it possible to test the plasma of donors who make subsequent donations within that period. If any of the tests for infectious-disease markers are positive at the time of the subsequent donations, the earlier donations can be destroyed before they are pooled and fractionation begins. Three months is considered a reasonable upper limit for the window period for HIV infection. The safeguard is, however, of limited value in protecting the safety of recovered plasma – as opposed to source plasma – because few persons donate whole blood as often as once every three months. In Canada, by far the greatest proportion of plasma used for fractionation is recovered from whole-blood donations.

The measures taken to inactivate viruses are far from perfect. None of the measures used or being explored is likely to be effective against prions – infectious proteins, such as the one suspected by many scientists as the cause of Creutzfeldt-Jakob disease (CJD). Some of the viral inactivation measures – for example, heat treatment – can also destroy, or significantly decrease, the biological activity of the product and thus decrease the yield. It is not yet possible to eliminate all known blood-borne pathogens. New, emerging pathogens will always present a risk to the safety of blood and blood products.

Because the plasma collected in Canada is not sufficient to meet the demand for all plasma derivatives, some are purchased from pharmaceutical manufacturers that use plasma that, for the most part, is collected, tested, and processed in the United States. Foreign fractionators also manufacture all plasma derivatives from domestic plasma. The foreign manufacture of these products means that the principal method of controlling their safety is to set standards for the manufacture of plasma derivatives and to ensure that the manufacturers and their products meet the standards before they are permitted to be distributed in Canada. This role belongs to the Department of Health, through its Bureau of Biologics and Radiopharmaceuticals.

Evidence of risk associated with the use of plasma derivatives

Because Canada, for the most part, does not manufacture its own plasma derivatives, the plasma derivatives distributed in Canada are the same as, or are manufactured in the same way as, those distributed in many other countries. Therefore, reports of infections or other adverse reactions related to the use of plasma – as appear in the international medical and scientific

literature – are important sources of information for the assessment of the safety of plasma derivatives in Canada and the effectiveness of any processes introduced to inactivate or to remove potentially contaminating substances or biological agents.

Reports in the mid-1990s of infection attributable to the use of plasma derivatives disclose a few isolated cases and two clusters of cases. A cluster of cases exhibiting the same infection suggests a common hazard that warrants close attention. One of the two clusters involved several cases of hepatitis C resulting from the use of intravenous immune globulins. Most of the cases in this cluster were shown to be associated with specific lots of immune globulins produced by a process that did not involve cold ethanol fractionation or include a solvent-detergent or other viral inactivation treatment.

The other cluster involved several cases of hepatitis A infection associated with the treatment with factor VIII concentrate. The cases in this cluster were reported in South Africa and in several countries in Europe. Genetic analyses have also linked several cases of hepatitis A virus infection in hemophiliacs in the United States to treatment with factor VIII concentrate. When these cases were reported, in January 1996, the U.S. Centers for Disease Control and Prevention said that “[o]ther plasma-derived factor VIII and factor IX concentrates manufactured using similar or different viral-reducing steps also may contain HAV [hepatitis A virus], although no documented cases of transmission have been reported.”

The fact that there are so few reports of infection associated with the use of plasma derivatives probably means that the risks are low. It is possible, however, that cases of infection have occurred but have not been recognized or reported. Some of the difficulties in obtaining the information needed to recognize an association between cases were described in 1996, in an editorial in the journal *Gastroenterology*:

The number of lots and the number of cases are uncertain because case finding is poor. Any given product is usually widely distributed throughout the United States and abroad. In any given locality, there may be only individual or a few cases from this potential source. To be documented, it has been necessary to have a common exposure to pooled plasma product of 2 or more patients in an individual practice, clinic, or category of patients. For a complete investigation, the manufacturer and lot number(s) must be recorded, which is seldom done. Although a shelf life of 2 years means that infections can be widely scattered in time, it is usually necessary for the dates of onset of derivative-transmitted viral hepatitis to be in relative proximity to each other to provoke an investigation. Finally, infections by pooled plasma derivatives are often subclinical and escape detection unless corecipients of the particular material are also screened by aminotransferase and/or serology.

Because the different plasma derivatives are processed differently, the risk from using factor concentrates is different from the risk from using albumin or immune globulins. Since the mid-1990s, most persons with type A hemophilia in Canada have used a factor VIII preparation that is produced by recombinant DNA technology and not derived from plasma. A recombinant factor IX preparation was licensed in Canada in 1997. Since the introduction of these preparations, the use of plasma-derived factor concentrates in Canada has decreased significantly.

In the early 1990s, the plasma derivative that was in greatest demand was albumin. Experience has shown that there is little risk associated with the use of albumin. It is probable that the risk is low because the way it is manufactured and the biological stability of the protein allow for the effective inactivation of contaminating microorganisms. Although synthetic substitutes are available, albumin is still used extensively as a therapeutic agent and often as a stabilizer for other, non-plasma-derived biological drugs, such as recombinant factor VIII preparations.

The immune globulins for intravenous administration carry a risk of transmitting the hepatitis C virus. However, the Department of Health concluded, in 1996, that a solvent-detergent viral inactivation step in the processing of immune globulins should be sufficient to ensure that the product will not contain infectious hepatitis C viruses.

The conclusion to be drawn from the international literature about the safety of plasma derivatives is that improved donor screening, along with the introduction of solvent-detergent treatment and other methods used to treat plasma derivatives, has almost eliminated the risk of transmission of the human immunodeficiency virus (HIV), hepatitis C virus, and hepatitis B virus.

For the most part, the measures used to inactivate or remove viruses and the assessments of safety have focused on viruses like HIV and hepatitis C virus that cause serious, long-term effects in many, if not most, infected persons. However, because plasma derivatives are used frequently – and often for treating chronically ill patients, many of them with suppressed immune systems – the risk of serious health effects from infection by other viruses, such as hepatitis A virus and parvovirus B19, has increased. Because these viruses are not inactivated by solvent-detergent treatment, other means of reducing risks are necessary. The manufacturing guidelines used in Europe now require that the production process for plasma derivatives use at least two different viral-inactivation steps. No such requirement is expressly stated for manufacturers distributing products in Canada. The risk to blood products from yet unknown pathogens can never be eliminated.

Changes in the regulation of biological drugs in the 1990s

The regulation of biological drugs, including blood components and plasma derivatives, is governed by the *Food and Drugs Act*. The application of the *Act* and its *Regulations* to blood and blood products in the 1980s is described in

Chapter 6 of this Report, as is the organization of the Health Protection Branch of the Department of National Health and Welfare, the federal department that then administered the legislation. The department that administers the health-related functions of the federal government is now called the Department of Health. The regulation of biological drugs is primarily conducted by the Bureau of Biologics and Radiopharmaceuticals, which, like its predecessor, the Bureau of Biologics, was part of the Drugs Directorate in the Health Protection Branch. In 1997, the Drugs Directorate became the Therapeutic Products Directorate.

Throughout the 1980s, a growing backlog of applications from manufacturers for approval to distribute drugs in Canada led to several studies of the goals, functions, and operations of the Drugs Directorate. The results of these studies have led to some amendments to the *Regulations*, as discussed below, and to administrative changes in the directorate's handling of new drug submissions.

The most important of the studies leading to these changes was the report in 1992 by Dr Denis Gagnon, the vice-rector of research at Laval University in Quebec, entitled *Working in Partnerships: Drug Review for the Future*. Dr Gagnon described the need for modification:

Over the last ten or fifteen years, the formidable development of drug therapies, the discovery of complex drugs from chemical or biological origin, the advent of new and sometimes life-threatening diseases, and the expectation of the Canadian population for drug treatments in a time frame comparable to that of other countries, have changed the rules and the ways of evaluating and approving drugs for human use.

All countries are faced with this changing scope of drug safety and efficacy evaluation. We in Canada have developed a traditional model of drug review based on *de novo* analysis of information submitted. We have tried to find new resources to meet the needs of the ever increasing workload; but we cannot keep up.

Dr Gagnon's report contained recommendations for substantial changes in the policies, the structure, and the processes for reviewing drug submissions, including the restructuring of the Drugs Directorate into seven functional units with multidisciplinary review teams.

Many of Dr Gagnon's proposals have been adopted completely or in part and have altered the procedures of the bureau in its regulation of plasma derivatives. Dr Gagnon proposed the creation of a network of teams in universities and hospitals to conduct external reviews of drugs and to encourage exchanges between experts both inside and outside the public service. Although not all aspects of this latter proposal have been implemented, some parts of the manufacturers' submissions are now reviewed by experts outside the department. Dr Gagnon's recommendations for setting time limits for the

reviews of new drug submissions and for decreasing the volume of information that must be submitted for an approval of changes in drugs have both been implemented. He also recommended the establishment of a “pharmacovigilance” program to monitor the effects of the use of drugs, which would include measures to encourage the reporting of adverse drug reactions. A program for drug surveillance that includes plasma derivatives has been implemented.

Many changes have been made to the directorate’s administrative processes to reduce the backlog of submissions. Among them are the reduction in the volume of data that manufacturers must submit for approval for changes in already-approved drugs. There is also a new policy of cost recovery in place. Other changes have been made by the bureau that specifically affect the reviews for biological drugs. The bureau has implemented standard operating procedures for reviewing submissions from manufacturers and for delegating tasks to members of the review teams. It now uses electronic templates for the data submitted by the manufacturers and also for the reports of the reviewers.

Cost recovery

The review of new drug submissions is time-consuming and expensive. Under a system of cost recovery, an applicant for a notice of compliance in Canada pays a fee to cover the cost of reviews, testing, and inspections. Cost recovery is a standard practice of national regulators. It was introduced in Canada in January 1995 to offset the effects of a 50 per cent reduction in the budget of the Drugs Directorate, announced to occur between the fiscal years 1995/96 and 1997/98. Fees were instituted, on a staggered basis, for the different aspects of the directorate’s reviews, with full implementation achieved by the end of 1996. The introduction of the cost recovery program was accompanied by a schedule that allocated the time for each stage of a review. The time limit imposed was determined by the directorate in consultation with drug manufacturers, with consideration given to the times allotted to reviews in other countries. By mid-1995, the backlog for most classes of submissions, except biologics, had been almost eliminated. In the course of the consultations with the drug manufacturers, the directorate agreed to reduce fees if it exceeded its time limit.

Because of the possibility that the level of fees resulting from cost recovery might deter manufacturers from applying to distribute certain drugs in Canada, especially drugs used only for the treatment of a small number of persons, there is a reduced-fee schedule for drugs of that category.

Amendments to the Food and Drug Regulations

Two amendments to the *Food and Drug Regulations* since 1995 have had a significant effect on the regulation of plasma derivatives. The first was the amendment of the *Regulations* in 1995 that required manufacturers to report to the

Health Protection Branch all information about serious adverse drug reactions. The second amendment, in 1997, repealed the exemption of manufacturers of biological drugs from the provisions governing good manufacturing practices. The effect of each of these amendments is discussed below.

Harmonization with international practices

The development of a new drug and the testing necessary to establish safety and efficacy for its intended use require the expenditure of large amounts of money. The compilation of the data needed to support an application to license a new drug for sale is also costly and time-consuming, involving thousands of pages of information. The desire of manufacturers to be able to prepare a single submission in a uniform format that is acceptable to all relevant regulators in the world is understandable. Nations do not always agree, however, about the appropriate extent of governmental regulation or the level of protection needed. Decisions about the drugs that may be made available to their residents are exercises in sovereignty.

International licensing harmonization is a matter of degree. The World Health Organization has recommended the harmonization of "intent," to be expressed in broad policies and goals. It is possible for nations to agree about certain standards of practice, such as "good manufacturing practices" (discussed below) or the standardization of the data required from manufacturers applying for licences for drugs. Collaboration among nations in the review of submissions and in the inspections of manufacturing plants is also possible. Full harmonization occurs when one nation accepts the licensing decisions of another nation or an association of nations.

Most industrialized nations today agree on the desirability of some form of harmonization. Even without harmonization, many regulatory authorities are influenced by the actions of other regulators. Approval of a drug by the U.S. Food and Drug Administration, for example, increases the probability that it will be approved by the regulatory authorities of other nations. In some countries, including Canada, the regulatory authorities request that manufacturers submit summaries of the findings of the regulators in those nations that have already licensed the drugs under review. Many nations have accepted good manufacturing practices as a common standard for the manufacture of drugs.

There are several international forums on pharmaceutical standards in which Canada participates. One is the International Conference on Harmonization, which creates standards for pharmaceutical and biotechnological products. Members in the conference include regulatory authorities of Europe, the United States, and Japan, and also major industry associations; Canada has observer status. Canada also participates with other nations, under the auspices of the World Health Organization, in an attempt to standardize information and reports of adverse drug reactions. In addition, there is a formal relationship for collaboration among the departments of health in

Canada, the United States, and Mexico under the North American Free Trade Agreement. Scientists at the Therapeutic Products Directorate and the Bureau of Biologics and Radiopharmaceuticals communicate about standards with their counterparts in the United States, the United Kingdom, Australia, and some other countries.

The European Commission has developed guidelines, incorporating those of the World Health Organization, for the regulation of blood components and plasma derivatives. Some aspects of the guidelines, however, are incompatible with those of the U.S. Food and Drug Administration.

Canada and Australia have agreed to exchange data and evaluation reports (with the agreement of the manufacturers). An agreement with Russia permits drugs approved in Canada to enter that country. Negotiations have been taking place among the regulatory authorities of Canada, the United States, Japan, and the European Union to reach “mutual recognition agreements,” primarily for inspections. Joint Canada–U.S. reviews and inspections, a few of which have taken place, are difficult, because they are possible only if manufacturers submit their applications to the regulatory authorities of both countries at the same time.

The amendments made to the *Food and Drug Regulations* in 1997 allow the Minister of Health in Canada to designate a country or an association of countries “as meeting standards equivalent to those set out in Divisions 2 to 4 [good manufacturing practices, radiopharmaceuticals, and biological drugs, respectively] in respect of the fabrication, packaging/labelling and testing of a drug.” The designated country’s conclusions from its inspections are acceptable in Canada.

The Bureau of Biologics and Radiopharmaceuticals’ assessment of safety

The bureau’s role in assessing the safety of plasma derivatives is twofold. The first task, through a pre-market assessment of safety, is to prevent unsafe products from entering the market. The second task, through the surveillance of products on the market (called post-market surveillance), is to respond to any indications that a product already in use may be unsafe. The same three sets of questions apply to both parts of the bureau’s role:

- 1 *Does the legislation give the bureau appropriate authority to protect Canadian residents from the sale, distribution, or use of a product considered unsafe (a) by requiring manufacturers to submit to the bureau all the information it needs to enable it to assess the manufacturing processes, the testing, and the safety of the products before they can be sold, and the products’ safety after they are on the market, and (b) by giving the bureau the authority to inspect manufacturing premises, to take action to prevent unsafe products from reaching the market, and to require the removal of products from the market that the bureau considers unsafe?*

- 2 *Does the bureau have the resources, organizational structure, and competence (a) to review the data submitted, (b) to perform the analyses necessary to identify any threats to safety, (c) to prevent unsafe drugs from entering the market, and (d) to ensure the removal of unsafe products from the market?*
- 3 *Does the bureau discharge its functions well enough to identify a plasma derivative as unsafe, to prevent unsafe products from entering the market, to remove unsafe products from the market, to communicate the information about the risks, and to make and enforce decisions in a timely manner?*

To attempt to answer some of these questions, independent reviews of the bureau were conducted for the Inquiry in 1995 by two experts: Dr John Finlayson, of the Office of Blood Research and Review, U.S. Food and Drug Administration; and Dr Elaine Walker, of the Molecular Biology Unit, Australian Therapeutic Goods Administration. Dr Finlayson had conducted an earlier review of the operations of the bureau, in 1994. His 1995 review was limited to specific aspects of the pre-market assessments performed by the Bureau of Biologics, now the Bureau of Biologics and Radiopharmaceuticals. He examined the files relating to the bureau's reviews of some plasma derivatives that had been conducted in 1984 and some conducted in 1994 to determine whether significant changes had occurred in the interval. I accept the reports and the conclusions of both outside experts. Some of the changes in the organization and practices of the directorate have corrected some of the weaknesses described by Dr Finlayson and Dr Walker.

Pre-market assessment

The bureau conducts a pre-market assessment of all new biological drugs listed in Schedule D of the *Act* to determine that they are not likely to be unsafe. There are three stages to a pre-market assessment of a plasma derivative: (1) a review of information submitted by the manufacturer about the safety, purity, and efficacy of the drug; (2) an inspection of the manufacturer's premises and a review of its manufacturing processes; and (3) testing, or a review of the manufacturer's testing, of every lot of the drug to be distributed. With approval at the first stage, the manufacturer receives a notice of compliance for the drug, and an identification number is assigned to the drug. With approval at the second stage, the manufacturer receives a licence to distribute the drug in Canada. With approval at the third stage, the manufacturer may sell vials of the drug derived from the same lot from which the sample vials were tested.

A drug that has not received the necessary approval may be made available in Canada. The *Regulations* permit the Therapeutic Products Directorate, of which the bureau is a part, to release a specified quantity of a drug that has not been authorized for sale in Canada to a requesting physician for use in the emergency treatment of his or her patient. The release may be authorized if the physician agrees to report to the manufacturer and the directorate about the use of the drug, including any adverse reactions encountered.

The review of information submitted by manufacturers

At the first of the three stages, the bureau reviews the scientific data, the labels, and the samples of the drug submitted by the manufacturer in the new drug submission. The relevant scientific data are a description of the chemistry and manufacture of the drug; the results of tests in animals for toxicity; and the results of clinical trials in humans for safety, efficacy, and the risk of side-effects.

The chemistry and manufacturing data are reviewed by scientists in the bureau to see whether the manufacturing process might produce a consistent, pure, and active product; whether the manufacturing process contains measures to reduce chemical and biological contamination and to inactivate or remove any contamination of the starting material, such as by viruses; and whether the methods have been shown to do what they are claimed to do. Data related to toxicity are reviewed to see whether the manufacturer's testing reveals potential problems of toxicity and side-effects and whether any toxic effects that do exist are serious.

The theory of good manufacturing practices is that careful processing, with accurate record keeping and internal checks and balances, increases the probability of safety in manufactured products. Determining whether these practices have been followed is critical in the reviews of the manufacturing data. The preventive measures that must be incorporated into the manufacturing process to ensure safety cannot be known before the risks they are meant to prevent are known. Rapid changes in technology and emerging potential hazards make it difficult to specify in regulations the measures that must be taken. The adequacy of the regulatory control and, ultimately, the safety of the product therefore depend largely on the knowledge and expertise of the manufacturer; on the knowledge, expertise, and foresight of the reviewers; and on the adequacy of the resources devoted to the exercise.

Dr Finlayson's assessment of the bureau's reviews of the scientific data was as follows:

The quality of the reviews that I examined was good. It was good in the past, and it appears to be good at present. If there is a change, it appears to be increased attention to the viral safety aspects of products and their submissions ...

Furthermore, viral safety is only one aspect of the safety of any plasma derivative. One must be concerned about both acute and long-term adverse effects, including loss of effectiveness. As a consequence, one must be alert to modifications in manufacturing – even when undertaken to achieve the most beneficial of outcomes – that could potentially contribute to any such effects. This type of alertness was evident in earlier reviews, and it is evident now.

His assessment was based on his examination of the notes of the bureau's own reviewers about the information received by the bureau.

The bureau requires the results of at least three levels of clinical trials. Approximately half the reviews of the clinical data are performed by external reviewers retained by the Department of Health. The importance of clinical reviews and of the use of experts in clinical matters is reflected in two of Dr Finlayson's recommendations:

Strengthen the clinical review capabilities of the Bureau of Biologics [now the Bureau of Biologics and Radiopharmaceuticals], especially those of the Blood Products Division.

Involve more than one person in each review of clinical data ... More than one person's expertise and critical insight are often needed.

Among the changes in the 1990s affecting the reviews conducted by the bureau is a reduction in the volume of information manufacturers must submit about clinical trials and about any changes there may be to existing products, processes, manufacturing premises, and indications for use. This change was made to reduce the expense to and the time needed by the bureau to conduct the reviews and, therefore, to reduce the backlog of applications for review. However, as Dr Walker pointed out, if the reviews of the information are to be sufficiently thorough to recognize potential risks, the reduction in the "workload" for the bureau will not be as great as the directorate estimates. Moreover, as Dr Walker said, the reduction in the volume of information manufacturers are required to submit about clinical trials should apply only to "products with proven viral safety."

When making a new drug submission, a manufacturer must submit samples of the drug from at least three consecutive lots. The bureau tests the samples in its own laboratories for consistency, purity, and, in some cases, biological activity. In the report of her review of the laboratory-testing program, Dr Walker said that "some staff recognized the level of responsibility was in excess of their training," and that she "was concerned about the underlying assumption that matching a company's result when using a company's method constituted method validation."

In its review of a new drug submission, the bureau compares the samples of all labels, package inserts, and product brochures for accuracy with the data submitted about the drug. A new drug submission must include a product monograph, defined in the Drugs Directorate guidelines as a "factual, scientific document on the drug product that, devoid of promotional material, describes the properties, claims, indications, and conditions of use of the drug, and that contains any other information that may be required for optimal, safe, and effective use of the drug." If approved, the product monograph is

attached to and made part of the notice of compliance and “serves as a standard against which all professional literature [and] promotional material ... about the drug can be compared.” It is to be distributed

by the manufacturer to practitioners or other members of the health professions whenever they request prescribing information or other information relevant to the clinical use of the new drug. ... [and] to practitioners prior to, or coincident with, the first direct promotion or marketing of a new drug, and to any practitioner to whom the manufacturer sells a new drug before it is generally available.

Dr Finlayson noted that “current Product Monographs contain much information, but the clinical sections are very brief and often quite general,” and he recommended that “a format for making the details of clinical trial results available publicly” be devised because “most physicians, even those working in academic or other teaching hospitals, currently receive only the information they read in the medical literature, which can present a very selective picture.”

Manufacturers often apply for authorization to sell a drug in several countries at approximately the same time. Because the Canadian market for certain drugs is relatively small, an application for authorization may be submitted in Canada many months after a similar application has been submitted to the U.S. Food and Drug Administration. If the period between the two submissions is months or years, the information in the Canadian application may no longer be accurate or complete. Omissions can be significant if, in that interval, a new risk from an infectious disease has emerged or an adverse reaction to the drug has been reported. Dr Finlayson, in his review of product monographs and package inserts that had been approved by the bureau, found several examples of information about risks that was, at the time of submission, no longer accurate.

The evaluation of the manufacturing process

The second stage in the bureau’s pre-market assessment of a biological drug is an evaluation of the manufacturer and of the processes it uses. Before a licence is issued, inspections of the premises are conducted to determine whether the drug is manufactured in accordance with the requirements of the *Regulations*. Because licences are valid for only one year, manufacturers must apply for their renewal annually.

Most of the plasma derivatives used in Canada are manufactured in the United States. Inspectors from the Therapeutic Products Directorate inspect plants outside Canada that manufacture plasma derivatives for use in Canada and may also inspect the blood or plasmapheresis centres where the plasma is collected. The inspections are conducted by inspectors from both the Bureau of Biologics and Radiopharmaceuticals and the regional offices of the Field

Operations Directorate. Inspections take place when the bureau is nearing the end of its review of the data in a new drug submission. By then, the inspectors have the necessary information to be able to make a thorough inspection of the premises. Any questions about the manufacturing process that were raised during documentary review can be answered at the manufacturing premises.

In practice, Canadian inspectors rarely conduct inspections of plasmapheresis and blood collection centres outside Canada. The bureau relies on the inspection reports from the country in which the collection centres are located and from the manufacturer that purchases the plasma. As part of the information they submit to the bureau with every lot of a plasma derivative that is to be distributed in Canada, manufacturers must include a list of all the centres that collected the plasma used in producing that lot. In the 1980s, the lists submitted to the bureau were not reviewed. The lists did not contain information about the inspections conducted by either the manufacturers or the regulatory authorities.

Lot-by-lot testing

The third stage in the pre-market assessment of plasma derivatives is the evaluation of samples of every lot of the drug that the manufacturer intends to sell in Canada. Because of the variability of the source material, this requirement applies only to biological drugs. The importance of testing is explained in the directorate's guideline entitled *The Lot by Lot Testing and Release Programme*:

The quality of the final product often depends on manufacturing variables which cannot be sufficiently controlled without end-product testing. In addition, the biological tests that must be conducted on these products are highly variable. Therefore, replication by the regulatory laboratory is needed to provide a satisfactory degree of confidence in the safety of the product.

The guideline also says:

Before the sale of each manufactured lot, samples and quality control protocols must be submitted to the Bureau of Biologics [and Radiopharmaceuticals] for evaluation, testing and lot release.

In 1996, the bureau changed its policy with respect to lot-by-lot assessment. It continues to test for consistency the samples submitted with new drug submissions. After a notice of compliance is issued, a "product profile" is made on the basis of a review of the nature, quality, and results of the tests conducted by both the bureau and the manufacturer. The purpose of the profile is to attempt to determine the probability that a lot will meet the specified standards. On the basis of its product profile, every drug is assigned to an "evaluation group." Each such group has its own lot-testing requirements.

For nearly every product, manufacturers are still required to submit information about their testing of every lot before that lot can be released. For products in certain evaluation groups, the manufacturers are also required to submit samples to the bureau; the bureau may conduct some testing on those lots of products within the evaluation group which are considered to contain drugs at highest risk of being defective. For products in other groups, the bureau authorizes the release of a lot after the information submitted by the manufacturer has been found to be satisfactory. Periodic testing is conducted on samples of any lot of any biological product that the bureau chooses. Manufacturers must report information about all lots that fail to meet the specifications.

The manufacturers of drugs that contain a human blood product as a stabilizer must inform the bureau before the sale of any lot and “maintain a traceable link between the drug and the lot number(s) of the blood product(s) used as excipients or stabilizers.” They must notify the bureau of all lots sold in Canada annually and must also maintain records and analyses of the results of their tests. The importance of this requirement is illustrated by an incident that occurred in 1995 when a pool of plasma was thought to carry the risk of transmitting Creutzfeldt-Jakob disease (CJD). All the plasma derivatives that were derived from the plasma were withdrawn. The withdrawal included the removal of all the lots of recombinant factor VIII that contained albumin from the potentially contaminated lot.

Both Dr Finlayson and Dr Walker commented on the need to improve the laboratory-testing and research capabilities of the bureau. With respect to the quality of the testing performed by the bureau, Dr Walker recommended that “laboratory methods should be re-examined” and that “[t]raining in method development and validation should be commenced.” She also recommended that the bureau participate in collaborative studies as part of an international quality assurance program.

Dr Finlayson noted a difference between the approach taken in reviewing the submissions for recombinant products on the one hand and that taken for plasma derivatives on the other. He commended the laboratory-based approach:

[The review at the investigational drug submission stage] allows the staff to develop “hands-on” familiarity with the product, to learn its characteristics and idiosyncrasies, and to evaluate the importance, usefulness, and reliability of lot release tests that the manufacturer has proposed (or in some cases, failed to propose) before a New Drug Submission is ever made. This is a highly commendable approach and, in the face of apparently unrelenting pressure to decrease lot release testing, may represent one of the best uses of laboratory personnel time.

Testing the samples of new drugs to assess the consistency of the production processes is an important aspect of the bureau's laboratory function. So is the testing that is performed to assess purity and potency. Although the bureau relies on the results of the manufacturers' tests, it must have the competence to review the information and the expertise to perform spot checks or carry out alternative testing. Until recently, the research devoted to developing new methods to be used for alternative testing was performed in the Bureau of Drug Research. Dr Walker's review of this arrangement led her to make the following recommendation:

Better communications need to be established between BoB [Bureau of Biologics] and BDR [Bureau of Drug Research] so that the expertise of both bureaux may be used to maximum advantage.

Post-market surveillance

The obligations of a manufacturer of a plasma derivative and the bureau do not end when the derivative is on the market. Manufacturers are required to keep records, report changes or defects in production, report adverse reactions to their drugs, and have procedures in place for recalling unsafe products.

Licence renewals

As noted, licences issued to drug manufacturers must be renewed annually. As a condition of the issuance or renewal of a licence, the Minister of Health may require an inspection of the premises and information about the process and conditions of manufacture. The manufacturer may be required to supply samples of the finished drug or any material used in its production.

Since 1997, when the *Regulations* were amended, the Minister may indicate in a manufacturer's licence a period for which records must be retained; and may set out terms and conditions respecting the tests to ensure that the drug is not unsafe, and "any other matters necessary to prevent injury to the health of consumers."

Dr Finlayson expressed the opinion that the process of reviewing applications for licence renewals is time-consuming for the bureau and suggested that "streamlining" be considered "while assuring that the information submitted is accurate, current, and complete." He found that the "administrative aspects of license renewal appear to be handled diligently." He also noted:

It was not always clear whether the persons responsible for processing the renewal requests were familiar with the scientific and technical aspects of the products involved. Nonetheless, I noted several comments that showed a great deal of regulatory insight. Frequently, there were comments directed to the recent inspectional history (or lack thereof) of the firm. Expressions such as "as soon as possible" and "urgently required" were often used in reference to future inspections.

Dr Finlayson discovered that a licence had been renewed for an unacceptable product that had not been distributed in Canada for many years.

Reporting of adverse reactions

Until the amendment to the *Food and Drug Regulations* in November 1995, the requirement for manufacturers to submit information about adverse reactions applied only to new drugs. Effective January 1996, all manufacturers are required to report, within fifteen days, all information in respect of any serious adverse drug reaction that occurs in Canada and any serious unexpected adverse drug reaction that occurs outside Canada. Manufacturers must, annually or on request, “conduct a concise, critical analysis of adverse drug reactions and serious adverse drug reactions ... and prepare a summary report in respect of the reports received ...”

Past experience has demonstrated that adverse reactions have not always been reported. Reporting depends on the knowledge and vigilance of physicians. A study conducted for the Department of National Health and Welfare in 1989 found that there was little done to encourage reporting of adverse drug reactions, little emphasis on verification or investigation, and little communication with those who did report. The regulatory impact statement that accompanied the publication of the amendments to the *Regulations* in 1995 requiring manufacturers to report adverse drug reactions states:

The Auditor General’s Report (1987) identified all aspects of pharmacovigilance (including ADR [adverse drug reaction] collection, analysis and communication) as deficient, and suggested that Canadians were being placed at risk.

The amendment was considered to be the only acceptable alternative. It not only provides the regulator with safety data for all drugs on an ongoing basis, but also coordinates the reporting by manufacturers in a format which is complementary to the World Health Organization (WHO) International Drug Monitoring Program. As recommended by Dr Denis Gagnon in his report “Working in Partnership” – a review of the Canadian drug approval system, pharmacovigilance must become an integral part of this system. The only way to determine the safety of a drug in the market place is to monitor its performance in that setting.

Dr Finlayson commented on the importance of encouraging physicians to report adverse drug reactions and suggested that the bureau develop an “outreach” program:

One aspect of such a program might be directed to making physicians aware of the need to record product lot numbers and to report adverse reactions, making it simple for them to do so, and convincing them that such

records and reports are not filed in a bottomless bureaucratic pit, but rather are much appreciated and intelligently used (e.g., in revising package inserts) to further the cause of patient care.

Until November 1995, adverse reactions were supposed to be reported to different bureaus, depending on the type of drug and reaction. Beginning in 1996, all adverse reactions from blood products are to be reported to a new bureau, the Bureau of Drug Surveillance, which was created as the post-market monitoring arm of the Drugs Directorate, replacing the Bureau of Pharmaceutical Surveillance and the Bureau of Dangerous Drugs. The Bureau of Drug Surveillance has a computerized system for collecting information about adverse drug reactions. That system is linked to the regional centres of the Health Protection Branch and to other national and also international organizations that collect or correlate information about adverse drug reactions.

In his review, conducted before this reorganization had occurred, Dr Finlayson observed that the files containing reports of adverse drug reactions

exhibited considerable heterogeneity. For example, one contained many reports but no indication of follow-up or Bureau of Biologics review; another contained a single case report with fairly extensive follow-up. All dated back to a period in which the product was not licensed because the Bureau of Biologics does not receive adverse reaction reports for approved products.

Dr Finlayson recommended the creation of “an information-flow system (even if only a very simple and informal one)” among the Bureau of Biologics, the Bureau of Pharmaceutical Surveillance, and the Laboratory Centre for Disease Control to ensure “that information (e.g., adverse reactions to a biologic product, product recalls, outbreak of blood-borne disease) arriving anywhere within the system will be transmitted quickly to the person(s) best equipped to act.”

Despite the reorganization, the Bureau of Drug Surveillance will not be the only bureau that receives reports of adverse drug reactions to plasma derivatives. Manufacturers are required to report to the Bureau of Biologics and Radiopharmaceuticals any adverse drug reactions that are known before or during the review of a new drug submission and also “unexpected effects or side effects found during clinical use.” The Bureau of Biologics and Radiopharmaceuticals must have access to the reports of adverse drug reactions that are submitted to the Bureau of Drug Surveillance. If, for example, an adverse reaction could be caused by a defect in a specific lot or batch, samples should be tested for defects or deficiencies. Dr Walker found no evidence that batch-related problems or suspected problems were referred to the bureau’s

laboratories for testing, and she recommended that the review of adverse drug reactions “include a mechanism by which batch-related reactions and complaints are referred to [the bureau] for laboratory investigation.”

Product recalls

When a biological drug is found to contravene the *Food and Drugs Act* or the *Regulations*, its manufacturer or distributor is expected to recall it from the market. Section C.02.012 of the *Regulations*, which since 1997 applies to plasma derivatives, provides:

Every fabricator, packager/labeller, distributor referred to in section C.01A.003, importer, and wholesaler of a drug shall maintain

- (a) a system of control that permits complete and rapid recall of any lot or batch of the drug that is on the market; and
- (b) a program of self-inspection.

It is not always possible to undertake a recall in a timely fashion. The information that prompts a recall may come from one or more sources, not all of them close to the manufacturer or distributor or the Health Protection Branch. The first warning may be in the form of adverse reactions to the drug reported by patients, physicians, or hospitals to the manufacturers, local public health authorities, or the regional or central offices of the branch. Adverse reactions reported in another country may or may not be communicated to the manufacturer or the regulatory authorities in that country, or to their counterparts in Canada. Attempts are being made to establish international links to exchange information about adverse drug reactions. Indications of potential health risks associated with a drug may also come from the scientific literature. A recall may also be prompted by new or inconsistent results from tests conducted by, or for, the manufacturer.

Because plasma derivatives are manufactured by corporations that sell their products internationally, the first notice of a hazard to health may come from the regulatory authority of another country. For example, in 1993 the regulatory authority in Germany reported that a manufacturer in that country had recalled some products because it had learned that plasma used in their production had not been adequately tested. The information came first to the Bureau of Biologics and then to the Canadian agent for the corporation that manufactured the products, with the instruction to issue a recall. In Canada, the response to the information was affected by several factors. First, it was difficult to obtain information from the manufacturer about which products were derived from the suspect plasma. Because there was uncertainty about the products involved, it was then difficult to identify the Canadian distributors and to find out who was monitoring the recall. There was also no mechanism for promptly and effectively communicating the

information to everyone who needed to know. Finally, assumptions were made that all products whose expiry date had passed had by then been used – so there would be no need to trace them.

Crisis and emergency management

During the reorganization of the Drugs Directorate, the Health Protection Branch's system for crisis and emergency management was modified to apply to drugs and further modified for blood products. When a problem requires special attention, an ad hoc team is formed to evaluate the hazards and to manage a crisis. The membership of the team varies according to the nature of the crisis. The team is always led by the director of the Bureau of Biologics and Radiopharmaceuticals and always includes persons from each of the Laboratory Centre for Disease Control and the Bureau of Drug Surveillance, a person to communicate with the regional offices, and a senior research scientist to communicate with the expert advisory committee on blood regulation for external, expert advice. In addition, other members may be required and are chosen for their expertise from the other bureaus. The approach used to evaluate the hazards is similar to that used to evaluate the need for a product recall.

A recall or withdrawal is one of the most important measures in managing a crisis in which the safety of a plasma derivative is involved. Communicating information promptly and ensuring that replacement products are available are also part of effective crisis management. The manufacturer and distributor of the drug involved and the bureau have clear and separate roles to play in managing crises.

An example of crisis management was the response in 1995 to the potential threat of contamination of the blood supply with CJD, noted earlier. A person who died of the disease had been a blood donor. It was thought possible that the components and products derived from his recent blood donations could have been contaminated with the agent thought to cause CJD. Bayer Inc., the manufacturer that fractionated the Canadian plasma, and the Canadian Red Cross Society (Red Cross), the collector of the plasma and the distributor of the plasma derivatives, decided to withdraw the products, and the Red Cross made arrangements to deal with the shortages that would result from the withdrawal. Decision making by the crisis management team of the Health Protection Branch was slow, however, because of its perception that the decision it reached in this "crisis" would set a precedent and, therefore, create a policy. On this occasion, as is often the case, there were early warnings of the potential risk because similar situations involving blood donors who were diagnosed with CJD had arisen earlier in the United States, and the affected products were then withdrawn. If a Canadian policy dealing with the risk of contamination of the blood supply from CJD had been developed before the incident occurred, there would not have been a crisis.

After analysing the way in which crises involving the safety of plasma derivatives were managed in the past, Dr Finlayson suggested that, because it was difficult “to discern the boundaries of responsibilities between the Red Cross and the Bureau,” the key to future responses is rapid communication. He wrote:

It seems probable that there are several different routes by which the Bureau could be alerted in a future crisis. In general, the earliest warning tends to be the most informal – a call from a physician, a pharmacist, a patient, a colleague, etc. The problem is to place this warning, as rapidly as possible, in the hands of the person or persons with the knowledge and authority to respond in a suitable fashion. Often, this problem is compounded by the fact that the reporter is uncertain of where to direct the report and simply grasps at the first available straw.

He added that an aspect of the “outreach program” that he had suggested to increase the reporting of adverse drug reactions should include meetings with the Red Cross, the Canadian Hemophilia Society, and similar groups. In Dr Finlayson’s opinion, such a program “might help immeasurably in laying lines of communication that will function automatically in crises”:

The question of crisis readiness is closely tied to post-licensure management. It implies that there is a mechanism for rapid receipt of adverse information, that there are knowledgeable people on hand to receive it, and that there are procedures in place for mounting a rapid and appropriate response. The last of these further implies that the lines of responsibility and authority are clearly drawn.

The role and performance of the bureau

Earlier in this chapter, three sets of questions were asked about the adequacy of the authority, the resources, and the competence and performance of the bureau in assessing the safety of plasma derivatives and controlling the distribution of products thought to be unsafe. I now return to these questions.

The adequacy of authority

The Bureau of Biologics and Radiopharmaceuticals, under the authority of the *Act* and *Regulations*, can obtain the information, gain access to manufacturing premises, and obtain samples of plasma derivatives that it must have to assess the safety, purity, and efficacy of new biological drugs and the processes used to manufacture them.

The *Regulations* contain detailed provisions dealing with human plasma collected by plasmapheresis and with preparations from human sources. Plasma separated from whole-blood donations is the principal source of plasma for the production of the plasma derivatives that are used in Canada.

Although the bureau has the authority to regulate the collection and processing of blood, no regulations have been made that deal specifically with blood collection and processing. This is an important gap in the regulatory framework.

The *Regulations* allow the bureau to set standards and obtain the information it needs to assess the safety of plasma derivatives and take action to prevent the distribution of unsafe plasma derivatives. The *Regulations* dealing with good manufacturing practices were amended in 1997 so that they now apply to biological drugs.

The volume of information that manufacturers must submit to the bureau about changes to products, processes, or uses of a drug has been reduced. The information that manufacturers must submit is not specified in the legislation. The scientists reviewing the information must evaluate the appropriateness and the adequacy of the information. The bureau has the authority to obtain more information if necessary.

After a plasma derivative is on the market, the Health Protection Branch can suspend or cancel its notice of compliance. The branch can suspend or amend the manufacturer's licence for the drug, and its inspectors can seize a product that they believe on reasonable grounds contravenes the *Food and Drug Regulations*. The Health Protection Branch does not have, although it should have, the power to order a manufacturer to recall a product that it considers unsafe.

The adequacy of resources

The second set of questions relates to the adequacy of the resources available to the bureau to review the data submitted and to perform the analyses necessary to identify threats to safety. It also addresses the effects, if any, of the organizational structure of the directorate on the ability to make decisions and enforce them in a timely manner.

Both Dr Finlayson and Dr Walker described problems with respect to the number, organization, experience, and expertise of the reviewers. The first "imperative" listed in Dr Finlayson's report was to "provide sufficient staff to deal with a severely backlogged, growing field." Of six imperatives that he listed, five dealt with the hiring, training, retaining, and deployment of staff members for the bureau. His report also contained recommendations that dealt with the need for "clinical review capabilities" and biostatistical support; the need for more than one person to be involved in the reviews; the need to reduce the backlog and avoid delays; and the need to improve communications. From Dr Finlayson's analyses, it is clear that the lack of resources played a role in the delays that occurred in the reviews of new drug submissions.

The Bureau of Biologics and Radiopharmaceuticals has undergone several organizational changes since 1994. An increase in the number of staff positions allocated to the blood products section has been authorized, although

not all the positions have been filled. The bureau's functions now include the regulatory assessment and control of radiopharmaceuticals, and tissues and organs.

The imposition of cost recovery, strict schedules for reviews, and other actions taken to reduce the backlog of applications has increased the work of the employees of the bureau. Recruitment of new staff members has been difficult, and of course even highly qualified persons require time to gain experience in the review process. Many positions have been filled temporarily. The resources and number of well-trained persons allocated to the bureau have been insufficient for the high-quality reviews, testing, and inspections that are required. Dr Finlayson stated:

I shall not recommend or comment on administrative reorganization, which was underway even during my visit ... There are however, a few messages that I consider worth emphasizing.

The first of these is that the Bureau has a nucleus of excellence. This consists of dedicated and concerned individuals whose knowledge of the scientific, technical and regulatory aspects of biological products is of the highest caliber. Whatever the administrative form of the organization, or the legal or political climate, it is this nucleus that must be fostered if Canada is to continue the regulation of biologics and Canadian citizens are to feel confident of that regulation.

Certain aspects of the Bureau's operation should expand. For example, there seems to be a desperate need for additional trained and credentialed inspectors. Expansion *per se* however, is not the answer. Recruitment, development and retention of scientist/reviewer/inspectors of the highest quality is the self-evident goal ...

Whatever the exact pathway taken, progress will be gradual. Confidence must be earned, and it is earned slowly. The challenge to managers is to initiate, encourage, and accelerate this progress without crushing the nucleus of excellence under the demand for instant perfection.

Clinical expertise at the Bureau of Biologics and Radiopharmaceuticals is needed to review the clinical data submitted in support of safety and efficacy for new drug submissions. Many of the clinical reviews have been conducted by persons outside the Department of Health. There are advantages in having the expertise at the bureau: consistency is enhanced, and there is familiarity with the bureau's practices and standards. Persons with clinical expertise must be available to consult and communicate with other members of the review team, and to interpret information about adverse drug reactions and advise on emergency and crisis management. The review of the safety

and efficacy of any new biological drug requires competence in the fields of protein chemistry, toxicology, clinical medicine, microbiology, immunology, laboratory testing, quality assurance, and industrial bioengineering. This range of knowledge can be attained only through the use of teams.

Until 1997, expertise in laboratory testing in the Therapeutic Products Directorate was divided between the scientists of the Bureau of Drug Research, who conducted research relating to both chemically and biologically derived drugs, and the scientists of the other bureaus, who reviewed the manufacturers' submissions and conducted some associated laboratory testing. In July 1997, it was announced that the Bureau of Drug Research was being disbanded and that drug research would be conducted outside the government – in universities and corporations. Such a change will inevitably reduce the number of persons at the directorate with competence and experience in laboratory science. The new policy for lot release has already decreased the amount of testing performed by the bureau. Competent laboratory scientists must be available at the directorate for collaboration and consultation in a number of processes: the review of data submitted by manufacturers applying for a notice of compliance; the release of lots of plasma derivatives; licence renewals; and the analysis of information obtained after plasma derivatives are on the market. Proponents of the change say that universities can be asked to undertake some of the highly technical aspects of the review process, using some of the best scientists in the country. At stake, however, is the risk of losing the core of expertise that has been developed in the government departments charged with the protection of the health and safety of Canadian residents.

Two of the “imperatives” in Dr Finlayson’s first report dealt with laboratory functions and expertise. He said:

Strengthen, do not lose, the research function. Maintaining and enriching it is an important way – and may be the only way – to

- a) deal with the new-era products
- b) maintain scientific credibility with regulated manufacturers
- c) retain a scientifically oriented, astute staff
- d) address product crises – regardless of whether “new” or “old” biologic drugs are involved.

The second set of questions has asked whether the bureau has adequate resources to allow it to review the data submitted, to perform the analyses necessary to identify threats to safety, and to take timely action. The answer is that the resources are inadequate.

The adequacy of review

The third set of questions considered whether the reviewers are able to recognize inadequacies or inaccuracies in the data provided by a manufacturer; whether actions are taken to prevent or remove plasma derivatives considered unsafe; and whether information about a new risk to the safety of plasma derivatives is communicated to the persons who need to know.

From the assessments conducted by Dr Walker and Dr Finlayson of the bureau's reviews of data submitted by manufacturers and the organization of the review process, I conclude that the quality of the pre-market reviews has not been inferior to that in other countries. This conclusion, however, does not justify complacency. Improvement is desirable. Significant delays occurred both in beginning and in conducting the reviews.

The performance of the bureau relating to post-market surveillance has not been easy to assess. Reviews of information submitted by manufacturers after the product is on the market have not been well documented. This is also true of investigations of adverse drug reactions, collation and analyses of accident and error reports, and inspections of manufacturers at the time of licence renewals. Dr Finlayson's assessment revealed that communication, both internal and external, has often been less than satisfactory.

Conclusion

The evaluation of safety in plasma derivatives is not straightforward. There are too many variables to permit certainty. The human plasma that is the starting material for every batch of plasma derivatives is obtained from thousands of different donors. The quality and safety of the donations are inconsistent, and every batch differs from the next. Although it should be possible in principle, if not in practice, to test a sample of every lot of every product, thorough regulation would require knowledge of, and a means of testing for, every possible hazard. Limitations on resources require the Bureau of Biologics and Radiopharmaceuticals, in considering submissions for approval of new drugs, to rely principally on a review of the manufacturers' data about the safety, efficacy, and purity of its products and the manufacturers' quality control; and on inspections of the manufacturers' premises and processes. The bureau conducts a limited amount of testing in its own laboratories, and, when plasma derivatives are authorized for sale, it reviews the results of the manufacturers' tests of lots of the plasma derivative before they are released for sale.

There are limits to the type and quality of data that can be collected before a product enters the market, and it is not always possible to know what questions to ask. Laboratory and animal studies may not reveal a new drug's effects on humans. The information obtained from clinical trials is often imperfect because of their finite duration and the limited number of subjects studied. Post-market surveillance is therefore as essential as pre-market

review. Manufacturers are required to report adverse reactions to the Health Protection Branch. The bureau must also have access to other information about the product gathered by the manufacturers, the capability to investigate and analyse the information, and the ability to conduct tests that may reveal problems in products that are on the market.

The efforts to protect a product's safety begin with the collection of the plasma and continue through the manufacturing process. One of the recommendations made in the Interim Report related to the computerized information system for centre operations, which in 1994 was in the process of being implemented. After the submission of the Interim Report, the Red Cross and the Canadian Blood Agency retained a consultant to review the computer system. He noted that some improvements had been made in management, but that several problems persisted. The project has had major setbacks in maintaining schedules and costs. By the spring of 1997, the pilot project had still not been completed. The lack of an adequate computerized information system remains a risk to the safety of blood components.

A review of the international scientific and medical literature yielded few reports of infections associated with the use of plasma derivatives. The cases that were reported resulted, for the most part, from the use of plasma derivatives that had not been processed in the same way as the plasma derivatives distributed in Canada, or from contamination with viruses that are not inactivated in the processing and not considered a serious risk to healthy persons. Few infections from known pathogens are associated with the use of plasma derivatives distributed in Canada. However, we cannot be complacent. The measures taken to inactivate viruses are not effective against all viruses, and a new or emerging pathogen could be transmitted by plasma derivatives.

Manufacturers of plasma derivatives must take measures to prevent contamination of the product during the manufacturing process and to remove hazards that were present in the starting material. Because the types and nature of all organisms that may be present in plasma cannot be known, it is not possible to know whether the inactivation techniques being used will be effective against them.

The role of the Bureau of Biologics and Radiopharmaceuticals is to assess the effectiveness of all the measures taken by manufacturers, to assess the likelihood that a plasma derivative will be unsafe, and to prevent unsafe products from being distributed. Except for their power with respect to recalls, the bureau has adequate authority to perform that role. It has inadequate resources.

PART VI

Towards a New Blood System

The Blood Supply System in Canada: Systemic Problems in the 1980s

Major systemic problems contributed to the contamination of the blood supply in Canada during the 1980s. Only by analysing these problems can one appreciate the reforms that are necessary to prevent similar events from occurring in the future. The brief descriptions in this chapter of the events that surrounded the contamination refer only to the ones that clearly reveal major systemic problems. Non-systemic factors, which are important to a full understanding of some of the events, are not mentioned. Other systemic factors that played a role in the events are not mentioned. In every case, different events could have been chosen to illustrate the systemic problems. Readers who are interested in the full account of the events surrounding the contamination should turn to the earlier relevant chapters. It is only by knowing the complete story that one can fully understand the systemic shortcomings and their consequences, and the reforms that are necessary. Concise propositions that are inherent in the recommendations for the future system (see Chapter 40) are listed at the end of each of the sections that follow.

The dysfunctional relationship between the Red Cross and the governments

Since 1947, the Canadian Red Cross Society (Red Cross), through its blood transfusion service and its blood donor recruitment, has been the operator of the blood supply system. In 1958, the Red Cross began to receive some financial support from the federal and the provincial governments for the blood transfusion service; in 1974, the financial support from both levels of government reached 100 per cent; and in 1977, the provincial governments took over full financial support. Blood donor recruitment did not receive financial support from the governments until 1974; it received 40 per cent support in that year, and the support was increased to 60 per cent in 1975 and to 80 per cent in 1976. The budgets for the Red Cross's blood program were subject to review by representatives of the governments – from 1973 to 1981 by the Federal-Provincial Program and Budget Review Committee, and from

1982 to 1991 by the Canadian Blood Committee. The relationship between the Red Cross and the governments, and their committees, was poorly defined and was often dysfunctional.

Defining the roles in the blood supply system

In 1976, the federal and provincial ministers of health decided that the blood supply system was to be governed by three principles: voluntary donation, national self-sufficiency, and gratuity of blood products to recipients. The three principles did not begin to define the respective roles of the Red Cross, as the operator of the system, and of the provinces, as the funders of the system. In 1981, when the Canadian Blood Committee, whose members were public servant representatives of the federal and provincial governments, was formed, one of its tasks was to create a comprehensive national blood policy that defined the respective functions of the Red Cross and the committee. The committee never created a national blood policy. As a result, no one was clearly in charge of, or accountable for, the safety of the blood supply. The roles of the Red Cross and the committee were blurred, and the continuing tensions between them interfered with efficient and effective decision making. The blood supply was consequently not as safe as it could and should have been (see Chapters 3, 4, and 5). If the functions had been clearly defined, many of the problems relating to safety that arose could have been more quickly and effectively solved.

Blood donations as a national resource

During the 1970s and 1980s, the Red Cross encountered a shortage of donors in some provinces. Because every provincial government paid the Red Cross for operating the blood program in its jurisdiction, the governments discouraged regular, non-emergency, interprovincial transfers of blood components. As a result, there was a chronic shortage of blood components in some urban centres in these two decades. A secondary result was that the Red Cross was reluctant to introduce any measures – including risk-reduction measures for both AIDS and hepatitis – that might have reduced the number of donors (see Chapters 3, 5, 11, and 24). If the Red Cross had been encouraged to operate a truly national system, one in which blood donations were treated as a national resource and provincial boundaries were not barriers to the rational distribution of blood components, it could have eliminated the shortage of blood components and the disincentive to introduce risk-reduction measures.

Financing the blood supply system

The Red Cross was unable to improve the safety of the blood supply, when the measures necessary to do so entailed significant costs, without the approval of the Canadian Blood Committee (see Chapter 5).

Blood products are made from plasma, the liquid part of whole blood. One of the key blood products distributed by the Red Cross, factor VIII concentrate, had to be made from plasma that was frozen soon after donation. To be self-sufficient in blood products, Canada needed to be self-sufficient in fresh frozen plasma. To achieve self-sufficiency in fresh frozen plasma, the Red Cross needed to expand the use of plasmapheresis, a process by which plasma only is collected from donors. This expansion required long-term capital investment and increased financial support for day-to-day operations. The Federal-Provincial Program and Budget Review Committee for the years 1980 to 1982, and the Canadian Blood Committee for 1983 and 1984, did not approve the full budgets for the plasmapheresis program that were proposed by the Red Cross. As a result, the expansion of the program was delayed and dependence on factor VIII concentrate made from U.S. plasma remained high. Cost was the main reason that the committees did not approve the full budgets; it was cheaper in the short term to buy factor VIII concentrate made from U.S. plasma than to make the long-term investment necessary to achieve self-sufficiency in fresh frozen plasma (see Chapters 4 and 14).

The Red Cross rightly concluded in October 1984 that factor concentrates, used in the treatment of hemophilia, were safer if they were heat treated. In November, the Bureau of Biologics, the regulator of blood products, directed that a conversion from non-heat-treated concentrates to heat-treated concentrates take place. The Red Cross did not begin to purchase the safer concentrates, which were more expensive, until December, however, when the Canadian Blood Committee authorized the purchase. As a result, the conversion to heat-treated concentrates, which almost completely ended the spread of AIDS among Canadian hemophiliacs, was unreasonably delayed (see Chapter 15).

In the autumn of 1984, the Red Cross began to consider the introduction of a test to detect the antibody to HIV in blood donations. The test became available in March 1985. The Canadian Blood Committee approved the budget for the introduction of the test on 1 August, and only then did the Red Cross begin to implement it. The test was not fully implemented until November. Although it was not perfect, the test identified almost all HIV-contaminated donations and eliminated all but a few cases of transfusion-associated HIV infection (see Chapter 12).

If the Red Cross's blood transfusion service had had the independent authority to improve the safety of the blood supply, it could have invested in improvements to the blood supply system without the constraint of the short-term budgetary concerns of the provinces. More important, it could have eliminated, or at least greatly shortened, the delays that occurred in introducing essential risk-reduction measures.

Operational independence

Blood products are made from plasma through a process called fractionation. In the late 1970s and early 1980s, the provincial ministers of health made decisions about the domestic fractionation industry that were influenced more by provincial industrial policy than by the needs of the national blood supply system. The ministers forced the Red Cross to cancel a fractionation contract it had made with a U.S. manufacturer and required it to allocate the future supply of domestic plasma among three Canadian manufacturers – only one of which was an active fractionator. None of the three domestic manufacturers was allocated the amount of plasma needed to be successful, and by the end of the 1980s, no domestic fractionator was making the principal blood products (see Chapters 4 and 17).

The decision of the provincial ministers of health to have plasma allocated to the domestic fractionators had an adverse impact on both the quantity and the quality of the factor concentrates that were distributed by the Red Cross. For most of the 1980s, Connaught Laboratories Limited (Connaught) was the only domestic fractionator making the principal blood products. As a result of the ministers' decision, the Red Cross had no choice but to enter into contracts with Connaught for the custom fractionation of plasma. Connaught was unable to achieve a reasonable yield of factor VIII concentrate, and, as a consequence, large volumes of domestic plasma were wasted. This waste caused a chronic shortage of factor VIII concentrate during 1983 and 1984 (see Chapters 4 and 14).

When, in October 1984, the Red Cross concluded that heat-treated factor concentrate was safer than non-heat-treated concentrate because heat treatment could inactivate HIV, Connaught had not yet developed a means of manufacturing heat-treated concentrate. The conversion to heat-treated concentrate would result in the suspension of fractionation by Connaught. Because the Red Cross was bound by the decision of the provincial ministers of health to use Connaught as a fractionator, it felt it could not commit itself to the conversion directed by the Bureau of Biologics and begin to purchase heat-treated concentrates until it had received approval from the Canadian Blood Committee. The Red Cross therefore postponed the purchase of the safer concentrates until the approval was received (see Chapter 15).

If the provincial governments had decided fractionation issues on the basis of the safety and supply of blood products, rather than provincial industrial policy, the shortage of factor VIII concentrate could have been avoided and impediments to the speedy conversion to safer factor concentrates could have been removed.

Conclusions

I conclude that:

- The role of the operator of the blood supply system must be clearly defined.

- There should be a national blood supply system in which blood donations are treated as a national resource, and provincial boundaries are not barriers to the rational distribution of blood components.
- The operator of the blood supply system must be financially self-reliant.
- Subject to regulation, the operator of the blood supply system must be free to contract in a manner it believes will best serve the needs of the system.

Delay in adopting preventive measures

The slowness in taking appropriate measures to prevent the contamination of the blood supply was in large measure the result of the rejection, or at least the non-acceptance, of an important tenet in the philosophy of public health: action to reduce risk should not await scientific certainty. When there was reasonable evidence that serious infectious diseases could be transmitted by blood, the principal actors in the blood supply system in Canada refrained from taking essential preventive measures until causation had been proved with scientific certainty. The result was a national public health disaster.

The threshold for action

In light of the evidence that existed about transfusion-associated AIDS at the time, the measures that were introduced by the Red Cross in the years 1983 to 1985 to reduce this risk were not as prompt or as vigorous as they should have been. One of the reasons for this delay was that, despite persuasive evidence, the Red Cross did not fully accept that the risk of transfusion-associated AIDS existed until HIV had been discovered and had been shown to be the blood-borne pathogen that was causing AIDS (see Chapter 11).

Hepatitis was the most common and, until the emergence of AIDS, the most serious infectious disease transmitted through blood transfusion. Until 1989, there was no specific test for any of the forms of hepatitis that were known as non-A, non-B hepatitis. In 1986, two surrogate tests for non-A, non-B hepatitis were introduced in the United States to reduce the rate of post-transfusion hepatitis. Although, when used together, the tests were thought to reduce the incidence of non-A, non-B post-transfusion hepatitis by only 60 per cent, they were introduced because, in the United States, there were high rates of post-transfusion non-A, non-B hepatitis and because as many as 20 per cent of the persons infected were developing serious liver disease. During the years 1986 to 1989, the question of whether the two tests should be introduced in Canada was under active consideration. One of the reasons why the tests were not introduced is that, although data from U.S. studies showed that the introduction of the surrogate tests would probably reduce the rate of post-transfusion hepatitis significantly, they did not prove conclusively that the tests would have that effect. Instead of introducing the tests in Canada, a study was conducted to determine whether the tests would be effective in reducing the rate of post-transfusion hepatitis. Before the study

could be completed, a specific test to detect the presence of hepatitis C (the most prevalent form of post-transfusion non-A, non-B hepatitis) was introduced in 1990. The study demonstrated that, before the hepatitis C test was introduced in 1990, the introduction of the surrogate tests would have greatly reduced the occurrence of post-transfusion non-A, non-B hepatitis. Rather than awaiting full scientific proof, the Red Cross could and should have accepted the estimates of the efficacy of the surrogate tests (see Chapters 24 and 25).

If the Red Cross had introduced appropriate risk-reduction measures promptly, without awaiting full scientific proof, fewer persons would have been infected with HIV and hepatitis. In the words of a U.S. authority, public health has never clung to the principle that complete knowledge about a potential health hazard is a prerequisite for action.

Estimating and disclosing the risk of transfusion-associated AIDS

In 1983, the Red Cross estimated that the risk of a transfusion causing AIDS was one or two in one million. The Health Protection Branch accepted the estimate and repeated it. This minimal-risk estimate encouraged the continuing use of blood components and reinforced the belief that prompt and vigorous preventive action was not required. The Red Cross arrived at its estimate by dividing the number of transfused persons reported to have AIDS-defining signs and symptoms by the number of persons transfused. This method did not recognize that there was a latency period after infection during which infected persons did not have signs or symptoms of the disease; it did not take into account reports of transfusion-associated AIDS-related complex (that is, reports of transfused persons who had developed the early signs or symptoms of AIDS); it did not consider the natural progression of the epidemic; and it did not recognize that a new disease is usually underreported. As a result, the risk of transfusion-associated AIDS was underestimated. It is now estimated that the rate of infection in 1983 was approximately one in 10,000 per unit transfused, and most persons transfused received more than one unit (see Chapter 11).

When the Red Cross and the Health Protection Branch stated that the risk of acquiring AIDS from a transfusion was one or two in one million, they implied that the risk was insignificant. If either the Red Cross or the Health Protection Branch had taken all the relevant factors into account to estimate the risk, it would have recognized that the risk was not insignificant. The Red Cross might then have introduced appropriate risk-reduction measures expeditiously. A more accurate statement of the risk might have encouraged patients and their physicians to be more cautious about the transfusion of blood components. The expeditious introduction of risk-reduction measures and a reduced rate of transfusion could have saved many persons from infection with HIV.

Estimating and disclosing the risk of infusion-associated AIDS

Hemophiliacs routinely used factor concentrates made from large pools of plasma. In 1983, the Red Cross estimated that the risk that the infusion of factor concentrates caused AIDS was minimal, if it existed at all. Again, the Health Protection Branch accepted this view and repeated it. The minimal-risk estimate encouraged the continuing use of factor concentrates and reinforced the belief that prompt and vigorous preventive action was not required. The estimate was based on the fact that only a few hemophiliacs who used factor concentrates had developed AIDS. The same errors that had been made in estimating the risk of transfusion-associated AIDS were made for infusion-associated AIDS; the estimate did not take into account that there was a latency period, that there were reports of hemophiliacs who had developed the early signs and symptoms of AIDS, and the natural progression of the epidemic. More important, the estimate also ignored the magnified risk that is inherent in blood products, including the factor concentrates used by hemophiliacs, because they are made from pools of plasma from thousands of donors. As a result, the risk of infusion-related AIDS was greatly underestimated. It is now estimated that, in 1983, the risk of exposure to HIV-contaminated lots of custom-fractionated factor VIII concentrate was 65 or 94 per cent, depending on the manufacturer, for hemophiliacs infusing concentrate from only one lot; and that the risk of exposure was almost 100 per cent for hemophiliacs infusing concentrate from five or more lots (see Chapter 14).

By early 1983, there was persuasive epidemiological evidence that persons who infused factor concentrates were contracting AIDS from them. The U.S. manufacturers whose products were distributed by the Red Cross did not begin to include AIDS warnings in the product inserts of their concentrates made from U.S. plasma until late 1983: the Armour Pharmaceutical Company (Armour), in October 1983; the Cutter Biological Division of Miles Laboratories Inc. (Cutter), in January 1984; and the Hyland Therapeutics Division of Travenol Laboratories Inc. (Hyland), in March 1984. The only Canadian manufacturer, Connaught, never included a warning in the product inserts of its non-heat-treated concentrates, which were distributed until June 1985. Neither the Red Cross, through contractual requirements, nor the Bureau of Biologics, through the licensing process or regulatory directives, required that an AIDS warning be added to the product inserts. Such a warning might have alerted hemophiliacs and their physicians to the importance of assessing the respective risks of continuing or stopping therapy with factor concentrates every time they were used (see Chapter 14).

In December 1983, Cutter told the Red Cross that it was going to add an AIDS warning to the product inserts of concentrates made from U.S. plasma, and it asked the Red Cross whether it should add a warning to the product

inserts of the concentrates made from Canadian plasma. The Red Cross instructed Cutter not to add the warning. The product inserts for the concentrates made by Connaught from Canadian plasma also did not include an AIDS warning. As a result, until heat-treated concentrates were introduced in the summer of 1985, none of the concentrates made from Canadian plasma came with a warning (see Chapter 14).

After the Red Cross concluded in October 1984 that factor concentrates were safer if they were heat treated, it made public statements that minimized the risk of HIV infection from the use of non-heat-treated factor concentrates. A reader of the Red Cross's statements would reasonably have inferred that the conversion to heat-treated concentrates was far from urgent. These statements, in part, may explain why, after the conversion to heat-treated concentrates was completed, some hemophiliacs continued to use non-heat-treated concentrates even though they had been "withdrawn" (see Chapter 15).

If either the Red Cross or the Health Protection Branch had taken all the relevant factors into account to estimate the risk of infusion-associated AIDS, it would have realized that the use of factor concentrates carried a significant risk. If this fact had been recognized, the Red Cross and the Health Protection Branch could have made it known that the risk of this fatal disease was significant. That recognition would have encouraged hemophiliacs and their physicians to consider whether transfusion with cryoprecipitate or fresh frozen plasma was a safer form of therapy. One way in which information about the risk could have been made known was through warnings in the product inserts. If the manufacturers and the Red Cross had consistently referred to the risk of AIDS in factor concentrates beginning in early 1983, some hemophiliacs and their physicians might have switched to the far safer cryoprecipitate or fresh frozen plasma for factor-replacement therapy.

Estimating the risk of post-transfusion hepatitis

Until 1985, the data collected in the United States about the rate of post-transfusion hepatitis were much more comprehensive than those collected in Canada. It became known in 1985 that the rate of post-transfusion non-A, non-B hepatitis in Toronto was similar to the rate in many U.S. urban centres. When, during the 1980s, discussions took place among the Red Cross, the Health Protection Branch, and the Canadian Blood Committee about whether surrogate tests for non-A, non-B hepatitis should be introduced in Canada, neither the Red Cross nor the Health Protection Branch relied on the U.S. data to recommend their introduction, although it was reasonable to believe that the rate of post-transfusion hepatitis here was similar to that in the United States. Because of the proximity of the United States to Canada and the ease of mobility and migration between the two countries, significance should have been attached to the U.S. rate of transfusion-associated disease, and

appropriate precautions should have been taken in Canada. In the absence of evidence that the rate was different in Canada, there was no sufficient reason to refrain from relying on the U.S. data and introducing the surrogate tests (see Chapters 22, 23, 24, and 25). If the surrogate tests had been introduced, the rate of post-transfusion hepatitis would have been reduced substantially.

Surveillance of transfusion-associated and infusion-associated disease

The Red Cross and the Health Protection Branch recognized in the early 1970s that information about the extent and nature of post-transfusion hepatitis B was needed, and in the late 1970s that information about post-transfusion non-A, non-B hepatitis was needed. Despite this recognition, the necessary data were not collected until the mid-1980s. The inadequacy of the available data contributed to the lack of action to curb the spread of post-transfusion hepatitis (see Chapters 22, 24, and 25). If timely surveillance of post-transfusion hepatitis had been conducted, its magnitude could have been recognized and the necessary risk-reduction measures could have been introduced.

In 1986, there were published reports that hemophiliacs using heat-treated factor VIII concentrate had been infected by HIV, suggesting that one of the heat-treatment techniques used to inactivate HIV in concentrate might not have been completely effective. The product associated with the infections was H.T. Factorate, the heat-treated factor VIII concentrate made by Armour. Although the reports did not identify H.T. Factorate by name, they gave enough information to identify it. The Bureau of Biologics did not recognize the identity of the manufacturer from the reports, and did not seek additional information to do so. It therefore did not demand that H.T. Factorate be recalled or withdrawn. Nor did the Red Cross implement a recall or withdrawal. In October 1986, when Armour withdrew H.T. Factorate from the United Kingdom after additional HIV infections associated with this product occurred there, the bureau still did not require the product to be recalled or withdrawn. Moreover, it interfered with the implementation of the Red Cross's plan to withdraw H.T. Factorate. In 1987, eight Canadian hemophiliacs who used H.T. Factorate, and who had previously been HIV negative, seroconverted (see Chapter 16).

Provincial public health services

By the 1980s, immunization and antibiotic treatment had significantly reduced the effects of most infectious diseases. The provincial public health services therefore allotted a decreasing amount of attention to the prevention of the spread of infectious diseases. Moreover, as the effects of most infectious diseases declined, the financial support for public health services, and an appreciation of their value, also declined (see Chapter 7).

Conclusions

I conclude that:

- The operator of the blood supply system and the Health Protection Branch must ensure that they remain informed about the spread of blood-borne diseases and, more specifically, about the occurrence of transfusion- and infusion-associated diseases, both in Canada and abroad; they must estimate the risk of transfusion- and infusion-associated diseases by taking into account the available epidemiological evidence and the accumulated knowledge about the course of the disease; they must design and implement strategies to reduce the risk of harm occurring through the use of blood components and blood products whenever it is known that a risk of mortality or significant morbidity exists; and they must communicate information about the risks that are known or believed to exist.
- The operator of the blood supply system and the Health Protection Branch must not wait for scientific certainty about the spread of a transfusion- or infusion-associated disease and the effectiveness of particular risk-reduction measures before they act to reduce risks.
- The operator of the blood supply system and the Health Protection Branch must ensure that all available information about risks known to the fractionators is obtained, and they should then communicate that information.
- The provincial public health authorities must monitor the occurrence of transfusion- and infusion-associated disease in order to encourage and help the operator and the regulator of the blood supply system to introduce timely and effective risk-reduction measures.

Failure to employ independent judgment

In the blood supply system, a decision to reduce a risk can come from the manufacturer of a blood product, the operator of the system, or the regulator of the system. If manufacturers, the operator, and the regulator do not exercise their independent judgment, opportunities to improve the safety of the blood supply are lost.

The introduction of risk-reduction measures

As previously mentioned, in the autumn of 1984 the Red Cross began to consider the introduction of a test to detect the antibody to HIV. At the time, the collection of whole blood was not regulated by the Bureau of Biologics. The Red Cross was left to decide whether the test should be introduced. Rather than make the decision, the Red Cross effectively delegated it to the National Advisory Committee on AIDS, an advisory committee that met infrequently and was ill-suited to make a timely decision. The Red Cross thought that a decision by a group that was not part of the blood supply system would carry more weight with the Canadian Blood Committee and would increase the chances for budget approval for the test (see Chapter 12).

In November 1984, the bureau directed that non-heat-treated concentrates be replaced by heat-treated concentrates. The Canadian Blood Committee held a consensus conference almost a month later. The chair of the conference stated that the purpose of the meeting was to determine how to carry out the bureau's directive "with due consideration given wherever possible to the particular interests of those represented here today," the interested parties being, he said, hemophiliacs, their physicians, the blood transfusion service, the domestic fractionators, taxpayers, and the committee. The conference failed to come to a clear conclusion; the representatives of the interested parties could not arrive at an agreement about the way in which the conversion should take place (see Chapter 15).

During the 1980s, the bureau did not decide independently whether to use its authority to require that measures be taken to reduce the risk of non-A, non-B hepatitis. Instead, it relied heavily on information given to it by the Red Cross and, in effect, made itself dependent on an organization whose activities it was supposed to regulate (see Chapters 23, 24, and 25). The relationship between a regulator and the regulated is often courteous, but it must never become one in which the regulator loses sight of the principle that it regulates only in the public interest and not in the interest of the regulated. The regulator must develop its own expertise and not rely on that of the regulated.

Removing potentially unsafe products from distribution

In January 1985, Connaught identified three lots of factor VIII concentrate that had been made from plasma pools that contained plasma from persons who had developed AIDS. Two of the contaminated lots had expired, but one had not. Connaught told the Red Cross and the Bureau of Biologics about the contaminated lots. Consultation occurred among the three organizations, but none of them took steps to see that the lots were withdrawn or recalled (see Chapter 14).

In October 1986, the Red Cross thought that Armour's H.T. Factorate should be withdrawn. It did so after forming the belief that the heat-treatment technique used by Armour was not completely effective in inactivating HIV. The bureau then wrote to the Red Cross and "advised" it to continue the distribution of the product. The advice was intended and construed as a regulatory directive, and it caused the Red Cross to refrain from exercising its independent discretion to withdraw H.T. Factorate. The Red Cross continued the distribution of H.T. Factorate and eight persons were later infected with HIV through the use of that product (see Chapter 16).

If any of the three organizations had made its own decision about the contaminated Connaught lots, they would have been recalled or withdrawn. If the bureau had not interfered with the Red Cross's decision that H.T. Factorate should be withdrawn, the distribution of that product would have been stopped.

Conclusions

I conclude that:

- The Health Protection Branch must set standards for the blood supply system.
- The Health Protection Branch must at all times act at arm's length from the organizations it regulates.
- The operator of the blood supply system must not only meet the standards set by the Health Protection Branch but exceed those standards whenever it believes that safety requires it to do so.
- The Health Protection Branch and the operator must not delegate their functions to others, nor rely on consensus decision making as a substitute for independent judgment.
- Manufacturers, the operator, and the Health Protection Branch must act independently to decide whether a risk-reduction measure should be instituted; and the regulator should never interfere with the decision of a manufacturer or the operator to take a risk-reduction measure that exceeds its regulatory standards.

Shortcomings of the operator of the blood supply system

The Red Cross, as the operator of the blood supply system during the 1980s, did not promptly introduce appropriate risk-reduction measures to enhance the safety of the blood supply. The internal structure of the Red Cross was not conducive to sound and timely decision making. The Red Cross adhered to principles that were not related to the blood supply system, and its board of governors supervised many programs that were not related to the blood program. The Red Cross's blood transfusion service and its blood donor recruitment each had partial management of the blood program. The national office of the transfusion service did not create and enforce comprehensive national risk-reduction measures, nor did it allow local centres to exceed the national safety standards that did exist. There were no formal links to the provincial public health authorities.

Principles not related to the blood supply system

The Red Cross's principal AIDS-risk-reduction measure was voluntary self-exclusion on the part of members of groups at high risk of contracting AIDS. The measure could work only if donors knew the groups that were at high risk. In March 1983, the Red Cross issued a press release that identified the high-risk groups and asked their members not to donate. The press release led to allegations that the Red Cross was acting in a discriminatory manner. Although the allegations were wrong, the Red Cross was particularly sensitive to them because two of the principles of the international Red Cross to which the

Canadian Red Cross adhered were impartiality and neutrality, both of which implied that there should be no discrimination against individuals. Partly because of this sensitivity, the Red Cross did not adequately educate the public about the groups at high risk of contracting AIDS (see Chapters 3 and 11).

The board of governors

The Red Cross operated many unrelated programs, only one of which was the blood program. The board of governors, whose members were volunteers, was responsible for governing all the programs. Except for two medical experts, the board members had no expertise in blood banking. The lay members did not acquire the knowledge necessary to govern the blood program.

Divided control of the blood program

The easiest way to ensure that donors were aware of the high-risk groups and the request that members of these groups not donate was to give all prospective donors the necessary information on their arrival at the blood donor clinics. Yet it was May 1984, more than a year after the Red Cross adopted the policy of voluntary self-exclusion, before the blood transfusion service began to distribute a pamphlet that contained this information. The process of creating the pamphlet was slow and bureaucratic. One of the reasons for the delay was that the transfusion service did not fully control the Red Cross's blood program. The Red Cross's blood donor recruitment, which had partial control of the program and was operated by volunteers, had views that had to be taken into account in creating the pamphlet (see Chapter 11). If the transfusion service had fully controlled the blood program, the AIDS-information pamphlet could have been introduced more quickly.

National standards

When the Red Cross issued the press release in March 1983 that identified the groups at high risk of contracting AIDS and asked their members not to donate, one of the groups identified was "sexually-active homosexual and bisexual men with multiple partners." The national office of the blood transfusion service asked its local medical directors to communicate with members of local gay organizations to seek their assistance in reinforcing the message of the press release. Some local medical directors made significant efforts to carry out this request; others made some efforts; and yet others made no efforts. The national office did not attempt to determine what efforts had been made or their success (see Chapter 11).

The distribution of the AIDS-information pamphlet to prospective donors, beginning in May 1984, was the most important AIDS-risk-reduction measure taken by the Red Cross until the test for the HIV antibody was introduced in the autumn of 1985. In the summer of 1984, the national office received reports from blood centres that some donors were not reading the

pamphlet thoroughly and that others were ignoring it completely. Despite these reports, the national office did not take adequate steps to ensure that the pamphlets were being used properly by all the centres (see Chapter 11).

Local autonomy

In January 1983, the national office of the blood transfusion service proposed that donors be questioned to discover whether they had any of the signs or symptoms of AIDS. Questioning was introduced at one of the local blood centres. Although the proposal to introduce questioning later received the unanimous endorsement of the medical directors of the blood centres, the national office decided against the questioning of donors and instructed its medical directors not to do so. This instruction caused the one centre that had introduced questioning to stop the practice (see Chapter 11).

In July 1989, the medical director of the Montreal blood centre suggested to the national office of the transfusion service that a surrogate test for non-A, non-B hepatitis be introduced at her centre, even if it was not going to be introduced elsewhere. She made the suggestion because there was a high prevalence of hepatitis in Montreal. Her suggestion was not acted upon (see Chapter 24).

Links to public health

The Red Cross did not carry out the searches known as trace-backs (identifying the donations that caused the HIV infection of recipients of blood components) and look-backs (identifying the recipients of blood components from donors who were HIV positive) as quickly or as fully as possible. Many of the searches carried out by the Red Cross either failed or were delayed because necessary records, both at the Red Cross and at hospitals, had not been retained or were in a form that made the searches difficult. Almost without exception, the provincial public health authorities did not encourage or facilitate the searches. Some searches never took place, some were delayed, and the results of others were not communicated promptly (see Chapters 13 and 20).

The general announcements made by the Red Cross about transfused persons being tested to determine their HIV status emphasized the supposed safety of the blood supply and must have discouraged some persons from being tested. Effective general announcements by provincial health authorities were not made until 1993 (see Chapter 13).

Many persons who were given HIV-contaminated components and who became HIV positive remained unaware of their condition, often for years. Because of the tardiness and incompleteness of the searches that were done and the ineffectiveness of the general announcements, some persons infected with HIV through transfusion were denied the opportunity to prevent the infection of their sexual partners and newborn children, and many sexual partners and children were unnecessarily infected. The persons infected through transfusion were also denied the opportunity of seeking early treatment for

themselves. If there had been formal links between the Red Cross and the provincial public health authorities, earlier and more effective means of notifying potentially infected persons could have been designed and implemented.

Conclusions

I conclude that:

- The operator of the blood system must be dedicated exclusively to the blood supply system.
- Blood donor recruitment is an integral part of the blood program, and it must be operated by the same persons who operate the rest of the blood program.
- The national office of the operator must create and enforce national standards, but it should permit its local centres to exceed them.
- Formal links between the operator and the provincial public health authorities must be established.
- The operator and the hospitals must retain in readily useable form the records that are needed to conduct trace-backs and look-backs.

Shortcomings of the regulator of the blood supply system

The Bureau of Biologics, part of the Health Protection Branch of the Department of National Health and Welfare, regulated the sale and distribution of blood products. With the exception of the directive of November 1984 that required the conversion to heat-treated factor concentrates as soon as possible, the bureau did not require that the manufacturers of blood products introduce AIDS-risk-reduction measures for blood products. In 1978, the bureau began to regulate the collection of source plasma through plasmapheresis. It did not begin to regulate the collection of whole blood until 1989. The bureau did not use its direct regulatory authority over plasmapheresis to require the Red Cross to introduce measures to reduce the risks from AIDS or from non-A, non-B hepatitis in source plasma. Nor did the bureau use its direct regulatory authority over blood products to require the manufacturers to use plasma that came only from those plasma and blood centres that used measures to reduce the risks.

Resources to perform regulatory functions

From the time of its creation in 1974, the Bureau of Biologics lacked the resources necessary to carry out all its regulatory functions. Because of the inadequacy of its resources, the bureau did not perform some of the functions it believed were appropriate for a regulator of blood products. For example, it did not carry out inspections of the Red Cross's plasmapheresis centres or the premises of the manufacturers of blood products as regularly or as frequently as it believed proper (see Chapter 6).

During 1983 and 1984, Connaught made factor VIII concentrate from U.S. plasma. Some of this plasma came from the Irwin Memorial Blood Bank in San Francisco. Plasma from San Francisco carried one of the highest risks of HIV contamination, and by early 1983 the U.S. fractionators had stopped making factor concentrates from it. Each year, Connaught gave a list of its plasma sources to the bureau; and, for every lot of blood product that was distributed, Connaught gave a list of the plasma sources for the lot to the bureau. In both ways, the bureau was told by Connaught that it was making blood products from plasma from San Francisco. This information was never reviewed by the bureau, which, although it had the information on file, remained effectively unaware of Connaught's plasma sources (see Chapter 14).

If the bureau had been given adequate resources, it would have been able to carry out regular inspections of both the Red Cross's plasmapheresis centres and the premises of the manufacturers of blood products. It also would have been able to consider the contents of the filings made by the manufacturers of blood products, rather than simply filing the information without consideration, and to decide whether that information disclosed that the manufacturers' products were "not unsafe."

Resources to extend regulatory functions

The inadequacies of the resources not only limited the ability of the Bureau of Biologics to perform the regulatory functions that were directly within its authority but also limited the bureau's ability to extend its authority. Financial constraints played a role in delaying, until 1989, the extension of regulatory control over the blood transfusion service's entire operation. As a result, during most of the period of the contamination of the blood supply, the Red Cross was the only pharmaceutical corporation in Canada that was in effect unregulated (see Chapter 6).

Inaction at the Bureau of Biologics

Even though the collection of whole blood fell outside the scope of its regulatory authority until 1989, the Bureau of Biologics could have required that measures be taken to enhance the safety of both the plasma from which blood products were made and, incidentally, the safety of the components used for transfusion. The bureau could have required the Red Cross to introduce in its plasmapheresis program appropriate measures to reduce the risk of both AIDS and non-A, non-B hepatitis. Moreover, the bureau could have required the manufacturers of blood products to use only plasma that came from blood and plasma centres that had introduced appropriate measures to reduce the risk of AIDS and of non-A, non-B hepatitis. The bureau passively sought compliance with its existing regulations rather than actively determining what new risk-reduction measures were needed to prevent unnecessary cases of AIDS and hepatitis, and requiring that the measures be implemented

(see Chapters 6, 11, 12, 14, 24, and 25). If the bureau had required the manufacturers of blood products to use only plasma that came from blood and plasma centres that had introduced appropriate risk-reduction measures, the Red Cross would have been compelled either to introduce such measures for whole-blood donations or to halt the shipment of the plasma that had been recovered from whole-blood donations to the manufacturers. If the Red Cross had been compelled to introduce the measures, not only would the risk of HIV and hepatitis in blood products have been reduced but many cases of transfusion-associated HIV and post-transfusion hepatitis from blood components would have been prevented.

Conclusions

I conclude that:

- The federal government must give the Bureau of Biologics the resources it needs to carry out all its regulatory functions.
- With the appearance of a new risk to the safety of the blood supply for which the current regulatory authority is not adequate, the Health Protection Branch must expeditiously seek the necessary appropriate authority.

The Need for Reform of the Current System

The first part of this Report examines the Canadian blood system as it existed in the 1980s. The institutions that administered the blood supply then suffered from serious shortcomings in the way they functioned internally and in the way they communicated and worked with one another. These shortcomings adversely affected their response to the contamination of the blood supply by the viruses causing AIDS and hepatitis C.

In the late 1980s and early and mid-1990s, as the extent of the infection through the blood supply came to be recognized, attempts were made to reform the blood system. Changes were made within the institutions of the blood system and in the relationships among them. Changes were also made to the principles governing the blood program. Some of these changes have been significant. This chapter reviews several of the important changes that have been made to the blood system since the 1980s, and examines whether the reforms have remedied important deficiencies that contributed to the contamination of the blood supply at that time.

The principles governing the blood supply in the 1990s

The efforts to develop a national blood policy in the 1970s and 1980s are described elsewhere in the Report (see Chapter 5). By 1989, the endeavour had been abandoned. In the absence of a national blood policy, all that existed were a few general principles.

In 1979, the federal and provincial ministers of health affirmed three principles governing the blood system. They were:

- (i) protection of the system of voluntary donation;
- (ii) national self-sufficiency in blood and blood products;
- (iii) gratuity of blood products to recipients.

A fourth principle, added in the early 1980s, recognized the desirability of not-for-profit domestic fractionation of blood products. In 1989, the four principles were expanded by the ministers of health to read:

- (i) The voluntary system should be maintained and protected.
- (ii) National self-sufficiency in blood and plasma collections should be encouraged.
- (iii) Adequacy and security of supply of all needed blood components and plasma fractions for Canadians should be encouraged.
- (iv) Safety of all blood, components and plasma fractions should be paramount.
- (v) Gratuity of all blood, components and plasma fractions to recipients within the insured health services of Canada should be maintained.
- (vi) A cost-effective and cost-efficient blood system for Canadians should be encouraged.
- (vii) A national blood program should be maintained.

These principles did little to answer the difficult policy issues that had been present in the blood system since the 1980s and earlier. In particular, they did not adequately address the issue of Canadian self-sufficiency in blood and blood products. They did not say whether self-sufficiency was intended to include the ability to manufacture domestically all the blood products needed in Canada. Although the second principle implied that self-sufficiency referred only to the collection of Canadian plasma, the third principle, by supporting “security of supply,” could be taken to mean that Canada should also be self-sufficient in the manufacture of fractionated products. This uncertainty contributed to the controversy over a plan by the Canadian Red Cross Society (Red Cross) to build a fractionation plant.

The principles also did little to address the fundamental tension between the need for safety and the need for cost-efficiency and cost-effectiveness. The potential for conflict was realized in 1995 after it was learned that some Canadian blood products had been prepared with the plasma from a donor found to have Creutzfeldt-Jakob disease and that there was a theoretical possibility that the disease could be transmitted through blood products. The subsequent withdrawal of suspect blood products, and the controversy over the fractionation plant, are discussed below.

The principles enunciated in 1989, moreover, did nothing to clarify the position of the Red Cross in the Canadian blood system and did nothing to set out the boundaries of the relationship between the Red Cross, which operated the blood system, and the provincial governments, which paid for the blood service.

Reforms to the blood system in the 1990s

In 1991 the Canadian Blood Committee, which had administered the funding of the Canadian blood program during the 1980s on behalf of the provinces and territories, was replaced by a new entity, the Canadian Blood Agency. The Canadian Blood Committee was a committee of federal, provincial, and territorial representatives that was not independent of governments and that had no corporate existence of its own. It could not enter into contracts with the Red Cross or other suppliers, borrow money, or make decisions about matters involving substantial amounts of money that would bind the governments it represented. As a result, major decisions, including the approval of annual budgets for the blood program and the funding of new safety measures such as the testing of blood donations for HIV antibody, required the approval of every provincial and territorial government before they could be carried out. Although the committee was primarily concerned with the funding of the blood program, and the Red Cross was primarily concerned with operating the system, it was often unclear where the authority of one organization ended and the other began. The committee's working relationship with the Red Cross was often hampered by ill will and miscommunication on both sides.

The Canadian Blood Agency is a federal not-for-profit corporation with the power to enter contracts and to borrow money. It is the instrument through which the provinces and territories fund the blood program. It has among its objects:

To direct, coordinate and finance the various elements of the Canadian Blood System requiring national direction in accordance with the principles established by the Honourable Ministers of Health of the Provinces and Territories of Canada for the therapeutic use of human blood, blood products or their substitutes.

The agency possesses a line of credit of \$3.5 million, which it can use to pay for emergency measures without having to obtain prior authorization from the provinces and territories.

The Red Cross has also undergone major changes in its structure. During the 1980s, blood donor recruitment and blood collection were two separate programs. Blood donor recruitment was carried out through the provincial divisions by volunteers; the blood transfusion service was operated by paid employees, both regionally and at the national office of the Red Cross. Authority over the two programs converged only at the national level, in the office of the secretary general. Not surprisingly, the operation of the programs was not always well coordinated. In particular, the recruitment procedures used by the blood donor recruitment program were not always responsive

to, and sometimes incompatible with, the policies of the blood transfusion service for donor screening. In 1985, the Red Cross began a process, completed in the early 1990s, of amalgamating the two programs, placing its recruitment operations under the authority of the blood transfusion service.

During the early 1990s, and throughout the course of the Inquiry, the Red Cross also fundamentally changed the way the blood program operated. Since its beginning in 1947, the blood program had been conducted as a medical service, as in a hospital or a clinic, and managed by physicians. In the early 1990s, the Red Cross began to move to a manufacturing model. By late 1996, most physicians in management positions had been replaced by professional managers.

In the 1990s, the Red Cross also began developing and implementing standard operating procedures and good manufacturing practices for the blood program. In my Interim Report, I recommended that these measures, which are intended to ensure a product of standard quality and minimum risk, be implemented.

The effectiveness of the reforms

It soon became apparent that the creation of the Canadian Blood Agency had not remedied several of the problems associated with its predecessor. The lines of accountability and authority between the Red Cross and the Canadian Blood Agency were still unclear, and the difficulties in the relationship between the two organizations were not resolved. One reason was the lack of a written agreement delineating the roles of the organizations. Although the Red Cross was clearly the operator of the blood system, the Canadian Blood Agency was given the power to direct the blood system. The Red Cross saw this power as potentially intrusive and a threat to its independence from government – one of the seven guiding principles of all Red Cross societies. The potential for conflict was apparent at the outset of the hearings during the testimony of the then secretary general of the Red Cross, Douglas Lindores, and the then executive director of the Canadian Blood Agency, William Dobson. The Red Cross took the position that, although the ministers of health were the members of the Canadian Blood Agency, there had been no formal delegation of authority from the provinces and territories to the agency. As a result, Mr Lindores said, “we [the Red Cross] will do the best we can to cooperate with the Canadian Blood Agency, but ... we do not consider ourselves bound by directives received from the Canadian Blood Agency.”

Until the fundamental issue of the nature of the authority of the Canadian Blood Agency with respect to the Red Cross was resolved, the smooth functioning of the blood system was impaired. For example, the issue of liability insurance for the Red Cross had been outstanding since the end of 1985 when the Red Cross ceased to have public liability insurance. The Red Cross obtained

liability insurance in April 1988 worth a total of \$10 million for all claims. The policy did not cover the period from 1 January 1986 to 31 March 1988, and does not cover claims made after the expiration of the policy in 1992. Soon after it was formed, the Canadian Blood Agency proposed to the Red Cross that a joint self-insurance fund be created that would administer claims against both parties and create a reserve for future claims. The Red Cross refused to cooperate with the agency in this matter until other disagreements about the roles and responsibilities of the two organizations were resolved. It chose, instead, beginning in April 1992, to become a self-insurer, and by the autumn of 1996 had accumulated a reserve fund that represents only a small fraction of the Red Cross's potential liability in outstanding claims from persons infected with hepatitis C from blood transfusions between 1986 and 1992.

In 1994, I appointed a committee (the safety audit committee). The members of the committee and those from whom they received assistance were experts from the United States, England, Scotland, Australia, Jamaica, and Canada who assisted in my examination of the current safety of the blood system for the purposes of the Interim Report. The committee studied the individual organizations and institutions that constituted the blood system and the relationships that existed among them. It found that structural problems interfered with working relationships and blurred responsibilities within the system. Its report reads, in part:

The committee found evidence of major problems with the current governance. Neither the structure nor process clearly focuses responsibilities and relationships. Moreover, the leadership of the CBA [Canadian Blood Agency] and CRCS [Canadian Red Cross Society] are adversarial ...

- No legislation, contract or other document clearly assigns responsibility for the management of the Canadian blood system. Responsibility and authority are unclear and diffuse.
- The CBA and CRCS do not agree on the interpretation of two key principles for the Canadian blood system as established by the territorial and provincial Ministers of Health in 1989.
- The planning, priority-setting and funding functions of the Canadian blood system are diffuse and poorly developed.
- The adversarial relationship between CBA and CRCS hinders communications and problem solving.
- The CRCS and CBA need to foster public awareness jointly and to maintain confidence of the Canadian people in the safety of the blood supply.
- Little evidence could be found that the system has developed a coherent crisis management strategy.

The committee went on to make the following recommendation:

The Canadian blood system must be restructured to eliminate conflicts among the participants and at the same time clearly define responsibilities for the safety of the blood supply and the operations of the blood subsystem.

It gave the following explanation for the recommendation:

Safety of the Canadian blood system is impeded by its structure. Relationships between the participants – the CBA, the CRCS and the BoB [Bureau of Biologics] – remain ill defined, and decision making regarding safety of the system is fragmented. The funding authority (CBA) is separated from the operations (CRCS), and the role of the BoB in protecting the safety of blood is incompletely developed. As a result, accountability and responsibility for system improvement have been diffused. The CBA appears to have been created primarily as a financial gatekeeper to control costs and the CRCS has historically been autonomous. As a result, the CRCS and the CBA are openly antagonistic. The committee found several examples where these governance difficulties adversely affected decisions about safety.

With respect to the Red Cross's internal changes, the safety audit committee found that, although the dedication of the staff at the blood centres was high, the rapid changes were causing considerable stress that could, if not relieved, jeopardize the safety of the blood supply:

There are two major sources of stress for the personnel working in the blood centres. The first is the loss of public confidence in the system. The second is the rapid rate of change imposed on the system. Although rapid change is the rule rather than the exception in every domain these days, the Canadian blood system is under more pressure than most because it has fallen behind in key areas such as the implementation of GMPs [good manufacturing practices] and integrated information systems. Although staff morale appeared satisfactory, staff were quick to point out concerns over the rate of change. As the pressure to catch up increases (i.e., to meet USFDA [U.S. Food and Drug Administration] requirements and implement GMPs and a new computer system) this problem will get worse before it gets better. The recommendations of this study will inevitably add to that pressure.

The committee reported that the staff members of the blood transfusion service “were working diligently at upgrading the current operations to state-of-the-art manufacturing practices,” but that there were major impediments to progress in these efforts. It found that the Red Cross “had fallen behind in this area and it cannot catch up without allowing a minimum of

time for people to absorb change. The implementation of quality processes based on [good manufacturing practices] requires profound changes in the working culture that cannot be accelerated beyond a certain point, even if resources are unlimited.” It then listed the following impediments to the process of organizational change:

- 1 *Lack of clear objectives and standards.* Staff were unclear as to which standards they should follow: BoB, National Office, or USFDA. The reports contain evidence of inconsistencies that led to confusion.
- 2 *National Office.* SOPs [standard operating procedures], directives and policy setting. A particular concern noted was “unreasonable demands for rapid, excessive and, at times, ill-conceived change.” At various points the auditors [who assisted the safety audit committee] recorded indecision, delay and a complete lack of communication from the National Office. As the auditors found differences in the systems at the three sites visited, they questioned the policy that controlling operations through National SOPs would produce a generic system.
- 3 *GMPs.* Concern was expressed that the overall comprehension and implementation of systems were in very early stages. Among the issues cited were the insufficient training, knowledge, responsibility and authority for the QA [quality assurance] specialists to function as QA managers in a GMP environment. Of particular concern was the plan to change the reporting lines from centre directed to National Office. They also thought there was too much emphasis on “inspecting out” errors and too little on prevention, i.e., that quality was not being designed into the system. They concluded that this indicates that error management systems need improvement.
- 4 *Computer systems.* The lack of an effective, fully integrated computer system was a major concern ...
- 5 *Finance.* Overall, there was concern that lack of money was preventing GMP compliance. Several examples are ... outdated equipment, poor facilities and inadequate cleaning and maintenance.

In its discussion of the lack of integrated data management systems, the safety audit committee said:

As the processes involved with the blood system become more complex and steps are added to promote safety, the opportunity for human error increases. At present, various steps are checked and vital processes are double-checked by different staff to detect errors. This system is laborious and not foolproof. There is potential for error in such important processes as duplicate record checking, recording transmissible disease testing results, labelling and product release. Duplicate records on donors are of particular concern. Such incidents have been described in the accident

and error reports to the Bureau of Biologics. Lack of a national integrated donor database and reliance on manual checks of donor status can result in failure to detect previously deferred donors. This adds unnecessarily to the residual risk in the blood supply.

The only data management system currently being used on a national basis is BLIS (Blood Information System). The CRCS recognizes the severe limitations of this.

I accept this analysis and agree with these recommendations of the safety audit committee.

The meaning of self-sufficiency and the proposal for a fractionation plant

The Red Cross and the Canadian Blood Agency interpreted the governing principle of self-sufficiency in the blood system differently. They disagreed about whether the term referred only to the amount of blood and plasma that had to be collected to satisfy domestic requirements for blood components and blood products, or whether it also referred to the manufacture in Canada of all blood products required to meet Canadian needs.

In 1992, soon after its creation, the Canadian Blood Agency invited several organizations to submit proposals to build a domestic fractionation plant. The two most important goals it would consider in evaluating proposals were to be “access to sufficient quantities of the full range of high quality plasma products/substitutes at the lowest possible price” and “achievement of self-sufficiency.” The Red Cross was not originally invited to make a submission, but it asked and was allowed to do so. The agency received five submissions in December 1992. Three of them did not include the building of a fractionation plant, but were only to supply blood products and to custom fractionate Canadian plasma. The other two proposals, one of which was submitted by the Red Cross in association with Bayer Corporation (Bayer), were for the building of a plant and the supply of blood products. The Red Cross’s proposal was the only one in the agency’s opinion that warranted further study. The cost of the other proposal for a fractionation plant was too high.

The Red Cross proposed building a plant that could process approximately 800,000 litres of plasma per year, later to be increased to 1.2 million litres. The initial budget was for approximately \$150 million, none of which was to come from governments; the plant was to be privately financed. The technology and expertise for building the plant were to be supplied by Bayer, which, in return, was given the right to use at least half the fractionation capacity. It was projected that Canadian needs could be met by processing approximately 400,000 litres of plasma in the first year of operation. Bayer was not required to contribute or guarantee any money to build the plant, which was to be owned by a not-for-profit corporation whose only shareholder was the Red Cross. The plant was to begin operating in 1998–9.

The Canadian Blood Agency asked its fractionation committee to review the Red Cross's proposal. The fractionation committee recognized several difficulties. The Red Cross was inexperienced in managing an industrial project; Bayer had no financial stake in the project and therefore did not have a sufficient incentive to ensure that it would be successful; by relying on the technology of one manufacturer, the plant would be restricted in its ability to produce new or improved products; and, if the capital budget was exceeded, the governments would be pressured to "bail out" the facility. The Canadian Blood Agency reviewed and rejected the Red Cross proposal in May 1993. It gave as its reasons:

- The Red Cross proposed that the agency enter into contracts for the purchase of blood products for at least ten years after the beginning of the plant's operations. Such long-term obligations would reduce the agency's flexibility in the choice of products that might be safer or more effective than those produced by the Red Cross.
- Alternative therapeutic products were being developed by recombinant DNA techniques. As a result, a plant that focused solely on plasma-derived products might be obsolete by the time it was built, or soon afterwards.
- The provinces and territories were not in a position to assume the significant financial risks associated with the construction and operation of a plant.

At a meeting in September 1993, the federal, provincial, and territorial ministers of health agreed that several issues relating to the blood system required further study, among them the question of a Canadian fractionation plant. They appointed a deputy ministers' task force to study the matters. In October 1993, the Red Cross announced that it was proceeding with a fractionation plant in partnership with Bayer and that it was to be located in Nova Scotia.

The deputy ministers' task force recommended that the issue of a fractionation plant be examined by a "blue ribbon panel." The ministers endorsed the recommendation and the panel was created in April 1994. It was asked to report on

- the need for a plasma fractionation plant in Canada over the next 15 years
- the management, technological and financial risks and benefits of the Red Cross/[Bayer] fractionation plant proposal and agreement
- the process followed by the Canadian Red Cross Society in the selection of a site for their proposed fractionation plant
- plans to make Canada self-sufficient in plasma.

The panel reported in June 1994. For the most part it was supportive of the Red Cross's proposal, but it recommended changes to the structure of the corporation and the development and management of the project.

Over the next three years, planning for the fractionation plant continued, although construction was not started. The Canadian Blood Agency did not support the project. Although a “master agreement” between the participants in the blood program, executed in April 1995, provided that the Red Cross would be the “preferred supplier” of blood products to the Canadian Blood Agency, it stated that the preference was premised on the Red Cross’s being “cost-efficient and cost-effective.” The agency’s position was summarized in the testimony of Philip Dresch, its interim executive director, in December 1995. When asked if the agency was willing to cooperate with the Red Cross with respect to the fractionation plant, he replied:

I do not know if I would go as far as to say we are willing to cooperate to make it work. I think we will work within the spirit of the master agreement. We will develop a supply agreement and within the context of those two agreements we will ensure that we retain our purchasing decision role and that an adequate, secure, supply of products is available for Canada.

By the autumn of 1995, the budget for the fractionation plant had increased from approximately \$150 million to at least \$300 million. By the spring of 1997, as the role of the Red Cross in the blood system became increasingly uncertain, it was clear that sufficient financing could not be secured. The deadlines set out in the contract with Bayer had not been met, and Bayer was therefore released from its commitments. The Red Cross had borrowed approximately \$30 million to pay for the planning and development of the project.

The master agreement

In April 1995, the Red Cross, the Canadian Blood Agency, and the governments of the provinces and territories entered into a master agreement that was intended to clarify their respective roles, rights, and obligations with respect to the national blood supply program. The obligation of the provinces and territories, according to the agreement, was to provide the necessary funds to the Canadian Blood Agency, in accordance with budgets approved by the agency, in order for it to “satisfy all obligations undertaken by it.” The principal roles and functions of the Canadian Blood Agency were to devise policy for the blood program on behalf of the ministers of health of the provinces and territories, to determine the “collective Canadian need for blood,” to decide the type and volume of blood to be acquired, and to pay for the blood to meet the collective Canadian need. The principal roles and obligations of the Red Cross were expressed as follows:

The Society shall maintain in a proactive manner the safety, efficiency and effectiveness of its products and services for the national blood supply program, and without limiting the generality of the foregoing the Society shall take such steps as are necessary to comply with all Health Canada and other relevant regulatory requirements.

The master agreement did not define what constituted a matter of policy within the authority of the Canadian Blood Agency, as opposed to a matter of management affecting safety within the authority of the Red Cross. A matter of policy, according to Mr Dresch, might simply be an operational matter that “carries a large price tag.”

Immediately after the completion of the master agreement, a disagreement arose between the Red Cross and the Canadian Blood Agency about the interpretation of the following clauses:

7.04: Provided it is cost-efficient and cost-effective, the CBA [Canadian Blood Agency] shall use every reasonable effort to select the [Red Cross] Society to be the supplier of fractionated products in preference to other sources.

7.05: In the event that the CBA does not select the Society to be the supplier of a fractionated product made from Canadian plasma, the Society, and the CBA, shall supply the Canadian plasma to the selected supplier chosen through a competitive tendering process managed by the CBA.

The Canadian Blood Agency interpreted these clauses to mean that the agency could obtain blood and blood products from suppliers other than the Red Cross if it believed that the Red Cross was not performing its functions properly. The position of the Red Cross was that the agreement gave the agency the power to purchase blood or blood products from an organization other than the Red Cross only after the fractionation plant was completed and operating. Ultimately, the agency decided that the two clauses would not come into effect until the fractionation plant was completed.

According to the master agreement, the Canadian Blood Agency was required to “set policies in accordance with the Ministerial Principles for the national blood supply program,” and the Red Cross was required to establish its operational policies within those of the national blood supply program and in keeping with its responsibilities to “comply with regulatory and other reasonable safety measures.” The master agreement incorporated the seven principles governing the blood system that had been affirmed in 1989, along with interpretive descriptions that had been added to the principles and approved by the ministers of health. The expanded principles read as follows:

1. Voluntary donations should be maintained and protected.

This principle refers to the collection of whole blood, plasma, platelets and white cell products, from unpaid donors which are used directly, and after further processing for therapeutic purposes. In only exceptional circumstances do donors receive payment for the time involved

in giving a donation. Donations from volunteers are used for the general population and, directed donations for oneself or for a specified individual are only available in the blood program in exceptional cases. While there are no legal restrictions to paying donors, Canadians have always supported voluntary donations to the extent that payment has never been required to meet Canadian needs for blood and plasma collections.

2. National self-sufficiency in blood and plasma collections should be encouraged.

This principle refers to the capability to collect all necessary blood and plasma required to meet Canadian needs. Canada has been able to collect sufficient blood to meet its needs, but has relied heavily on plasma collected in other countries, often from paid donors, for plasma processing requirements. This principle is based on the premise that Canadians will have more control and perhaps more choice, in the processing of plasma required to meet its needs if it produces its own plasma. Efforts to increase the voluntary plasma donor base are underway. It would not be realistic to expect Canadians to become self-sufficient in plasma required for all plasma fractions, as some of the plasma fractions required by Canadians are highly specialized products, with relatively low volume requirements.

3. Adequacy and security of supply of all needed blood, components and plasma fractions for Canadians should be encouraged.

This principle refers to maintaining in all regions of Canada, an adequate and secure supply of all needed blood, components and plasma fractions required for therapeutic purposes, whether by collecting and processing them in Canada, or by securing long term contracts with reliable suppliers. This principle is particularly important in preparing for national emergencies in peace and in wartime, and for assurance to heavy users of blood products such as hemophiliacs.

4. Safety of all blood, components and plasma fractions should be paramount.

This principle refers to the quality and safety of all aspects of the collection, processing, distribution and therapeutic use of blood, components and plasma fractions. In Canada the *Food and Drugs Act* covers blood (as of September 1, 1989) and plasma, and all derivatives produced or imported into Canada. This legislation affords a good measure of public health protection for blood and plasma donors and for recipients of blood products. This principle also includes the safe and appropriate medical use of all blood products.

5. Gratuity of all blood, components and plasma fractions to recipients within the insured health services of Canada should be maintained.

The principle requires that recipients of blood, components and plasma fractions are not charged for these products provided within the insured health programs of Canada. It does not exclude charges being introduced to hospitals or other health care institutions in order to improve the management of the blood supply program.

6. A cost-effective and cost-efficient blood supply program for Canadians should be encouraged.

This principle refers to managing all aspects of the blood supply program in a cost efficient and effective manner. This includes not only the financial management of government funds, but the responsible and efficient collection, processing, distribution and utilization of blood, components and plasma fractions. This principle would not preclude the existence of a non-profit blood industry in Canada. It only asserts the desirability of one that is both cost-effective and cost-efficient.

7. A national blood supply program should be maintained.

The blood supply program in Canada is uniquely national, with blood and plasma being collected in all regions of Canada and being used by individuals in the region needing them. National policies and inter-provincial/territorial funding maintain this program.

The interpretive descriptions of the seven principles clarified some of the ambiguities but not others. The meaning of self-sufficiency was no longer uncertain. The term meant self-sufficiency in Canadian blood and plasma, not self-sufficiency in Canadian fractionation capacity. In this interpretive description, the paramountcy of safety was, in part, related to compliance with regulatory standards. However, if the operator took safety measures that were not required by the regulator, whether those measures were cost effective or cost efficient could be the subject of dispute.

In their testimony, the representatives of the Canadian Blood Agency and the Red Cross discussed the potential for conflict between safety on the one hand and cost-efficiency and cost-effectiveness on the other. Mr Dresch said:

Another ministerial principle relates to safety. Now, this one is in the middle. It can pose some difficulties. Safety should be paramount. Now, does that mean it should override everything else? My understanding of "paramount" is that is what it should be, the one and foremost. However, when you have a policy down below of cost effective and cost efficient, you may start to run into some inconsistencies or some difficulties in balancing those two Ministerial principles.

Mr Lindores said:

I look at this agreement as an improvement on the no agreement that existed before, but it is very clear that the continuing difficulty of reconciling safety levels with available financing continues to exist. And I don't think there is any agreement that one could ever negotiate that would remove that ongoing conflict.

A team of management consultants retained by the Inquiry to examine the structure of the blood system reported "a continuing pattern of disagreement over virtually every aspect of the funding relationship" between the Canadian Blood Agency and the Red Cross, and concluded:

We think that the structural relationship between these two organizations is such that they could never be expected to have anything other than very strained, difficult relationships unless fundamental changes are made. And we do not think that the new Master Agreement represents such a fundamental change.

We wish to emphasize most strongly that the current antagonism between the two organizations is not the result of poor inter-personal relationships. Rather, the opposite is more likely – we think that the systemic pressures on the heads of each organization would cause even the best relationship to deteriorate into mutual acrimony.

The operation of the master agreement: The Creutzfeldt-Jakob disease withdrawal

The master agreement was put to the test three months after it was signed when, in July 1995, Creutzfeldt-Jakob disease (CJD) emerged as a potential threat to the safety of the Canadian blood supply. CJD had been recognized as a potential threat to the U.S. blood supply in the previous year. The disease results in a fatal degeneration of the brain. There is no test for it, and it can be diagnosed with certainty only by a post-mortem examination of brain tissue. Its transmissibility was clearly demonstrated in the mid-1980s, when seven young adults in the United States died from CJD after receiving human growth hormone that came from a donor who developed CJD. Experimental evidence from animal studies also suggested that there is a theoretical risk that CJD may be transmitted through blood donated by a person before any symptoms of CJD have developed.

In November 1994, Bayer, then operating under the name Miles Inc., began a voluntary withdrawal of certain lots of Prolastin, a plasma-derived product used in the United States; some of the plasma used in the manufacture of the withdrawn lots had come from a person who was reported to have died

from CJD. The next month, a meeting of the blood products advisory committee of the U.S. Food and Drug Administration met to consider whether there ought to be a policy for action when a donor of blood or plasma was found to have CJD. Staff members of the Canadian Blood Agency, the Canadian Red Cross, and the Bureau of Biologics attended the meeting. As a result of the meeting, a policy was adopted for the United States; if a blood donor was subsequently discovered to have CJD, there would be a recall of all red cells, platelets, and plasma that had been derived from that person's blood. To ensure the continuous availability of blood products, factor concentrates and other blood products made from plasma that were implicated in a case of CJD would not be recalled, nor would pools containing implicated plasma that had not yet been processed.

No policy was adopted for Canada. In fact, there was no discussion after the meeting by the Canadian Blood Agency, the Red Cross, or the Bureau of Biologics to consider whether one should be adopted.

On 22 June 1995, the special advisory committee of the U.S. Food and Drug Administration met to discuss CJD. That meeting was attended by officials of the Canadian Red Cross and the Bureau of Biologics. The incidence of CJD was said to be one case per million persons per year. The committee decided that although there was no direct scientific evidence that CJD was transmissible by blood products, there was a theoretical risk. The committee recommended that implicated blood products be withdrawn and that any persons who had used them be informed of the risk. It also recommended that the products that were withdrawn not be destroyed, but stored for use in case of a shortage; the stored products could then be used if a physician and patient decided that, in the circumstances, the benefit of treatment outweighed the risk.

Given the incidence of the disease, it was only a matter of time before one or more cases of CJD were identified among Canadian blood donors. Although the Red Cross and the Canadian Blood Agency had internal advisory committees that considered the issue of possible contamination of the blood supply with CJD, they, and the other persons and organizations that would be affected by a withdrawal, did not come together to prepare for this eventuality and discuss how they might coordinate their response.

At the hearings on 10 July 1995, Dr Nathan Kobrinsky, a hemophilia-treating physician from Manitoba, expressed the opinion that CJD posed a potential threat to the blood supply. His comments were widely reported. On 11 July 1995, the Red Cross's Vancouver blood centre received a telephone call from a woman who said that her father had died from CJD and that he had been a blood donor. The Red Cross found that the man had made twenty-one donations in the previous six years. A withdrawal of his most recent donation was started.

The Red Cross discussed the matter with officials of Bayer, which manufactured blood products in the United States from plasma supplied by the Red Cross. Bayer and the Red Cross jointly decided that a voluntary withdrawal of blood products manufactured from pools that included the donor's plasma was warranted and consistent with Bayer's withdrawal policy in the United States, and the Red Cross wanted to err on the side of caution.

Officials of the Red Cross and the Bureau of Biologics met and agreed that the appropriate action was a voluntary withdrawal undertaken by the Red Cross, rather than a recall supervised by the bureau. The decision to withdraw rather than recall the products made it possible to store them and redistribute them in the event of a shortage in supply. Recalls are imposed only when there has been a violation of the *Food and Drugs Act* or its *Regulations*. In the face of a recall, it would be difficult to justify the redistribution of the implicated products.

The Red Cross decided to withdraw the blood products independently of the Canadian Blood Agency. It informed the agency only after the decision had been made.

On 14 July, the Red Cross ordered the withdrawal of all plasma products derived from the pool that contained the last donation of the man who had died from CJD. The only exception was a blood product known as "albumin 25%," of which there was a very small supply.

On 18 July, the Red Cross received reports of two more blood donors who had been diagnosed as having CJD. Blood products derived from the plasma of one of those persons, who had last donated in 1994, were still in inventory and were withdrawn.

The Red Cross notified all Canadian hospitals about the withdrawals and sought replacements for the withdrawn blood products. The Canadian Blood Agency took the position that it would pay for the replacement of products that had been ordered recalled by the regulator. The organization said that, "[g]iven that this withdrawal is not mandated by the BoB [Bureau of Biologics], but has the BoB's approval," it would discuss the financing of the withdrawal with the Red Cross.

On 27 July, the federal Department of Health issued a "health professional advisory" with respect to the withdrawal from the market of blood components and blood products related to donors who had developed CJD. It described the main forms of CJD and said that the Red Cross's voluntary withdrawal was a "prudent" action, even though the risk was only theoretical.

The cost of replacing the withdrawn blood products was estimated to be approximately \$12 million. Of 58,000 vials of products bought for this purpose, all but 11,500 were bought from brokers at a price of up to 20 per cent more than the price charged by the manufacturers. The additional cost of buying through brokers was approximately \$1.8 million.

On 31 July, senior members of the provincial and territorial departments of health, including some deputy ministers, held a conference call to discuss the Red Cross's withdrawal of blood products. The result of that discussion was a telephone call from one of the provincial deputy ministers of health to Mr Lindores, who recorded their discussion in a memorandum to file:

[The deputy minister] indicated that while cost is an issue ("cost is always an issue"), the main concerns expressed to him arose from the medical ethics involved. The view of the provinces generally was that the notification decision was a "bad decision." It did not make any sense to be out there notifying thousands of people when there was nothing that can be done for them. It would simply create unnecessary anguish which was not in the best interests of the patient. I expressed some sympathy for that position, but indicated that I felt precedent had been established of the right of patients to be informed in such circumstances.

[The deputy minister] went on to express his concern about the lack of consultation with the provinces on this issue prior to taking action. I indicated that we had kept the CBA informed, but that it had often been difficult to reach people due to the vacation schedule. I indicated that on at least one occasion we had been forced to leave a report on a telephone answering machine. [The deputy minister] stated that we should have considered convening a discussion with the Deputies Steering Group. I said we would be glad to use that channel, if the DMs [deputy ministers] agreed.

The action of the deputy ministers in contacting the Red Cross directly was inconsistent with the master agreement that had recently been completed by the provinces and territories, the Canadian Blood Agency, and the Red Cross. From the perspective of the Red Cross, the decision to notify recipients was a "straightforward operational issue which stemmed from the decision to withdraw" and, if it was appropriate for anyone to discuss the matter with the Red Cross, it was the Canadian Blood Agency.

On 11 August 1995, Mr Dobson, the executive director of the Canadian Blood Agency, wrote to Mr Lindores about the fact that the agency had not been involved in the decision to withdraw the products. He said:

The Master Agreement provides for the independent role of the Red Cross to proactively maintain the safety of its products. However the Master Agreement is also a document which commits all parties to a high level of cooperation and consultation.

I believe that there ought to be an established process put into place in which the views of the CBA [Canadian Blood Agency] are sought before the decision is made and which provides ongoing information to the CBA

as events unfold. Our mutual interests under such a process would be protected, but such a process would have to be designed both to acknowledge your right to make an independent decision and to cause no delay in reacting to the situation. Our interests could be defined as follows: ...

- there may be situations in the future for which a policy decision is required because the enhancement to product safety is undefined or ambiguous; ...
- there are costs (i.e. public expenditures) which may be created by the [Red Cross's] effort to protect the safety of its products; and,
- there are obligations to provide full information to Ministers and their Deputies.

I do not believe that the actions taken by the Red Cross in situations such as these are strictly “internal matters” and I believe that it is essential for the full and effective operationalization of the Master Agreement that a process is established to cover our joint needs for emergency responses in the future.

By the end of the process of withdrawal, it was clear that the confusion and disagreement about the roles and responsibilities of the Red Cross, the Canadian Blood Agency, and the governments had persisted, despite the master agreement, and perhaps had worsened. The Red Cross had made what it believed to be an operational decision to safeguard the blood supply. The agency considered it a policy decision, because the risk was theoretical. The provincial governments that, according to the master agreement, should have communicated with the Red Cross through the agency had communicated with it directly. The Red Cross was left uncertain about the cost to it of the withdrawal and about who represented the provincial and territorial governments.

Ultimately, the Canadian Blood Agency reimbursed the Red Cross for the cost of replacing the withdrawn products.

Continuing structural deficiencies in the blood system

The reactions to the withdrawal of blood products in 1995 demonstrated that, despite the master agreement, the confusion of roles and responsibilities in the blood system had not significantly improved. Several groups have since examined the blood system in Canada. The management consultants retained for the purpose of this Inquiry were in the midst of their study when the master agreement was signed. They concluded that “[w]hile the [master] agreement does formalize the working relationship between the two organizations, it does not, in our opinion, resolve the basic structural problems between them.” I accept this conclusion.

In April 1996, a year after the master agreement was executed, representatives of the federal, provincial, and territorial governments began an “initiative on blood governance” to study the blood system and recommend reform. The first report from that study, in September 1996, read in part:

The governance structure of the current blood system is characterized by ill-defined roles and responsibilities, multiple lines of authority, and an adversarial relationship between the manufacturer and the financier. These issues, among others, have led to a fragmented approach to managing the national blood system. There is no clear, single line of accountability.

The several organizations and institutions of the blood system recognized the continuing structural problems in their final submissions to the Inquiry. The Canadian Blood Agency said:

[I]t may well be that there is a legitimate concern about the respective roles of those who are accountable for the delivery of the NBS [national blood services program] – the members of the CBA – and the program operator. Perhaps the better question is whether that operator’s entrenched principle of independence has a proper place in the delivery of the NBS, and whether it requires alteration or amendment so as to eliminate the perceived conflict which the authors of the management consultants’ report would lay entirely at the doorstep of the CBA.

The Red Cross said:

Many of the issues of the current blood system, from the point of view of the operator, evolve along the familiar axis of safety and cost. While the phrase “safety is paramount” is frequently used, experience indicates that the word “paramount” is highly qualified. Few would argue that the pool of funding is unlimited, and therefore every possible new approach to gain however small an incremental gain in safety, must be pursued. For how much safety is the Canadian blood system prepared to pay?

The problem with the Canadian blood system is not that this eternal question exists, but that the methods of resolving it are so imperfect. Policy, co-ordination and financing of blood operations, are all handled by the CBA, which itself is tightly controlled by health ministries who are preoccupied with lowering costs. Safety standards are essentially established by the federal government, which itself plays no role in the funding of blood operations. The Red Cross is particularly constrained by the expectation that it will meet the full national demand for blood, but with no control over either funding levels or regulatory requirements, nor even access to binding arbitration. It does of course have control over the efficiency of its own operations.

Cost vs. safety trade-offs are matters of public health policy that can only be decided by governments. Evidence would indicate, however, that responsibility is often transferred to the Red Cross, the organization least empowered to take such decisions. Several methods are used to accomplish this:

- open-ended regulations to which there is no limit on the operator's requirement to pursue safety,
- extensive and often redundant bureaucratic processes that add little to the quality of the blood supply,
- unclear decisions or refusal to take decisions, thus forcing the operator to either interpret or to act without direction,
- delayed funding decisions,
- the demand for *perfect information*, which normally is manifested through repeated demands for more information or more studies, and
- through a variety of mechanisms that imply that *costs are too high*, with no commitment to test that conclusion through independent channels.

Whatever else may be done in the system, until governments develop a mechanism that can, and does, assume full and proper accountability for those decisions that can only rest with government, then the position of any operator of the blood supply program will be difficult.

There has been considerable discussion about the need to clarify roles and responsibilities within the Canadian blood system. That is agreed, but there is a critical second step – to ensure that the required authorities and resources are in place to fulfill those responsibilities. [Emphasis in original.]

Few would argue that the present arrangement is acceptable and should be continued.

The future role of the Red Cross in the blood system

The ministers of health have decided that the Red Cross should no longer have a role in Canada's blood system. The decision was made after the Red Cross had been told that it would cease to be the operator in the system, but could, if it chose to do so, continue to be involved in blood donor recruitment. One of the most important lessons to be learned from the past is that it is a mistake to separate blood donor recruitment from operations. In making their offer, the ministers showed that they had not learned this lesson. In rejecting the offer, the Red Cross, to its credit, showed that it had.

The reason for relieving the Red Cross of its role was that the operator had to be an instrument of government policy, and not independent of it. The Red Cross's necessary adherence to the principles of the international Red Cross movement prevented it from subordinating itself to government policy and direction as the operator of the blood system. I agree with the decision that has been made, despite its perceived risk to the security of the

blood supply. I have emphasized the essential contribution Canada's blood donors make to the well-being of their fellow citizens. There are some who say that the blood donors' loyalty to the Red Cross is so strong that they will no longer donate when the Red Cross is replaced as the operator by its successor. I believe that this view does a disservice to Canadian blood donors. It is demonstrable that they donate from no other motive than altruism, to make a "gift of life." They know there may come a time when any one of us may need that gift. They also know that although their donations have been through the Red Cross, they have not been to the Red Cross. I am confident that their humanitarian impulses will not fail them when a new blood collector succeeds the Red Cross.

The Initiative of the Federal, Provincial, and Territorial Governments to Reform the Blood System

In March 1996, the federal Minister of Health, David Dingwall, began discussions with the provincial and territorial ministers of health with a view to correcting the deficiencies in the blood system that had been described in my Interim Report. He wrote to them as follows:

As we are all aware, the current system is multi-faceted, dynamic and continues to undergo rapid changes. The existing division of roles and responsibilities of the major participants in the system has given rise to concerns about fundamental difficulties of accountability and governance which hinder the efficiency of the present system.

Justice Horace Krever clearly identified this in his Interim Report. He stated "In its report the safety audit committee concluded that responsibility for the blood system is fragmented ... the various functions integral to the supply of blood, such as regulation, funding and planning, are undertaken by different stakeholders. The respective functions, authority and accountability of each party are not well defined ... This lack of definition may affect accountability within the system, and ultimately its safety." This observation contains sound advice on the problems and the direction that reform of the system must take.

While we look forward to his final report, I do not think we can or should wait before taking action on what Justice Krever said in his Interim Report. I suggest that now is the time to begin to plan for the restructuring of the system. This is in line with our efforts to act on all of Justice Krever's Interim Report recommendations. As we work towards a new approach to governance of the system, we will, of course, accommodate the recommendations contained in Justice Krever's final report.

The ministers of health began a process of planning for the reform of the blood system that was parallel to, and independent of, the Inquiry. The process became known as the federal, provincial, and territorial initiative on blood. The health ministers of all provinces and territories met with the federal Minister of Health in Ottawa on 25 April 1996. They concluded their meeting by making a commitment to resolve the problems of Canada's blood system. The ministers released a communiqué which said that a reformed blood system must be governed by the following principles:

- safety of blood supply is paramount;
- a fully integrated approach is essential;
- accountabilities must be clear;
- the system must be transparent.

The communiqué also said that the process of reforming the blood system required:

- agreement among governments on all aspects of the use and management of blood and blood products;
- agreement on what must be managed in common and what must be integrated into provincial health systems; and
- an appropriate single agency to manage an integrated system including supply and distribution of blood and blood products.

The Minister of Health of Quebec announced that his province would not be a part of a national blood program.

The other ministers created a working group of officials and experts to develop a series of options for reforming the blood system, based on the principles set out above. The group was co-chaired by three persons – one federal government official from Health Canada and two provincial government health officials. The other five members were experts in blood and public health issues. The working group was directed to report to the ministers with its options by September 1996.

The working group was assisted by several experts and consultants who possessed expertise in fields such as medicine, science, management, government, and law. In addition, a number of focus groups and forums were held to elicit the assistance and opinions of other persons, including consumers of blood and blood products, who had knowledge of, or an interest in, the blood system.

Throughout the summer, the working group considered three different options for reforming the blood system. The model favoured by the working group was a new independent agency that would be centrally funded and that would be in charge of all major aspects of the blood system.

The health ministers met in Toronto on 10 September 1996. At the end of the meeting, the federal Minister of Health announced that a new agency, created by government but operating at arm's length from government, would be managing the blood system within a year. The ministers did not decide on what role, if any, the Red Cross would play in the new system. The federal Minister of Health said that the Red Cross would be given the opportunity to continue as the operator of the blood system, although under the management of a new agency, if it could comply with standards set by the agency. The ministers directed the working group to have a plan for the new blood group prepared by 15 February 1997.

In response to the announcement of the federal Minister of Health, the Red Cross stated that, although it would consider new arrangements for the management of the blood system, it would not submit to government management of its operations. It intended to adhere to the principle of the international Red Cross movement that it remain independent of government.

At their meeting on 10 September 1996, the ministers of health appointed a "federal, provincial territorial implementation team on the blood governance initiative." The implementation team's mandate was to plan, manage, and coordinate all aspects of the implementation of a new national blood agency within a year. The team was required to collaborate with "stakeholders, professionals and consumer organizations" and also to conduct its own independent analysis. It was chaired by the same federal official and one of the provincial officials who had co-chaired the working group. The implementation team reported to a steering committee on the blood governance initiative that was made up of deputy ministers of health. The steering committee, in turn, reported to the ministers of health.

The implementation team completed a draft master implementation plan in January 1997. It proposed that a national blood authority perform the following core operational functions:

- donor recruitment and management;
- whole-blood and plasma collection;
- testing and laboratory work;
- processing;
- storage and distribution; and
- inventory management.

It also proposed that the national blood authority be responsible for

- setting standard policies and guidelines;
- research and development;
- surveillance and monitoring; and
- professional and public education and information.

The plan proposed that the national blood authority be federally incorporated and later enshrined in legislation. The federal, provincial, and territorial ministers were to be the “members” of the corporation whose principal tasks would be to appoint the board of directors and to approve the corporate plan and financing of the national blood authority. The board of directors, which would select the chief executive officer, would include representatives with scientific and technical expertise, persons from business and industry, and consumers of blood and blood products. The board would also give policy direction to the national blood authority, give advice to the ministers, and prepare an annual report to Parliament and the provincial legislatures.

It was proposed that the authority be funded by the federal, provincial, and territorial governments. For the first three years, the provinces and territories would contribute the same amount of money that they contributed to the Canadian Blood Agency in the 1997 and 1998 budget. The federal government would contribute money to set up the infrastructure of the authority as well as for research and development. The federal government would also provide money for an enhanced public health surveillance system in the Laboratory Centre for Disease Control and for enhanced regulatory activities to be carried out by the Bureau of Biologics and Radiopharmaceuticals. The implementation plan proposed that there be a finance committee that reported to the board of directors. The finance committee would, in cooperation with a chief financial officer, prepare annual budgets, which would be presented to the board for its approval. There would be two advisory bodies to the chief executive officer of the national blood authority. The first would be a consumer advisory committee, and the second would be a research and development advisory committee.

One of the principles governing the reform of the system was full integration. Similarly, the master implementation plan proposed that a national blood authority perform functions at all stages of the blood collection, processing, and delivery system. The implementation team did not mean, however, that the national blood authority necessarily had to perform these functions itself. Instead, it could enter into contracts with third parties who would perform these functions in accordance with standards specified in the contracts.

In the spring of 1997, there were reports of new and more severe blood shortages in several parts of Canada. At the end of May, the provincial health ministers met in Montreal. They agreed that the new blood system should not be operated by the Red Cross. The provincial health ministers requested a meeting with the federal Minister of Health.

A meeting was held between the provincial ministers of health and the new federal Minister of Health, Allan Rock, in Montreal on 25 July 1997. The ministers agreed that there would be a new blood agency and that it would operate at arm's length from government. They decided that the Red Cross would

not be the operator, although it could take on a role in “non-exclusive donor recruitment.” The details of the agreement of the ministers were described in a press release as follows:

Ministers have confirmed their intent to meet their target of September to establish a new agency (the NBA) [National Blood Authority] operating at arm’s length from all governments. This will ensure rapid response to new and emerging threats to our national blood supply.

The agency will have a Board of Directors appointed by PT [provincial and territorial] Ministers, except Quebec, which will develop its own approach to blood system management. Quebec has already indicated it will be interested in business partnerships with the NBA.

In order to emphasize the arm’s length relationship between the Board and Ministers, civil servants will not be eligible to sit on the Board.

Day-to-day decisions will be made by the Board and management of the NBA.

The NBA Directors will prepare a three-year business plan and an annual budget that are presented to and approved by PT Ministers. The Board will enjoy a degree of flexibility that will enable it to deal with emergencies, consistent with its role of ensuring safety.

Ministers will now turn their attention towards the work required to prepare more detailed designs based on these decisions, so that the September objective can be met. Consumers and stakeholders will be invited to participate in that process.

The ministers also decided that, unlike his provincial and territorial counterparts, the federal Minister of Health would not be a member of the new blood authority. They did not make any decision with respect to the future of the Red Cross fractionation plant, but decided to leave the resolution of that issue to the new national blood authority.

The Red Cross rejected the suggestion that it carry out the task of non-exclusive donor recruitment. In a statement on 1 August 1997, the president of the Red Cross said that it was “in the best interest of all Canadians to allow the new agency to keep all the blood program operations integrated,” and that integration was the “only way to ensure clear accountabilities, transparency of the system and safety and security of supply.”

As of the end of October 1997, no further details about the proposed national blood agency had been announced.

The Government of Quebec decided to assume full control over the management of its blood system in order to integrate it into its health care system. The Minister said that the system “could, if necessary, involve a working relationship with other governments and the organizations involved.” On

6 June 1996, he established a committee on the supply, management, and distribution of blood. In November 1996, the committee released its report, "The Quebec Blood Supply System," which contained recommendations for the creation of a decentralized, hospital-based blood system. Soon after the release of the report, the Quebec government adopted the recommendations and began to implement this new system.

Financial Assistance for Blood-Associated Injury

The compassion of a society can be judged by the measures it takes to reduce the impact of tragedy on its members. Although the risks to the users of blood components and blood products today may be low, serious disease and some deaths will continue to occur as a result of the therapeutic use of blood. There is, moreover, always the likelihood that a new and mysterious blood-borne pathogen may strike. As I pointed out in my Interim Report, it is of little consolation or even relevance to those unfortunate members of our society who suffer from infection caused by blood transfusions or blood products that the blood supply now is adjudged relatively safe. A system that knows that these consequences will occur and what brings them about has, at the very least, a moral obligation to give some thought to the question of appropriate relief for those affected by the inevitable events.

In our current legal system, and in the absence of an existing public or private financial assistance scheme, the primary mechanism in every province and territory for compensating someone who has been harmed through the fault of others is a civil action for damages. In the common law provinces and in the territories, these actions are most commonly framed in negligence – that is, a breach of duty to exercise reasonable care resulting in harm. In Quebec, a civil law jurisdiction, claims are made under the provisions of the Civil Code of Quebec and particularly Article 1457, which reads, in part:

Every person has a duty to abide by the rules of conduct which lie upon him, according to the circumstances, usage or law, so as not to cause injury to another. Where he is endowed with reason and fails in this duty, he is responsible for any injury he causes to another person and is liable to reparation for the injury, whether it be bodily, moral or material in nature ...

Under both the common law and the Civil Code, the claimant must prove fault before being entitled to compensation from the “wrongdoer.” Even if fault actually existed, if no fault can be proved, the claimant must bear the entire burden of the injury, both financial and non-financial. It is the opinion of many legal scholars that this mechanism, the “tort system” or the “delict-based

system," is unsatisfactory as a means of compensation for harm. Its disadvantages, including the cost, delay, and adversarial nature of the proceedings, are especially pronounced for a plaintiff who is seriously ill or dying.

No amount of money can make up for the pain, suffering, and premature death of those infected with the human immunodeficiency virus (HIV), hepatitis C, or any other blood-related injury. The financial burden of living with HIV or other blood-related illnesses can, however, be quantified for the purpose of providing financial assistance to injured persons or their families.

HIV-infected persons require many expensive social and medical support services, and therefore may face severe financial difficulties that increase in magnitude as the disease progresses to its final stage. The degree of care required varies over the course of the illness, with months of relative well-being occurring between periods requiring hospital or intensive home care. The cost of health care depends on several factors, including the patient's age, the duration of infection, the severity of symptoms, and the availability of publicly funded medical treatment and community services. Many people living with HIV simply cannot afford necessities such as adequate food, nutrition, housing, and medication.

Many infected persons are forced to give up their jobs as their health deteriorates. Even before that occurs, some are forced out of work because of the social stigma of being HIV positive. Others, still willing and able to work, accept unemployment as a prerequisite to obtaining enhanced drug coverage under provincial social assistance schemes or private long-term disability insurance. This is not to suggest that all the costs of HIV or AIDS medication are covered by provincial medicare schemes and welfare drug-benefit programs. Coverage varies from province to province and territory, and not all provinces and territories include the experimental or preventive therapies that can be helpful in treating and caring for HIV or AIDS. Many witnesses testified that their monthly drug costs alone were in the thousands of dollars. These costs, particularly combined with loss of work, cause serious financial losses and severe anxiety and despair, particularly among families with little or no discretionary income.

The infected are not the only ones who suffer financially. They must increasingly depend on others to take care of them, their housekeeping, and perhaps their dependants. Most care for HIV infection is provided outside the hospital, and the trend in the care of HIV or AIDS is in this direction. As a result, spouses or parents give up their jobs to provide nursing care at home. Friends also help. The financial consequences are serious, and particularly so for the families of hemophiliacs, who will often have had difficulty obtaining life, mortgage, or disability insurance because of their underlying condition. They are even more catastrophic when a spouse is also infected. Today, a positive HIV test usually results in the rejection of an application for individual life or disability insurance. After an AIDS patient dies, surviving family members may face enormous debts and, not infrequently, are themselves out of work.

The financial cost of hepatitis C can also be measured. Treatment with alpha interferon usually lasts six months and costs more than \$3,000; it is not covered by most provincial health care plans. Chronic fatigue and other symptoms prevent many hepatitis C carriers from working, thereby causing additional financial hardship.

At the hearings, witness after witness testified to the financial disaster that accompanied personal tragedy. The timely provision of adequate financial assistance would clearly alleviate some of the suffering of blood-injured persons.

Financial assistance for persons infected with HIV

Assistance to the victims of HIV-infected blood has come under separate programs from both federal and provincial sources.

The Canadian Hemophilia Society presented a report on the financial impact of AIDS on hemophiliac families to the federal Minister of Health and Welfare on 15 August 1988. In April 1990, the federal government began making payments to each person (or to his or her estate) who had contracted HIV through blood components or blood products. The payments, in four equal annual instalments, totalled \$120,000 tax free, and were *ex gratia* (that is, made without any recognition of legal obligation). The deadline for application under this Extraordinary Assistance Program was originally 31 December 1990, but was extended to 31 March 1994, or even later in special circumstances. The program initially applied only to those who had received HIV-infected blood components or blood products between 1978 and 1989, but this too was amended so that those infected after 1989 could receive assistance. To be eligible, applicants must have been Canadian citizens or landed immigrants at the time of infection, and resident in Canada at the time of application. They had also to waive their right to institute a civil action against the federal government. Any who were ruled ineligible could appeal from the ruling to the Federal Court of Canada.

Nova Scotia was the first province to announce plans to assist people who had contracted HIV from blood components or blood products. Its program, announced on 27 May 1993, also covered infected spouses. Beginning that summer, compensation agreements were negotiated on a case-by-case basis within limits set by the government. The assistance included an annual tax-free payment of \$30,000, free drugs for treating HIV or AIDS, and post-secondary education for four years for each child and caregiver. It also provided survivor benefits, including \$5,000 for funeral expenses and a \$50,000 death benefit to a surviving spouse or child. The benefits did not affect qualification for social assistance, nor did they preclude simultaneous assistance from the federal government. In exchange, claimants had to agree to release the provincial government from all future claims for compensation. They had also to agree to inform the provincial Minister of Health before taking legal action against any other party, and to share any benefits from such

actions equally with the Ministry of Health. The impact of one further provision remains to be seen. The agreement stipulates that, if a claimant is “cured of AIDS and related and ancillary illness and conditions,” the agreement may be renegotiated at the sole discretion of the Minister. In the light of improved drug therapies which, although still in their early stages, are showing evidence of strengthening the immune response to HIV so as to avoid the onset of AIDS, it is unclear at what point, if at all, a claimant who is HIV positive but does not have AIDS might be deprived of benefits.

The other provinces and territories followed Nova Scotia’s example on 15 September 1993, but less generously. Anyone eligible under the federal Extraordinary Assistance Plan was automatically eligible for the new Multi-Provincial/Territorial Assistance Program – but not simultaneously. Applications had to be submitted by 15 March 1994. Payments begin in the first April following the claimant’s last federal payment. Under the program, patients receive \$22,000 within thirty days of enrolment, plus \$30,000 annually for life. Estates are not eligible. Survivor benefits include \$20,000 per year for a spouse and \$4,000 per year for each child for five years. Dependent children are defined as persons under eighteen years of age, or under twenty-five if attending a post-secondary school. Payments are tax free and are not considered income in determining eligibility for social assistance. If a cure or a drug to control HIV or AIDS becomes available, lifetime payments end. In exchange, applicants and their spouses and dependent children must sign a release relieving the provinces, territories, the Canadian Red Cross Society (Red Cross), the Canadian Blood Agency, blood product manufacturers, hospitals, physicians, and their insurers of any liability. The program is administered by the Canadian Blood Agency.

Most infected individuals and their families accepted the assistance packages out of an immediate need for financial assistance. A day before the deadline, the first Canadian judicial decision in an HIV-transfusion injury case, *Pittman Estate v. Bain* (1994), was delivered. Many witnesses who testified at the hearings criticized the “arbitrary” deadline for application because it did not give them adequate time to consider pursuing legal action, under which they might have been able to secure greater compensation. Many testified also that they would have liked to have heard more evidence from the Inquiry’s public hearings before making the choice between accepting the package or taking legal action. In September 1996, the Canadian Blood Agency extended the application deadline to 15 March 1997. Unlike the Nova Scotia package, the federal and multi-provincial/territorial assistance programs do not cover infected spouses or children, nor are drug, funeral, or post-secondary education expenses for dependants or caregivers specifically covered.

Governments in other countries have also offered financial assistance to persons who have contracted HIV or AIDS from blood components or blood products. The conditions vary, but in general the assistance is tax free and

not considered income when qualifying for social assistance. Government-sponsored financial assistance has had the additional effect of reducing litigation against those responsible for the blood system. The programs of several other countries are described in Chapters 27 to 34 of this Report. The figures are not particularly meaningful without taking into account the cost of living in the country concerned and its social and health insurance systems. The World Federation of Hemophilia has compiled information on compensation for hemophiliacs in its member states.

Financial assistance for persons infected with hepatitis C

In Canada, government financial assistance for blood-transmitted disease is restricted to persons with HIV or AIDS. More Canadians have been infected through blood therapy with hepatitis C than with HIV, and they too face loss of income and high costs for care. The financial consequences, documented by the Canadian Hemophilia Society and others, are felt especially by persons with severe liver damage and by dependants of those who have died. During this Inquiry, many witnesses infected with hepatitis C demanded government assistance. None has been forthcoming. Canada is not alone in failing to compensate this group. Only Italy and the Republic of Ireland have offered special financial assistance to patients who have been infected with hepatitis C through blood or blood products.

In Italy, legislation was enacted in February 1992 to provide government-funded assistance to hemophiliacs infected with HIV or suffering from irreversible liver damage caused by post-transfusion hepatitis (including hepatitis A and B in addition to hepatitis C). Although there have been some difficulties in administering the plan, the statute distinguishes between eight categories according to the severity of damage, with monthly pensions for life ranging from 1,049,840 lira (Can\$921) to 1,175,632 lira (Can\$1,031). A lump sum of 50 million lira (Can\$43,850) is paid in the event of death.

Ireland's program, begun in 1995 and by far the most comprehensive, covers everyone infected with hepatitis C from blood or blood products. Dependants may apply for assistance after a person dies as a result of the infection. Caregivers who have incurred financial loss or expenses as a result of caring for an infected person can also apply for assistance. Compensation payments are calculated by a tribunal appointed by the Minister of Health, according to the principles governing the measure of damages in tort law. Exemplary damages, sometimes referred to as punitive damages (damages, in addition to actual damages, that are awarded to deter the "wrongdoer" who acted intentionally or with complete disregard for the consequences of his or her actions) are not included. Awards consequently vary considerably among individuals. Claimants must prove that their infection was caused by blood or blood components on a balance of probabilities; they are entitled to legal representation before the tribunal, but have no right of appeal from

its decisions. The tribunal makes a lump-sum award which, at the claimant's request, is either final or provisional. The provisional award allows a claimant to be assessed in stages and thus be eligible for further compensation if the disease becomes more severe. In accepting an award, a claimant must agree not to bring a civil action because of the infection. Claimants are also entitled to primary and secondary health care services free of charge.

New Zealand has compensated blood-injured persons infected with hepatitis C under an existing no-fault compensation plan for all personal injury, as discussed later in this chapter. In contrast, the British government has taken the position that it will not extend the terms of its trust fund for the HIV infected to persons infected with hepatitis C. This decision led Lord Addington to point out in the House of Lords the absurdity demonstrated by a case involving a family with three hemophiliac sons, all of whom received blood products. The family received compensation for the two hemophiliac sons who died of AIDS, but not for the hemophiliac son who died of hepatitis C, despite the fact that all three deaths resulted from the same medical treatment.

The adequacy of the tort or delict-based system

In this section, the expression "tort system" is intended to include the common law concept of liability for personal injury and the civil law concept of delict under the Civil Code of Quebec. To recover damages under the tort system, a plaintiff or claimant must be able to prove fault on the part of the defendant. Tort liability requires a wrongdoer to pay for damage caused to another in order to compensate that person for the harm suffered. According to the theory, by having the wrongdoer pay the damage personally, members of society are deterred from engaging in careless behaviour. Most tort actions for medical injury allege negligence – that is, a failure to exercise reasonable care. Compensation, or "damages," can cover the cost of care and loss of future earnings, and non-quantifiable matters such as pain and suffering, loss of expectation of life, and impairment of social activities. However, attempting to prove negligence or other fault in an adversarial system results in lengthy, complex, and costly proceedings, with results that are unpredictable and often unsuccessful for the injured plaintiff.

There is extensive evidence that tort liability not only fails to deter careless behaviour but too often fails to compensate those who have been injured through no fault of their own. In Canada, despite an increase in litigation, only a modest percentage of persons suffering avoidable health care injuries receive compensation. The 1990 Report to the Conference of Deputy Ministers of Health of the Federal-Provincial-Territorial Review on Liability and Compensation Issues in Health Care (the Prichard Report) estimated "that the percentage receiving compensation is certainly less than 10 per cent of potential viable claims." In 1987, although \$200 million were invested in liability insurance, "less than 250 injured patients received compensation of

any kind from medical malpractice litigation, whether by way of settlement or trial judgment, anywhere in Canada.” Some persons received significant sums, while others received much less than their actual financial losses. Even advocates of the tort system acknowledge that the system is ineffective in ensuring compensation for all who need it.

However uncertain the results may be, the costs of litigation are unreasonably high. Delays in legal proceedings are common, and their associated costs are exceptionally high. Taxpayers shoulder a major portion of that cost, but litigants who are also taxpayers assume a double burden. The costs of a single case are high, even for the successful party. The Ontario Civil Justice Review, a provincial government task force, concluded in its first report in March 1995 that costs to the user of the civil justice system “are considerable, sometimes insurmountable. They pose a significant problem in respect of access and the affordability of civil justice.”

The drawbacks associated with traditional litigation are well illustrated in the first Canadian judgment in an HIV-transfusion injury case, *Pittman Estate v. Bain*, referred to earlier. Kenneth Pittman received an HIV-infected blood component during heart surgery at what is now the Toronto Hospital in November 1984. In November 1985, the Red Cross learned that the donor of the blood transfused was HIV positive, and in June 1987 traced the potentially infected unit to the Toronto Hospital. In February 1989, the hospital traced that blood to Mr Pittman and notified his family physician. The physician decided not to tell Mr Pittman because he was afraid of the effect of the news on Mr Pittman’s health and because he did not believe Mr Pittman and his wife were having sexual relations. In March 1990, Mr Pittman died of AIDS. That September, Mrs Rochelle Pittman, Mr Pittman’s widow, learned that she was HIV positive. The estate of Mr Pittman, his wife, and his children commenced legal action against the Red Cross, the Toronto Hospital, and the physician. The trial, with interruptions, lasted an entire year.

Madam Justice Lang, the trial judge, ruled that the Red Cross had not been negligent in collecting the infected blood. She also denied the claim against the hospital for breach of warranty of fitness on the basis that the contract between Mr Pittman and the hospital was for a service, and not for the sale of a product. In her view, it was not reasonable to suppose that a hospital was impliedly warranting that transfused blood, supplied on demand and gratuitously, would be disease free, or that the donor had made such a claim. The characterization of blood as a service, and not as a sale of a good, was recently approved by the Supreme Court of Canada in *ter Neuzen v. Korn*, [1995] 3 S.C.R. 674, although that case dealt with the transmission of HIV through semen during artificial insemination. In the *Pittman* case, Madam Justice Lang held that the Red Cross, the Toronto Hospital, and the physician were negligent in failing to notify Mr Pittman more rapidly about the potentially infected blood transfusion, concluding that faster action might have

prevented Mrs Pittman's subsequent infection. She apportioned liability, 40 per cent to the physician and 30 per cent each to the Red Cross and the hospital.

The court assessed the plaintiffs' costs at \$370,000 in fees and disbursements. Mr Pittman's estate was awarded \$8,000 for Mr Pittman's pain and suffering, Mrs Pittman was awarded damages of \$461,318, and her children \$45,759. In addition, even though costs were not awarded in full, the defendants faced costs of a trial that consumed eighty-one full days and twelve half-days. The public also bore significant costs of the litigation. The Ministry of the Attorney General of Ontario estimated in 1994 that it cost slightly less than \$475 per trial hour for the judge's salary, benefits, secretarial assistance and supplies, court clerk and reporter, and a portion of the office expenses and court services. In light of the costs, the expense of a blood-transfusion claim through conventional litigation clearly can be great.

Supporters of tort liability claim that it serves an important psychological function for the victims to "have their day in court." On the other hand, the Ontario Civil Justice Review observed that claimants for the most part do not care whether their cases are resolved in a courtroom or elsewhere; they simply want them resolved quickly and cheaply. In transfusion injury cases, that is rarely possible through the courts. Madam Justice Lang commented in *Pittman Estate v. Bain* that "[l]itigation is a fault-driven process where each case must be decided on its own merits. It is ill-suited to an expeditious resolution of such tragic situations." In his judgment in a case in England involving multiple plaintiffs either suffering from, or at risk of contracting, Creutzfeldt-Jakob disease as a result of being treated with human growth hormone *Re Human Growth Litigation; The Plaintiffs appearing in Schedule 2 to the Order made on 14 November 1994 v. The United Kingdom Medical Research Council and Another* [unreported] 19 July 1996 (Queen's Bench Division), the trial judge wrote: "Litigation of this scientific complexity on a subject of general public importance might be better resolved by an inquisitorial rather than an adversarial system."

Proponents of the current system argue that tort liability decreases the risk of injury because it creates an incentive to exercise care. Many studies of the deterrent effects of tort liability are inconclusive at best. Professor Terence Ison listed the problems in *Compensation Systems for Injury and Disease: The Policy Choices*: "Any connection between moral turpitude and payment of damages is undermined by the objective standard of care, the coverage of most claims by liability insurance, evidentiary problems, settlement practices that are unrelated to fault, the tendency for the incidence of liability to follow the incidence of liability insurance ... and the lack of any necessary connection between the measure of damages and the degree of culpability. The evidence does not show an increase in morbidity and mortality rates

in jurisdictions which have abolished tort liability.” Although conceding the desirability of the goal of maintaining good social accounting, said by some to be the purpose of the liability system, Professor Ison concludes that that system is a poor way of achieving it.

Even the theoretical benefit of tort liability in deterring carelessness is limited when the defendant carries liability insurance. As Professor Ison points out, if tort liability creates an incentive to prevent injury, it does so principally by controlling the cost of liability insurance. This effect is not the same as creating an incentive to prevent injury. Liability insurance ensures that the defendant does not personally have to absorb the entire burden of a judgment for damages. In the *Pittman* case, the Canadian Medical Protective Association, which provides liability indemnity to the vast majority of physicians, indemnified the physician in full for the damages awarded against him.

The primary function of the law of negligence, a branch of tort law, has evolved in modern society from one of deterring careless behaviour to one of shifting losses from those who cannot bear it to those who can or to society at large. In the words of Canadian scholar Dr C.A. Wright, in *Cases on the Law of Torts*, “The purpose of the law of torts is to adjust these losses and to afford compensation for injuries sustained by one person as the result of the conduct of another.”

This compensation function, however, is not being achieved efficiently. Mr Justice Sopinka of the Supreme Court of Canada, in his dissenting judgment in *Just v. British Columbia*, [1989] 2 S.C.R. 1228, pointed out that “[t]he basic premise of adjusting losses on the basis of fault is being subjected to intense criticism. In the United States there is a growing consensus that the tort system is responsible for the crisis in liability insurance. There is now substantial support for wholesale legislative reform of the tort system.”

When liability insurance cannot be obtained, it is not only the likelihood of compensation for the injured that may be compromised; so too may the supply of an essential product. The unpredictability of product liability costs may lead manufacturers to withdraw a product from the market. The Red Cross has struggled to maintain affordable liability insurance for all its blood services since its last policy expired on 31 December 1985. Since then, it has for the most part been able to afford only a restricted general liability insurance policy for its blood operations, one that does not extend to blood components and blood products. The Red Cross has tried to develop a self-insurance plan against liability arising from blood components and blood products. It has also sought, to date without resolution, assurances from the Canadian Blood Agency (and earlier from its predecessor, the Canadian Blood Committee) with respect to indemnification for damage awards or settlements arising out of transfusion cases under the general blood program. Failing an indemnification agreement, the assets of the publicly funded charity are at risk.

The availability of insurance also affects the relationship between a manufacturer of inherently risky but essential products and a person injured by those products. Insurance contracts contain a standard clause preventing an insured party from admitting liability to a potential claimant. Policies for liability insurance normally contain a standard term to the effect that “[n]o admission of liability or offer or promise of payment, whether expressed or implied, shall be made without the written consent of the insurer, which shall be entitled at its own discretion to take over and conduct in the name of the insured the defence or settlement of any claim.” The Red Cross is contractually bound by its insurance policy not to make any admission of liability whenever a claim is made. Douglas Lindores, the former secretary general and chief executive officer of the Red Cross, agreed during his testimony that one of the reasons why the Red Cross declined to apologize to persons infected through blood components or blood products was that an apology might be construed as an admission of liability.

Proving fault is a formidable task for an individual injured by a blood transfusion or blood product. As Mr Justice Dickson, the former Chief Justice of Canada, put it in *Andrews et al. v. Grand and Toy*, [1978] 2 S.C.R. 229 at page 236:

The expenditure of time and money in the determination of fault and of damage is prodigal. The disparity resulting from lack of provision for victims who cannot establish fault must be disturbing.

The view I expressed in 1983 in *Ferguson v. Hamilton Civic Hospitals et al.* (1983), 144 D.L.R. (3d) 214, is pertinent here. That was a medical malpractice action involving a previously healthy man who had become quadriplegic immediately after undergoing an angiogram, a diagnostic test. His action was dismissed because he was unable to prove negligence in the performance of the test or in his after-care. The need for compensation was palpable, but could not be awarded. I concluded my reasons for judgment with the following statement:

I confess to a feeling of discomfort over a state of affairs, in an enlightened and compassionate society, in which a patient, who undergoes a necessary procedure and who cannot afford to bear the entire loss, through no fault of his and reposing full confidence in our system of medical care, suffers catastrophic disability but is not entitled to be compensated because of the absence of fault on the part of those involved in his care. While it may be that there is no remedy for this unfortunate and brave plaintiff and that this shortcoming should not be corrected judicially, there is, in my view, an urgent need for correction.

In dismissing an appeal from this judgment, the Court of Appeal for Ontario said:

[W]e are in complete sympathy and agreement with the penultimate paragraph of the learned trial judge's reasons. OHIP [the Ontario Health Insurance Plan] is the product of a socially conscious society, but we agree that in situations such as the instant one "an enlightened and compassionate society," to use the words of the learned trial judge, should do more.

Similar expressions of dissatisfaction with the current state of the law have been expressed by other judges in a number of medical injury cases.

A leading case in Quebec, *Lapierre v. A.G. (Quebec)*, [1985] 1 S.C.R. 241, illustrates the inadequacies of a fault-based system of compensation. A few days after being vaccinated against measles as part of a government-sponsored vaccination program, a five-year-old girl developed acute viral encephalitis that resulted in permanent total disablement. At trial, the parents were successful in an action for damages against the government on the basis of no-fault liability in reliance on the doctrine of necessity. The trial judge held that damages suffered by an individual for the benefit of the community must be borne by the latter. However, the Court of Appeal of Quebec, and subsequently the Supreme Court of Canada, held that, according to Quebec law, no liability could exist without fault. Both courts expressed the view, however, that "an obligation independent of any fault in circumstances such as those of the case at bar, would be an excellent thing, but it does not exist in our law at present." In 1985, following the Supreme Court of Canada's decision, the government of Quebec enacted legislation providing for an immunization victims' compensation program. Under the legislation, compensation does not require proof of fault.

Alternatives to compensation

Abolish tort liability and replace it with a no-fault system

The most comprehensive scheme substituting a no-fault system of compensation for the traditional fault-based tort system is New Zealand's accident compensation legislation. The scheme compensates all injuries resulting from any "accident," irrespective of fault on the part of anyone. The right to commence an action in tort for most accidental injuries was abolished in New Zealand by the *Accident Compensation Act 1972*, in force on 1 April 1974, and replaced by a social insurance system based on five principles: community responsibility, comprehensive entitlement, complete rehabilitation, real compensation, and administrative efficiency. The scheme provides a set of benefits related to earnings for victims of accidents in and outside the workplace and on the highways, and for victims of "medical misadventure."

Compensation can be claimed for medical treatment and rehabilitation, dental treatment, home care, and funeral expenses. The objective is income maintenance, and not compensation for all harm sustained. The plan is financed by employers, the self-employed, and motorists, and by general tax revenues.

The New Zealand program recognizes transfusion-related AIDS and AIDS contracted from blood products as an accident resulting from medical misadventure. Under the *Accident Compensation Act 1982*, which amended the 1972 scheme, victims were entitled to lump-sum compensation payments based on the degree of loss or impairment of bodily function. The Accident Compensation Corporation, which administers the scheme, considered that HIV infection alone, while constituting a personal injury by accident, does not give rise to a disability sufficient to warrant payment of lump sums, and began payments only after an infected individual had contracted full-blown AIDS. The person then received NZ\$27,000 (Can\$25,761) in lump-sum compensation, in addition to compensation for any additional medical expenses not covered under the public health insurance system. Those unable to work received further compensation related to their previous weekly earnings. All lump-sum payments for HIV infection had been paid out by the end of 1991. The Accident Compensation Corporation also recognized the transmission of hepatitis C as a medical misadventure.

The legislation was again amended by the *Accident Rehabilitation and Compensation Insurance Act 1992* and now limits the scope of coverage by defining medical misadventure as personal injury resulting from "medical error" or "medical mishap." Medical error is defined as the failure of a registered health professional to observe a standard of care reasonably to be expected in the circumstances. Medical mishap is defined as an adverse consequence of treatment by a registered health professional that is rare and severe. For a mishap to be rare, it must not occur in more than 1 per cent of cases where the treatment in question was given. A mishap is considered severe if it results in hospitalization for more than fourteen days or significant disability lasting more than twenty-eight days, or if the claimant qualifies for an independence allowance under the *Act*.

Lump-sum compensation has been replaced by an independence allowance for non-financial losses (physical disability, pain and suffering, and loss of enjoyment of life) of up to NZ\$40 (Can\$38) per week tax free, based on the degree of disability. Compensation for mental suffering is disallowed altogether, except where it arises directly from physical injury, but victims can make a claim for indirect mental consequences through the tort system. To qualify for an independence allowance, claimants must demonstrate at least a 10 per cent functional disability within one year of the date of diagnosis. Compensation is still available for some medical expenses and for lost income on the basis of 80 per cent of relevant earnings; however, after six months, the Accident Compensation Corporation assesses the claimant's "capacity

for work” to determine if the person is able to return to the workforce. Payments can be made for life, but are subject to annual periodic reassessments. Claims are not accepted later than twelve months after the date of diagnosis.

Although claims made by blood-transfused AIDS patients will likely be accepted under the 1992 *Act*, the amendments appear to reduce the payments that blood-injured persons will receive, primarily because they no longer have the benefit of lump-sum compensation. Furthermore, it is not clear whether all blood injuries giving rise to significant disabilities will be covered under the new regime because of the degree of disability required within one year of diagnosis. Hepatitis C infection in particular is unlikely to be a “medical error” because it does not result from the failure of a registered health professional to observe standard care or skill. Nor is it a “medical mishap” as defined by the *Act* because it is neither “rare” nor “severe,” since significant disability is unlikely to be certified within one year of diagnosis. In recognition of this problem, the New Zealand Hemophilia Society obtained an extension for making claims for lump-sum payments for hepatitis C infection under the 1982 *Act* from 30 September 1992 to 30 June 1995.

The greatest strength of New Zealand’s initial plan was that compensation depended primarily upon the needs of the injured person, regardless of how the injury occurred. A compensation scheme for all Canadians for all forms of injury was in fact considered by the Ontario Task Force on Insurance in 1986, but it concluded that “[f]or all practical purposes ... although a comprehensive disability program was endorsed by the Macdonald Commission [the Royal Commission on the Economic Union and Development Prospects] it appears that universal disability may have to await ... Universal disability compensation, although logically compelling, is realistically unattainable in the short-to-medium term.”

Maintain tort liability but provide an option of no-fault benefits

In 1990, a report of the findings and recommendations of the Prichard Report was made to the Conference of Deputy Health Ministers. The review was conducted because of a concern for the rise in civil litigation against health care providers and the effects of litigation on the quality, cost, and availability of health care in Canada. One of the principal findings was that current liability and compensation systems are very expensive, but very few injured persons are compensated. The report stated that “[w]hen account is taken of all the legal fees, the costs of the court system, and the time and energy of everyone concerned with the litigation, in excess of 50 per cent of all the money spent on malpractice goes to the expenses of litigation and not to the injured patients for purposes of compensation.” It concluded, nevertheless, that the threat of tort litigation improves the quality of health care, despite acknowledging that information supporting that conclusion was conflicting. Consequently, it recommended maintaining the tort system. At the same time, the

report recommended that a no-fault compensation system for persons suffering significant avoidable health care injuries be developed to improve accessibility to financial assistance, to compensate a greater number of people, and to limit the growth in civil liability claims. The report, which specifically addressed the question of liability and compensation for injury through blood and blood products, recommended that persons suffering injuries related to blood products be able to choose between accepting compensation benefits offered by a no-fault scheme and pursuing a tort action.

Optional no-fault compensation plans have been devised for other drug injuries, most notably those arising from immunization programs. The governments of Denmark, France, Germany, Japan, Switzerland, the United Kingdom, and the United States have all compensated vaccine-related injuries out of a concern that, without some protection for manufacturers, vaccine production would decline. Their no-fault compensation plans for vaccine-related injuries are useful models for the blood system, given the state's interest in maintaining an adequate and safe supply of both vaccines and blood. The Quebec and U.S. plans are examples and are discussed below.

As already pointed out, Quebec established a compensation program for immunization victims in 1985. It is the only province in Canada that compensates these victims. The scheme was established under *An Act to Amend Various Legislation Respecting Social Affairs 1985*. The regulation implementing the program was made in 1987, and the first claim was submitted in 1988. Under the program, compensation is paid to any "victim" of "personal damage" resulting from voluntary or compulsory immunization, irrespective of anyone's fault. "Victim" includes an immunized person, a person who contracts a disease from a person immunized in Quebec, the fetus of one of those persons, or, in the case of death, a person who is entitled to a death benefit. "Personal damage" means any serious permanent damage, whether physical or mental, including death. Compensation is paid in accordance with the benefits available under the Quebec automobile insurance program. Under the *Automobile Insurance Act*, compensation is provided to replace lost income, to compensate for income replacement, bodily injury, and to pay rehabilitation expenses. A medical evaluation committee consisting of three physicians examines the claimant's medical file to determine if there is a probable chain of causation between the damage incurred by the victim and immunization, as well as to determine the amount of compensation. Although the burden of proof is on the claimant, the only requirement is that the claimant's medical file be submitted for evaluation by the committee, the cost of which is borne by the Ministry of Health and Social Services. If compensation is granted under the program, the Minister assumes the legal right of the claimant to recover damages from those responsible. If a claim for compensation is denied, the claimant has a right of appeal to the Commission des affaires

sociales. Of the 120 claims submitted for compensation by 13 September 1994, sixty-five had been evaluated by the committee, forty-two had been withdrawn, twenty-four decisions had been appealed, all unsuccessfully, and thirteen had been awarded compensation.

In the United States by 1967, drug manufacturers were growing reluctant to produce childhood vaccines because of the increasing costs of litigation arising from unavoidable adverse reactions. By 1986, only two manufacturers were producing polio vaccines, and only two firms and two state health departments were producing diphtheria-pertussis-tetanus vaccines. As a result, the vaccine supply fell below levels recommended by the Centers for Disease Control. In response to the threat of an inadequate supply, Congress enacted the *National Childhood Vaccine Injury Act of 1986*, which created a statutory no-fault compensation scheme to limit the liability of vaccine manufacturers for vaccine-related injuries. A petition may be made by an injured individual or the family of the individual. For injuries sustained from a vaccine administered before 1 October 1988, petitioners can choose between agreeing to a compensation award determined by a special vaccine injury committee and bringing a civil action against the person who administered the vaccine or the vaccine manufacturer. For injuries resulting from a vaccine administered on or after 1 October 1988, petitioners must exhaust their remedies under the compensation program before making a tort claim. If a petitioner accepts an award under the vaccine compensation plan, he or she cannot subsequently pursue compensation under the tort system.

Under the *Act*, a manufacturer is not liable for injuries arising from unavoidable side-effects and is not liable solely because of failure to provide direct warnings. Claimants may be compensated for medical care, lost earnings, reasonable legal fees, and up to U.S.\$250,000 for pain and suffering and emotional stress, or death. Exemplary or punitive damages are not allowed. Injured parties are thus encouraged to forgo conventional litigation by swift and certain compensation and by limits on the amount of compensation that can be awarded through tort law to claimants who bypass or refuse an award under the program.

Unlike the Quebec plan, the U.S. scheme has a predetermined table of compensation for specified injuries. Claimants need merely demonstrate that their injury is related to the administration of a vaccine covered under the program in order to be compensated. If the injury is listed in a table of known injuries and occurred within a prescribed time period, it is presumed to have resulted from the administration of that vaccine. If the injury is not listed, the claimant must demonstrate by a preponderance of evidence that there is a relationship between it and the administration of a covered vaccine. Hearings to determine eligibility under the program last one to two days. The fund is supported by an excise tax on every purchase of a vaccine dose covered under the program. The amount of the tax varies according to the

vaccine, and constitutes a substantial portion of the ultimate price. Amendments introduced in Congress in 1996 would introduce a flat tax, regardless of the particular vaccine.

During the first twelve months of the program beginning October 1988, seventy of the eighty-one claimants received compensation totalling US\$38 million, and no claimant pursued civil action against a vaccine manufacturer. As of 1996, awards to individuals have averaged US\$854,470 (Can\$1,153,535). It is reasonable to conclude that the National Vaccine Injury Compensation Program creates a more stable environment for vaccine production by decreasing litigation costs and damage awards. It also provides a speedy compensation system for victims.

In 1987, U.S. blood organizations tried, but failed, to convince Congress to add transfusion injuries to this legislation. The idea resurfaced in 1995 in the recommendations of a report by the Institute of Medicine, following a review of decision making surrounding HIV in the early 1980s by the Committee to Study HIV Transmission through Blood and Blood Products. That committee recommended that the federal government establish a no-fault compensation system for individuals suffering adverse consequences from the use of blood or blood products. It concluded that, had such a no-fault compensation system existed in the early 1980s, it could have relieved much of the financial hardship suffered by many who became infected with HIV through blood and blood products. In August 1996, the Committee on Government Reform and Oversight recommended to Congress that it consider establishing an alternative to the tort system, such as the National Vaccine Compensation Program, to compensate persons who suffer adverse consequences from the use of blood components and blood products.

Although no national no-fault scheme for blood injuries had been developed in the United States by the end of 1996, a no-fault pilot project has been implemented in Arizona. It is an optional private dispute resolution mechanism for persons injured by blood components or blood products, covering all blood-borne pathogens and transfusion errors, and operating without regard to issues of negligence. The injured person is offered an immediate settlement package to cover actual financial losses.

Conclusions

An optional no-fault system would serve to limit the number of tort claims, but would not avoid the unpredictable outcome of tort actions or the inconsistent financial awards for blood-related injuries. More important, it would make possible the development of a two-tiered justice system, one for those who can afford to go to court, and the other for those who cannot. Furthermore, the public cost of maintaining both systems would be significant. I recommend the creation of a no-fault scheme for blood-related injury. I do not favour the retention of an optional system.

I acknowledge the force of the argument made by, among others, the Prichard Report, that it is difficult to treat blood-related injury compensation differently from compensation for other health-care injuries. Given my terms of reference, however, it is not for me, here, to consider compensation for any injuries other than those that are related to blood therapy.

Shifting the focus from finding fault to compensating the injured party will not compromise the safety of blood. The objective of deterring careless behaviour need not be accomplished within a scheme for compensating people who have suffered harm. Tort liability is too episodic and irregular to provide the surveillance necessary to prevent the introduction of unacceptable risks. Rather, safety of the blood supply may best be achieved through strict regulation. I fully endorse the views of the judges referred to above who have criticized adversarial litigation as the means of resolving the complex technical issues that arise in these cases.

Until now, our treatment of the blood-injured has been unequal. After years of suffering devastating financial losses, many persons infected with HIV from blood or blood products, or their surviving family members, finally did receive financial assistance. Other Canadians who have suffered injuries from blood therapy have not received any compensation. Yet the needs of those who have been harmed are the same, regardless of their cause, and whether or not fault can be proved. Compensating some needy sufferers and not others cannot, in my opinion, be justified. The provinces and territories of Canada should devise statutory no-fault schemes that compensate all blood-injured persons promptly and adequately, so they do not suffer impoverishment or illness without treatment. I therefore recommend that, without delay, the provinces and territories devise statutory no-fault schemes for compensating persons who suffer serious adverse consequences as a result of the administration of blood components or blood products.

The Blood System for the Future

One of the purposes of the Inquiry is to make “recommendations on an efficient and effective blood system in Canada for the future.” The recommendations in this chapter take into consideration the tragic circumstances surrounding the contamination of the blood supply that are described in this Report. I am confident that if the recommendations are implemented, the likelihood that the tragedy will happen again will be markedly reduced. But in our hope for the future we must not forget that a terrible tragedy did occur. It is for that reason that my first recommendation is for compensation for blood-related injuries incurred in the past or that may occur in the future.

I recommend the creation of a national blood service that will carry out all major functions of the blood supply system, with the exception of the fractionation of plasma, from the recruitment of donors to the distribution of blood components and blood products. The national blood service must be part of the public sector, and have control over its own budget.

COMPENSATION

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- 1 It is recommended that, without delay, the provinces and territories devise statutory no-fault schemes for compensating persons who suffer serious, adverse consequences as a result of the administration of blood components or blood products.**
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A full discussion of the issue of compensation is found in Chapter 39.

THE CANADIAN BLOOD SUPPLY SYSTEM: BASIC PRINCIPLES

- 2 It is recommended that the Canadian blood supply system be governed by five basic principles:**
- a) Blood is a public resource.**
 - b) Donors of blood and plasma should not be paid for their donations, except in rare circumstances.**
 - c) Whole blood, plasma, and platelets must be collected in sufficient quantities in Canada to meet domestic needs for blood components and blood products.**
 - d) Canadians should have free and universal access to blood components and blood products.**
 - e) Safety of the blood supply system is paramount.**
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a) Blood is a public resource.

A fundamental value that must guide the blood supply system in Canada is that blood is a public resource, given altruistically by persons in Canada for the benefit of other persons in this country. Profit should not be made from the blood that is donated in Canada. The operator of the blood supply system must act as a trustee of this public resource for the benefit of all persons in Canada.

b) Donors of blood and plasma should not be paid for their donations, except in rare circumstances.

Blood and plasma from unpaid donors are safer than blood and plasma from paid donors. It is for this reason that the World Health Organization has recommended that blood components and blood products be made from donations from unpaid donors. This principle is premised on the belief that well-informed, altruistic donors will not donate if there is the possibility that their donations will do harm rather than good. By contrast, persons who receive money in exchange for blood and plasma donations may have an incentive to donate even when they know they should not. In rare circumstances, the collection of plasma for specialized blood products may require an offer of compensation.

c) Whole blood, plasma, and platelets must be collected in sufficient quantities in Canada to meet domestic needs for blood components and blood products.

There must be an adequate supply of blood components and blood products derived from Canadian donations to meet domestic needs. Although shortages continue to occur, Canada is self-sufficient in blood components. It is

not, however, self-sufficient in blood products, many of which are made from plasma collected from persons in other countries who are paid.

Self-sufficiency in blood products is a desirable goal for several reasons. First, although complete safety is impossible, the plasma obtained from Canadian donors will be safe in relative terms. Canada has fewer infectious diseases than many other countries have, including parts of the United States, and all Canadian residents have access to good health care services without charge. Moreover, volunteer donors have no incentive to donate other than the desire to assist other persons. If plasma collection is controlled by a national authority and regulated by the Health Protection Branch, there will be domestic control over both the quality of the donor-screening procedures and the collection and processing of plasma. If good donor-screening measures are applied to altruistic donors, it is probable that the quality of the plasma will be superior to that obtained from remunerated donors in countries over which Canadian regulatory authority is diminished. The second advantage of being self-sufficient in blood products is that the supply of blood products in Canada will not be affected by shortages on the world market. The third advantage is that if a blood-borne pathogen emerges in another country, there will be time in Canada to take precautionary action.

The principle of self-sufficiency does not mean that plasma must be fractionated by a domestic fractionation facility.

d) Canadians should have free and universal access to blood components and blood products.

The blood supply system is an integral part of the health care system. In keeping with the principles governing health care in Canada, including universality and accessibility, blood components and blood products that are essential for the health and safety of Canadians should be free to recipients. This goal is not difficult to achieve for blood components and blood products that are administered in hospitals, because all drugs provided in hospitals are free to the residents of Canada. Blood components and blood products that are used outside hospitals should continue to be distributed free of charge, as in the past.

e) Safety of the blood supply system is paramount.

The goal of the blood supply system must be to supply safe therapies to persons who need them. The principle of safety must transcend other principles and policies.

The costs of promoting safety may well be high. For example, when new pathogens appear and new tests are required, when newer and more sensitive tests are developed to identify known pathogens, or when blood products must be withdrawn or recalled and be replaced because they are or may be unsafe, the promotion of safety may well require that substantial sums

of money be spent. When enhanced donor-screening measures are needed to identify a new pathogen, the cost to the blood supply system may be a reduction in the number of donors.

The safety of the blood supply is an aspect of public health, and, therefore, the blood supply system must be governed by the public health philosophy, which rejects the view that complete knowledge of a potential health hazard is a prerequisite for action.

The balancing of the risks and benefits of taking action should be dependent not only on the likelihood of the risk materializing but also on the severity of the effect if the risk does materialize, on the number of persons who could be affected, and on the ease of implementing protective or preventive measures. The more severe the potential effect, the lower the threshold should be for taking action.

Preventive action should be taken when there is evidence that a potentially disease-causing agent is or may be blood borne, even when there is no evidence that recipients have been affected. If harm can occur, it should be assumed that it will occur. If there are no measures that will entirely prevent the harm, measures that may only partially prevent transmission should be taken.

Estimates of the risk of transmission should not be calculated exclusively on the basis of past experience of occurrences. They should also take into account such factors as latency periods, geographical spread, and other possible modes of transmission.

THE OPERATOR: A NATIONAL BLOOD SERVICE

Principles underlying a national blood service

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- 3 It is recommended that Canada have a national system for the collection and delivery of blood components and blood products.**
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A series of local or regional blood supply systems should be avoided for several reasons. A national blood supply system will have national standards to ensure that all persons in Canada needing blood components or blood products have access to products of uniform quality. A national system will have a national inventory of blood components and blood products that will give persons in all parts of Canada equal access to them.

Experience has demonstrated that densely populated urban areas with several tertiary care hospitals usually have greater demands for blood components than can be met from local collection centres. Chronic shortages in one region can be met by increasing donations in other regions. Although the

national blood service will attempt to achieve self-sufficiency in blood components within each region of its operations, there should be a national pool of blood components to ensure that supplies are available to meet demands in all regions. In short, the national blood service must collect blood where it is available and distribute it where it is needed.

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- 4 It is recommended that the core functions of the national blood supply system be performed by a single operator and not be contracted out to others.**
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The core functions of the blood supply system are (1) recruitment of donors; (2) collection from donors; (3) testing of the donations for blood type and the presence of known pathogens; (4) processing of the donations into components; and (5) distribution of the components and blood products to hospitals and local health authorities for final administration to persons who use the components and products. The functions are interrelated. Recruitment of donors and collection of blood determine the safety of the blood collected. Testing, storage, and processing determine the safety of the blood components that are distributed and administered. Blood products require an additional step, that of manufacturing, during which the plasma of many thousands of donors is pooled and fractionated to obtain various therapeutic products.

Information derived in the course of one stage in the process may well become important at another stage. For example, information from a test for a pathogen that shows that a donor is infected is important not only to the donor but also to the recipients of components made from previous donations, to the manufacturer of blood products made from plasma from previous donations, and to the recipients of those blood products. Information must flow quickly and accurately among the various stages in the process. Speed of communication is a critical factor in preventing the use of contaminated units and in identifying the recipients of contaminated units that are used.

An integrated system, unlike a series of systems or a decentralized system, can function efficiently, expeditiously, and uniformly in all parts of the country. For example, if a new pathogen that is endemic to a particular geographic region is described, the operator of an integrated blood supply system can require the amendment of the affected region's recruitment practices to prevent donations from persons from that geographic region. It can ensure that changes are made quickly and satisfactorily.

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- 5 It is recommended that the operator of the blood supply system not operate its own fractionation plant or be bound to use a domestic fractionator for the custom fractionation of Canadian plasma.**
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Although it is important to integrate all the functions that contribute to the safety of the plasma from which blood products are made, it is not essential to have a fractionation plant or plants in Canada. The capacity to manufacture fractionated products requires significant capital investment. The manufacturing processes of blood products are complex and subject to rapid and expensive change. The national blood service should not own or operate a fractionation plant, nor must it become bound to produce blood products by any particular process when a safer process becomes available.

Canadian plasma should be custom fractionated, in batches consisting only of Canadian plasma, based on specifications negotiated between the fractionator and the national blood service. These specifications should include requirements for the manufacture of the safest and the highest-quality products.

6 It is recommended that the blood supply system be operated in an open and accessible manner.

The current lack of confidence in the blood supply system affects donors of blood, consumers of blood components and blood products, and the public at large. This lack of confidence results, in no small measure, from the absence of public participation in the decision-making process that, until now, has characterized the system.

It is integral to the success of any new blood supply system that it have the confidence, trust, and commitment of the public. The public must have access to information about the policy, management, and operations of the blood supply system and be represented in the decision making.

The risks inherent in blood components and blood products should be fully disclosed, even when the gravity or likelihood of a risk is still uncertain. Recipients of blood components and blood products must be able to make informed choices, in consultation with their physicians, about the relative benefits and risks of receiving blood or blood products. Members of the public are entitled to know the risks and uncertainties. Actions that are taken to minimize the risks must be communicated to the public, including the reasons for choosing one action or measure over another.

7 It is recommended that the operator of the blood supply system be independent and able to make decisions solely in the best interests of the system.

To minimize the danger inherent in blood components and blood products, the operator of the blood supply system must be able to adopt important safety measures without any political interference.

Political considerations, unrelated to the safety of the blood supply, must not be allowed to interfere with the ability of the operator of the blood supply system to deliver safe products efficiently and effectively. The operator of the blood supply system must be sufficiently insulated from political decision makers so it is not forced to make decisions that are incompatible with the safety of the blood supply or the efficiency of the blood supply system.

8 It is recommended that the authority for the operation of the blood supply system be clearly defined.

The decision maker or decision makers, whose identity must be clearly known, must be answerable for the decisions, and must be subject to appropriate sanctions for any failure to discharge the function satisfactorily.

Decisions that affect safety are often difficult decisions. Frequently, they must be made in the face of incomplete data and can have repercussions in cost, supply, harm, and public dissatisfaction.

These decisions must be clearly defined and assigned to persons who have sufficient and appropriate authority to carry out their functions.

9 It is recommended that the operator of the blood supply system promote appropriate use of, and alternatives to, blood components and blood products.

Blood components and blood products will never be without risk. The best way to reduce that risk is to reduce their use. This decreased use can be accomplished by prescribing blood components and blood products only when their use is essential and only in the smallest amounts required.

The operator of the blood supply system must develop and coordinate educational programs for physicians to encourage the appropriate use of blood components and blood products. Educational material should be developed for and distributed to persons who are users of blood or alternative products, such as persons with cancer or with deficiencies in their clotting systems, or persons about to undergo surgery that could require the use of blood. These persons would then have the knowledge to enable them to discuss intelligently with their physicians the appropriateness of their treatment.

Increasingly, blood products are being replaced by new and alternative treatments that do not use blood components or derivatives. For example, most factor VIII currently used in Canada is no longer made from plasma, but from recombinant DNA. However, the recombinant product is stabilized in a plasma derivative.

Similarly, the need for transfusion of blood components is being reduced in some cases by the use of medical techniques that allow the patient's blood to be conserved or reused during surgery. As the Interim Report stated, the transfusion of a person's own blood (autologous transfusion) is safer than the transfusion of blood components made from the donations of other persons (allogenic transfusion).

The operator of the blood supply system should be fully informed of the risks and benefits of alternative therapies and promote their appropriate use.

The national blood service

10 It is recommended that the blood supply system be publicly administered by a national blood service, a corporation to be created by an Act of Parliament.

The blood supply system is part of the health care system and therefore should be publicly administered. The operator of the blood supply system should be a corporation that is dedicated exclusively to the operation of the blood supply system. It is essential that the blood supply system be integrated. The national blood service must perform all the important functions and processes: it must recruit donors, collect and process blood, and distribute blood components and blood products. It should not be able to issue contracts to other organizations or institutions to perform any essential function, such as donor recruitment or the testing of donations, that could have an impact on the safety of blood or blood products.

The principles, policies, and governing structure of the national blood service should be set out in its incorporating legislation.

11 It is recommended that the provincial and territorial ministers of health be the members of the corporation.

The ministers of health of the provinces and territories administer legislation providing for the delivery of health care services in their respective provinces and territories. Their ministries and departments also pay for the blood supply system. They, therefore, should be the members of the corporation.

The federal Minister of Health must not be a member of the corporation because the Department of Health is the regulator of the blood system in Canada. To permit the Minister of Health to be a member of the corporation is to create an apparent conflict of interest and, possibly, an actual conflict.

12 It is recommended that the members of the corporation appoint an independent board of directors to supervise the management of the service and that the members of the board carry out their duties at arm's length from government.

The ministers of health of the provinces and territories, even though they are the members of the corporation, must not operate the service or interfere with its operations. The operations must be directed by an independent board of directors, appointed by the members. The board of directors must be at arm's length from the provincial and territorial governments. To protect their independence, the directors must not be elected officials or public servants.

It is essential that the board be committed to the safety and efficacy of the blood supply system. The term of appointment must be long enough to allow the directors to develop a knowledge and understanding of the blood supply system, but should allow for a sensible turnover in membership. The introduction of new directors should be done on a graduated basis to preserve continuity. Although it is necessary that the board reflect a variety of expertise and interests, it should not be so large as to hamper expeditious decision making.

The directors need not be experts in the field of transfusion medicine. It would be desirable to have representation on the board from the following fields: science and medicine, ethics, hospital management, health care services, public health, and business and finance. Some of the directors should be persons selected from among the consumers of blood components and blood products as well as blood donors.

The annual report of the national blood service should be tabled in all of the provincial and territorial legislatures. In addition to the customary financial information, the report should contain a comprehensive assessment of the safety of the blood supply, including summaries of the numbers and types of accidents and errors that occurred in the operation of the national blood service.

Subject to the need from time to time to proceed *in camera*, the meetings of the board of directors should be open to the public.

13 It is recommended that the national blood service be subject to regular audits.

Independent regular audits should be conducted of both the finances and the operations of the national blood service. The results of these audits should be published in the annual report.

14 It is recommended that, in addition to the customary committees of a corporate board of directors, the following standing committees be created to facilitate the work of the national blood service:

- A *safety committee*, consisting of persons from the fields of infectious diseases, epidemiology, public health, medicine, and blood banking, as well as consumers. The purpose of the committee is to advise the board about the safety of the blood supply, including existing and emerging pathogens. It should also assist the board in the process of risk assessment.
- A *technical and scientific committee*, to keep abreast of the frequent and rapid technical and scientific developments that affect the blood supply system. This committee should ensure that the board of directors always has current information about scientific developments. It should also advise the board about the expenditure of the research funds for the blood supply system and should monitor technical developments affecting the blood supply system, including alternatives to blood components and blood products, and methods of improving the safety and efficacy of blood components and blood products.
- A *liaison committee*, consisting of representatives of community and consumer organizations. This committee should ensure that special interests are brought to the attention of the board and that there is adequate communication between the national blood service and any pertinent external organizations, including community and national organizations for recipients, public health organizations, and national and international health and blood-banking organizations. It should also advise the board about the development of educational material for donors and consumers.

To promote the principle of openness, all committees should have as members representatives from consumer groups and the public. The board must not delegate decision making to its committees and, in times of crisis, must not delay its decision making to an extent that could risk health and safety as it awaits advice about a specific issue. The committees must be given sufficient resources to carry out their duties. Minutes of the meetings and background materials should be available to the public.

Funding of the national blood service

- 15 It is recommended that the national blood service be funded by payments from hospitals for the blood components and blood products supplied to them by the blood service.**
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- 16 It is recommended that the provinces and territories, no longer bound to finance the blood supply system by making grants to the Canadian Blood Agency, increase the budgets of hospitals using blood components and blood products by amounts that will enable them to pay the national blood service for these components and products without affecting their other programs and services.**
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Recent history shows that if the national blood service is to be successful in responding to challenges to safety, it must control its own budget. The best means for it to gain this financial control is by charging a price for the blood components and blood products it delivers. Two other advantages can be expected from this system of payment for products supplied: first, the fee will act as an incentive for the appropriate use of blood components and blood products; and second, the arm's-length relationship between the governments and the new blood service will reinforce the principle that safety, and not political considerations, must be the criterion for decision making.

The prices paid for blood components and blood products should be fixed by the national blood service at levels sufficient to pay the cost of its operations, but must not include any profit. The cost of operations includes the costs of collecting, testing, and processing blood donations, and of storing and delivering blood components and blood products. The prices should include a component to support research, a compensation fund, and a contingency fund.

Although the expense of delivering blood components and blood products may vary from place to place, the prices must be the same throughout Canada because of the principle of universal access to blood components and blood products.

The national blood service should determine unilaterally the price structure. There should be a procedure, however, by which one or more of the provinces or territories can challenge the blood service's decision on the ground that the prices are unreasonable. In most cases, an informal fact-finding process that explains the reasons for the price may be all that is necessary to resolve the dispute. In other cases, a more formal process will probably be needed. The Patented Medicine Price Review Board is one example of a formal price review tribunal with the power to regulate the prices charged for therapeutic products to ensure they are not excessive.

Management and operation of the national blood service

- 17 It is recommended that the principal functions of the national office of the national blood service be the setting and enforcement of standards, the setting of prices for blood components and blood products, the management of inventory, and the coordination of regional centres.**
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The national blood service will require a national office, regional blood centres, and a national laboratory. The national office must perform the following functions: the setting of national standards, and special local standards where necessary; the establishment of quality assurance programs, including audits and inspections of regional centres; the management of a national inventory of blood components and blood products to ensure that all regions have access to sufficient supplies; the selection of fractionators and the purchase of blood products; the formulation of plans for cost-efficient operations; the communication with Canadian and international organizations concerned with blood; the setting of prices; the administration of the funds created by surcharges; and the coordination of the operations of regional blood centres.

The national blood service must determine the optimal number of regional blood centres that are required to obtain the maximum number of blood donations, without compromising safety. This assessment should not be based on provincial or territorial boundaries. The national office must set a global budget for each blood centre based on the cost of operations in its region.

The major functions to be performed by the regional blood centres are blood donor recruitment, the collection and processing of blood donations, and the storing and distribution of blood components and blood products. The national blood service should decide whether all centres need to perform all these functions. In particular, it should decide whether each centre needs to carry out its own tests or whether testing can be performed at central locations. This decision should be based on regional needs as well as cost-efficiency.

The national blood service should decide whether plasmapheresis and plateletpheresis should be performed only at the regional blood centres or also at specialized clinics.

Some regional blood centres may want to engage in activities that fall outside the essential, or core, functions of the national blood service. The national office should ensure that any other activities that the regional centres perform do not compromise the expertise or resources necessary for the operations of the blood supply system.

18 It is recommended that the operation of the national blood service be managed by both administrative and medical personnel.

The national blood service will have a double role to play. On the one hand, it will manufacture therapeutic products, and for this role it will need an experienced and capable administrator. On the other hand, it will provide medical services in an era of rapid innovation, and for this role it will need highly trained medical and scientific personnel.

This double role requires the appointment of two officers with different skills: a chief executive officer and a chief medical director. The chief executive officer must manage the operation of the corporation and execute the policies of the board. The chief medical director must be in charge of all the medical issues that relate to the functions of the blood service, and must supervise and direct the medical directors of the regional centres. Their spheres of authority must be clearly delineated. On administrative issues, the chief medical director should report to the chief executive officer; on medical and scientific issues, however, the chief medical director should answer and report directly to the board of directors.

At least two advisory committees will be necessary to assist the national office:

- A *blood component and blood product use committee* should monitor the use of blood components and blood products and facilitate the development of guidelines for their use. It should monitor the medical and scientific literature for new information and developments that affect the use of blood components and blood products. It should also give advice with respect to inventory, and act as a liaison with hospital transfusion committees to promote the appropriate use of blood components and blood products.
- A *blood product selection committee*, consisting of treating physicians and consumers of blood products, should advise the national office about the use of blood products. Even if Canada is self-sufficient in plasma, it is important for the national blood service to have a clear understanding of the needs and preferences of the users of blood products when decisions are made about the fractionation procedures and the types of alternatives that should be made available.

The regional blood centres should have a similar organization to that of the national office. There should be a senior official for administration; there should also be a medical director for medical, scientific, and technical issues, particularly the processing and testing of donations and the supervision of issues relating to blood donors. The medical director should be a physician. Whether the medical director of a given regional blood centre must be a full-time appointment is a decision that the national office must make.

19 It is recommended that the national blood service have a safety auditor.

The national blood service should employ a safety auditor, a senior officer of the corporation. Unlike the chief executive officer and the chief medical director, the safety auditor should not be part of the organizational hierarchy of the national blood service but should report directly to the board of directors. The safety auditor should be an *ex officio* member of the board and of any committee that deals with safety issues. The safety auditor must have a full knowledge of all the operations of the national blood service that can affect safety, and must also be familiar with scientific and technical advances, and with new or emerging threats to health that relate to the safety of the blood supply. The safety auditor should be informed of quality assurance audits, error and accident reports, results of surveillance and other research, and all inspection reports. The safety auditor should prepare that part of the national blood service's annual report that is the comprehensive assessment of the safety of the blood supply. The safety auditor should be given adequate resources to perform these duties satisfactorily.

The safety auditor should give the Bureau of Biologics and Radiopharmaceuticals copies of any formal safety recommendations that have been made to the board of directors. The safety auditor should also obtain from the Bureau of Biologics and Radiopharmaceuticals and the Bureau of Drug Surveillance any information they have about the safety of products distributed by the national blood service.

20 It is recommended that the national blood service permit regional blood centres to develop procedures responsive to local needs.

Although every regional blood centre must adhere to the standards of the national office with respect to the quality of the blood and plasma collected in its region, there should be a degree of regional independence in the way in which they meet these goals. Regional blood centres should be encouraged to develop unique solutions for problems that arise in their regions. Regional blood centres should have the freedom to exceed national standards if they are able to do so.

The national office should ensure that there is coordination and communication with and among the centres through the medical directors, the administrative officials, and the personnel in charge of quality assurance, laboratory services, and donor recruitment. The independence of the regional centres is not incompatible with the national office's obligation to audit the operations to ensure that standards are met and to facilitate communication among centres. If a centre manages to exceed national standards, its methods

or processes should be communicated to other centres and the national standards should be raised. The national office should coordinate and facilitate change rather than inhibit innovation.

The independence of regional blood centres implies that, from time to time, important medical and scientific decisions may be made elsewhere than at the national office. Many of these decisions will require medical expertise and medical judgment, qualities that are possessed by physicians and not by administrators. It is for this reason that every regional blood centre must have a medical director.

21 It is recommended that a national integrated database be created to store and manage information about donors, donations, and recipients.

A national integrated database is essential to the protection of the safety of the blood supply. It must contain information about donor deferral, the testing and processing of blood donations, and the storing and distribution of blood components and products.

In particular, the donor deferral database must be national in scope. Many persons in Canada live in more than one region of the country in the course of their lives, and they may often donate in different regions of the country. Donor information, particularly the reasons for deferral, should be available wherever blood is collected. If, for example, a prospective donor is deferred in Montreal and later moves to Calgary, the blood centre in Calgary must know about the deferral and the reasons for it.

A national integrated database is essential to allow tracing, and, if necessary, deferring donors in cases where there is reason to suspect that their donations may have been contaminated. For example, when a recipient shows evidence of a transfusion-associated infection, an integrated database facilitates the rapid tracing of the donor. The donor can then be given important information about his or her health and the opportunity to obtain timely treatment, if appropriate. Earlier donations can also be traced and, with the assistance of hospitals, the recipients of the donations can be notified.

Such a database makes it possible for all information, such as donor identity, laboratory testing for markers of infectious diseases, and blood typing, to be integrated. The label to be applied to the blood components would then be accurate and would be issued only if all phases of the process have been completed successfully.

22 It is recommended that there be an effective exchange of information between the national blood service and all hospitals that supply blood components and blood products.

- 23 It is recommended that the national blood service make it a condition of supplying blood components and blood products to hospitals that they maintain adequate records and that the blood service's standards for storing blood components and blood products be observed.**
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Much important information about blood components and blood products is beyond the control of the national blood service. For example, it will not know the identity of persons who receive transfusions of blood components or infusions of blood products, and it will not learn of adverse reactions to blood components or blood products unless it is informed by treating physicians or hospitals. It will not know, without being told, the current inventory of blood components and blood products in the possession of hospitals.

Effective communication of information between the national blood service and hospitals is required. In cases of transfusion-associated infectious disease, the donor of the infectious component must be traced, as must the recipients of other potentially infected components derived from the donations of the same donor. Moreover, to be able to correct any deficiencies in its processes that may have caused adverse reactions, the blood service must also be given information about other adverse reactions to blood components or blood products. Hospitals should require physicians to submit post-transfusion reports to their blood banks. The blood banks, in turn, should report to their transfusion committees and to the national blood service.

To manage its inventory effectively and to plan for the future supply of blood components and blood products, the national blood service must have current and reliable information. Much of the inventory in the system will be held not by the blood service but by hospitals. The blood service must therefore regularly receive current inventory information from hospitals. The most efficient way to communicate the information is by daily electronic transfer.

- 24 It is recommended that an amount equal to 10 per cent of the annual operating budget be allocated to research and development.**
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Research and development is the means by which an organization keeps abreast of changes in medical techniques and technology. The blood service should have the facilities and the competence to conduct in-house research, but should also administer a program for external research and collaborative work between the national blood service and other organizations. All this research should be subject to peer review. Both in-house and external research support should be divided among basic scientific research, applied research, and the surveillance of donors and recipients.

Donors and recipients

- 25 It is recommended that significant efforts be made to ensure that blood components and blood products used in Canada are made from the blood and plasma collected from unpaid donors.**
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In Canada, blood and, with very few exceptions, plasma have always been collected from unpaid donors. Although there have been continual shortages in some regions since the late 1970s, Canadian voluntary blood donations have usually been sufficient to supply Canadian needs for blood components.

The volume of plasma recovered from whole blood and collected by plasmapheresis is not sufficient to meet the demand for plasma-derived products. A strong effort should be made to achieve self-sufficiency in plasma within a limited period, and progress towards that goal should be carefully monitored. Plasma collected by plasmapheresis should be increased to a level high enough to make up the difference between the total amount of plasma needed and the amount obtained from whole blood. Because most hemophiliacs in Canada no longer use plasma-derived products, the goal of becoming self-sufficient in plasma should be easier to achieve than in the past.

Some special blood products, such as Rh immune globulin, can be made only from the plasma of donors who possess high concentrations of rare antibodies, or who acquire the antibodies through immunization. The manufacturers of such products rely on a small number of donors who donate plasma as often as once a week. Despite the policy of gratuitous donations, it may be necessary to offer compensation to these persons for their time and effort in order to attract a sufficient number of donors.

- 26 It is recommended that the national blood service make the process of blood donation more accessible and more convenient for donors.**
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The national blood service's greatest immediate challenge will be to recruit enough donors to supply the needed volume of blood components and plasma. There are hundreds of thousands of persons in Canada who have repeatedly demonstrated their commitment to others by donating blood. It must persuade them to continue their humanitarian and generous behaviour and, at the same time, encourage new donors to emulate that behaviour.

Donating blood and plasma has become more difficult in the last few years. There are fewer clinics, their hours of operation are restricted, and waiting times have increased. Donating must be made more convenient.

For example, waiting times can be reduced if donors are given appointments. Clinics should stay open on evenings and weekends, and parking and child care should be provided.

The screening of prospective donors has become more extensive and more intrusive. Careful screening is essential to maintain the safety of the blood supply, and it must continue. It may be possible to develop a means of obtaining the necessary information with less intrusion. Moreover, if the reasons for the more careful screening are properly explained to prospective donors, they will tolerate the inconvenience as an essential step in protecting the well-being of the recipients of their donations.

Significant efforts should be made to attract new groups of donors. Evidence heard during the Inquiry suggests that blood donation has not been customary among some cultures in our increasingly multicultural society. It may be that, without any impairment of cultural values and attitudes, new donors may be found in these groups. In any event, donor recruitment and research into donor recruitment must be a principal activity of the national blood service.

27 It is recommended that persons whose donations are not accepted for use be told why the donation was not accepted and, where appropriate, be offered counselling.

Before a blood donation is accepted for use, the blood donor is questioned, a limited physical examination is conducted, and the donated blood is tested. During the questioning and the physical examination, it may become apparent that a person should not donate. Whatever the reason for not using the donation, the person should be told the truth. The donor should never be misled into believing that the donation will be used when there is no intention of doing so.

Blood donations are tested for the presence of factors indicative of infectious disease, including HIV, syphilis, and hepatitis. Blood donors whose donations test positive must be informed at the earliest possible time. This information should be communicated personally. A form letter is not sufficient. The medical directors of the regional centres should promptly provide counselling to these donors, particularly if any delay increases the risk to the health of the donor or to persons with whom the donor is in contact. If necessary, a medical director should refer such a donor to a physician for treatment.

28 It is recommended that, on learning of potential risks to the safety of blood components or blood products, the national blood service cause the recipients to be informed.

From time to time, information about the potential infectiousness of a donation is discovered months or years after a donation is made. The blood components or blood products derived from the donation have long since been transfused or infused. The recipients of these blood components or blood products are entitled to be informed of these risks, even in circumstances where the risk is theoretical and no treatment is currently available.

The national blood service will not know who the recipients of these blood components or blood products are. That information will be known only to hospitals. The blood service's information system must have the capability of exchanging information in such a way that either the blood service or the hospitals will notify these recipients.

THE REGULATOR: THE HEALTH PROTECTION BRANCH

The blood system for the future will need a strong regulator. In any national blood system, the regulator must set minimum standards for all phases of the collection, processing, and storage of blood and plasma; enforce compliance with the standards; and take actions to protect public health and safety by ensuring that unsafe products never reach the market. If hazards are detected that affect the safety of products on the market, the regulator must ensure that the products are promptly removed from distribution.

29 It is recommended that there continue to be a bureau that is dedicated to the regulation of biological drugs, including blood components, blood products, and their substitutes.

There are important differences between biological drugs and chemically derived drugs. For example, there is a greater variance in the contents of biological drugs than of chemically derived drugs. Every plasma pool is different from every other plasma pool. Each consists of plasma from many donors, who have different levels of biological activity and have been exposed to different pathogens. By contrast, every lot of chemically derived drugs should consist of identical raw material. Applications for the distribution of biological drugs therefore require more intensive review than is necessary for chemically derived drugs. In particular, each lot of biological drugs must be assessed. The Therapeutic Products Directorate of the Health Protection Branch must contain a separate bureau for the regulation of biological drugs.

Because of the greater complexity of biological drugs compared with chemical drugs, the bureau should have its own standards for time limits for reviews, the fees charged, and the procedures used for conducting post-market surveillance.

30 It is recommended that the Bureau of Biologics and Radiopharmaceuticals adopt a policy of active, not passive, regulation of the national blood supply system.

The purpose of the *Food and Drugs Act* is to protect the health and safety of Canadians. That purpose can best be accomplished if the Bureau of Biologics and Radiopharmaceuticals is active. Regulatory officials must try to identify risks that could threaten the safety of the blood supply and develop policies to deal with them before they materialize. There must be frequent inspections of the premises of licensed manufacturers, one of which is the national blood service, and strict enforcement of all regulatory requirements. Decisions about risk management must be made, implemented, and communicated promptly.

The Bureau of Biologics and Radiopharmaceuticals must foster and maintain effective lines of communication with the manufacturers and distributors of the products it regulates, and it must review manufacturers' applications promptly and fairly. An active regulator does not rely solely on, or defer to, manufacturers for information, expertise, and judgment, but seeks its own information about the safety and purity of blood products. It must also be independent, so that, in exercising its duty to enforce compliance with regulations, it does not even appear to have a conflict of interest. The bureau may work with manufacturers to improve compliance.

The Bureau of Biologics and Radiopharmaceuticals must constantly review the scientific and medical literature for information about new technologies that may increase the safety and effectiveness of blood components and blood products. It must also constantly be on the look-out for the risks of contamination or adverse reactions from these products. Whenever possible, the bureau should use means other than those employed by the manufacturers to verify or validate the results of tests and studies submitted by them. It must not assume a passive or responsive role, or rely on a philosophy of voluntary compliance, to protect the health of Canadians. The regulations governing blood and blood products must be strictly enforced, and the actions taken by the manufacturers to comply with regulatory directives must be closely monitored.

The review of data submitted by manufacturers in support of their applications for licensing must be thorough and inquiring. When there is any doubt about the meaning of data or questions about claims for enhanced safety, the Bureau of Biologics and Radiopharmaceuticals must satisfy itself that it has all the information it needs to perform its task. If it does not, it must demand more information, independently check data, or take whatever action is needed to assure itself that the information is complete and that the conclusions reached by the manufacturer are valid. Information about failed or aborted studies should also be demanded.

The Bureau of Biologics and Radiopharmaceuticals must continually assess the risks associated with any potential threat to the safety of the blood supply. It may seek advice from any quarter, but it must reach an independent determination of the magnitude and seriousness of a risk. It must also determine whether the appropriate management of the risk includes a regulatory component. It cannot allow uncertainty to paralyse the need for action. It must communicate its decisions and monitor their implementation. And it must constantly assess the effects of its decisions, and adjust them when necessary. It should coordinate any risk management responses that are necessary with the actions of others involved with the protection of the safety of the blood supply system. It should never assume that others will take appropriate action or act in its stead.

31 It is recommended that the Bureau of Biologics and Radiopharmaceuticals make decisions with respect to the safety of blood components and blood products independently of those made by manufacturers and distributors.

32 It is recommended that the Bureau of Biologics and Radiopharmaceuticals accept manufacturers' or distributors' decisions to take actions that exceed the standards of safety set by the bureau.

Safety decisions made by the Bureau of Biologics and Radiopharmaceuticals may relate to a single batch of one manufacturer's product or to an entire type of plasma-derived drugs. Whatever the scope of the decision, the bureau's duty is independent of the decisions of both the manufacturers and the Canadian distributors of blood products. When a manufacturer or a distributor decides to withdraw a product, the bureau must accept that decision.

To be able to make independent decisions, the Bureau of Biologics and Radiopharmaceuticals must develop its own reliable sources of information and its own capacity to analyse the information it collects, including information about the effects of its regulatory decisions. The bureau's duty to make decisions with respect to safety is a continuing one. It arises at the time of reviewing applications for licensing and relicensing. It also arises after a product is on the market when information becomes available that raises questions about its safety or efficacy, the processes used in its manufacture, or the integrity of the manufacturer.

33 It is recommended that the federal Minister of Health appoint an advisory committee to assist the Bureau of Biologics and Radiopharmaceuticals in its assessment and management of risk.

The Bureau of Biologics and Radiopharmaceuticals should be assisted in its task of making decisions about safety by a standing advisory committee. The membership of the committee should include persons from the different fields of interest and expertise that relate to the protection of the safety of the blood supply, such as representatives from relevant medical, scientific, and public health professions, ethicists, manufacturers, and consumer groups. No one interest group or profession should dominate the committee. The committee's recommendations with respect to any issue that affects the safety of the blood components and blood products used in Canada must be forwarded directly to the federal Minister of Health. The meetings of the advisory committee should be open to the public.

Under no circumstances may the Bureau of Biologics and Radiopharmaceuticals use the advisory committee as a means of deferring or delaying a pressing regulatory decision.

34 It is recommended that the decision-making process of the Bureau of Biologics and Radiopharmaceuticals be open and accessible to the public.

Public confidence in the federal Department of Health will be restored and maintained if its decision-making process is as open as possible. However, much of the information on which its decisions are based is necessarily confidential for commercial reasons.

Reports of the Therapeutic Products Directorate, including reports of both the Bureau of Biologics and Radiopharmaceuticals and the Bureau of Drug Surveillance, should be made available to the public. These reports include inspection reports of manufacturers' premises and blood centres, adverse drug reaction reports, information about recalls and manufacturers' product withdrawals, information about risks in certain products, and collations of accident and error reports. In this way the openness of the regulatory process can be promoted.

35 It is recommended that the *Food and Drug Regulations* be rewritten to make them intelligible.

36 It is recommended that the *Food and Drug Regulations* be amended to give the Therapeutic Products Directorate the authority to order a manufacturer or a distributor to recall a drug.

37 It is recommended that the *Food and Drug Regulations* be amended to contain regulations for the collection and processing of whole blood.

38 It is recommended that the *Food and Drug Regulations* be amended to require that labels on biological drugs contain information about the risks or potential risks of infectious diseases associated with the use of the drug.

The *Food and Drug Regulations*, as they are structured at present, are complex, hard to read, and difficult to interpret, largely because of the many amendments that have been made over the years. It is essential that any regulation be intelligible to the regulated, and it is desirable that it also be intelligible to the public. The current regulations fail on both counts. Regulations invariably become out of date as new therapies and treatments are developed. There must be regular re-evaluation of the regulations to ensure that they are currently appropriate. For example, regulations governing the collection and processing of whole blood are long overdue.

There may be times when a product is considered a risk to the health of consumers, but its complete removal from the market may pose an even greater risk to the health of some of these consumers. The Therapeutic Products Directorate must have the power to “quarantine” a product so that it is released only if patients consent and if no alternative product is available. The distributor must also have a power, which it does not now have, to recall a product.

The regulations prescribing the requirements for warning labels on or in drug packaging do not require that users be informed of the risks inherent in using blood products. They should require that the risks of infectious diseases associated with the use of these products be disclosed.

39 It is recommended that the Bureau of Biologics and Radiopharmaceuticals communicate regulatory requirements to manufacturers and distributors of blood products and blood components in a formal and unambiguous manner.

From time to time, the predecessor of the Bureau of Biologics and Radiopharmaceuticals gave instructions to manufacturers and distributors of blood products and blood components in language or in a form that has made it difficult for them to know what was being asked of them.

The Bureau of Biologics and Radiopharmaceuticals should communicate regulatory requirements in directives that specify actions that must be taken to comply with the regulations. Other types of communication can be contained in guidelines, policy statements, or advisories. A guideline sets out the views of the bureau on a particular issue and sets out specific actions

that, if taken, are likely to ensure regulatory compliance. A policy statement also sets out the views of the bureau, but does not prescribe specific actions. An advisory alerts members of the industry about potential problems.

40 It is recommended that there be an active program of post-market surveillance for blood components and blood products.

The continuing safety of blood components and blood products depends on an active program of post-market surveillance. One of the most important aspects of post-market surveillance is the reporting of adverse drug reactions, which must first be reported by physicians to manufacturers or the national blood service and then reported to the Therapeutic Products Directorate. The directorate should establish networks of scientists and physicians to investigate adverse reactions, and it should report the results of the investigations to physicians.

Other essential aspects of post-market surveillance include monitoring medical and scientific literature, establishing communication links with provincial-territorial and national public health authorities, establishing communications with groups of persons who use particular products, and communicating with regulatory authorities in other countries about such matters as adverse reactions, product withdrawals, and recalls.

In 1995, a new bureau, the Bureau of Drug Surveillance, was established to collect reports of adverse drug reactions and other information relevant for a program of pharmacovigilance. Both the Bureau of Drug Surveillance and the Bureau of Biologics and Radiopharmaceuticals receive reports of adverse drug reactions to blood components and blood products. Collaboration is needed between the two bureaus with respect to the collection and analysis of all the information gathered by the bureaus. Also necessary is the allocation of sufficient resources and persons with expertise in biological drugs to conduct inspections, investigations, or testing.

41 It is recommended that the Bureau of Biologics and Radiopharmaceuticals conduct frequent and thorough inspections of the operations of the national blood service.

The inspection of regional centres is one of the principal means by which the Bureau of Biologics and Radiopharmaceuticals is able to confirm that blood and plasma are being collected, processed, and distributed in a safe manner, and thereby to protect the safety of blood components.

42 It is recommended that the Bureau of Biologics and Radiopharmaceuticals re-evaluate the safety of blood products on the market during its review of manufacturers' applications to renew their licences.

When a manufacturer applies to renew a licence, the Bureau of Biologics and Radiopharmaceuticals has an important opportunity to re-evaluate the safety of the products listed on the licences. In most cases, except for blood collection and processing, an application to renew a licence does not require the same level of scrutiny as is exercised on an original application. The renewal should, however, not be granted automatically. As part of this review process, the bureau must conduct periodic inspections, including inspections of the premises of plasmapheresis centres that collect the plasma used in the manufacture of derivatives distributed in Canada.

43 It is recommended that the Bureau of Biologics and Radiopharmaceuticals be given sufficient resources to carry out its functions properly.

The single most important factor determining whether a regulator will perform its functions adequately is whether it is given sufficient resources to do so. Since its inception, the Bureau of Biologics and Radiopharmaceuticals has had insufficient resources. Without sufficient resources, the bureau cannot perform adequately, and the safety of the blood supply is threatened. Earlier recommendations by independent reviewers for the allocation of adequate resources to permit the bureau to discharge its important duties have not been implemented.

The bureau must have sufficient numbers of qualified and trained persons to review the manufacturers' submissions to distribute products in Canada, conduct regular inspections of manufacturing facilities and blood centres, and, in collaboration with the Bureau of Drug Surveillance, collect and analyse data obtained during post-market surveillance. Persons assessing safety must be public servants dedicated to the goals of the Therapeutic Products Directorate. There should be no contracting out of the reviewing process. This prohibition does not mean that there should not be collaboration and exchanges of competent persons with universities and other organizations, for these practices serve to increase the level of competence in the bureau. Members of the bureau must be given opportunities to improve their skills and to participate in continuing education and research. The bureau should employ persons with competence in clinical matters to conduct the reviews of clinical data and advise other reviewers.

The Bureau of Biologics and Radiopharmaceuticals must also have laboratory facilities and competence in laboratory sciences. It must be able to conduct tests to determine the quality, consistency, and safety of biological products and to conduct random tests of lots of licensed blood products. These essential functions should not be delegated to others.

Persons in the bureau with competence in laboratory sciences also have an essential role to play in the development of new and better tests to identify potential hazards. Only through experience in testing new products and exploring measures to assess safety, purity, and potency can the bureau develop the expertise necessary to recognize the potential for risk in a product under review.

44 It is recommended that Canada continue to participate in efforts to develop international harmonization in many aspects of drug licensing, but that it retain the duty and authority to make decisions about the products to be distributed in Canada.

The international harmonization of drug licensing offers many advantages to manufacturers, cost savings to regulators, and potential benefits to persons who require earlier access to new drugs.

The valuable aspects of harmonization that should be encouraged are standardized formats for the submission of information to regulatory authorities in different countries; collaboration in the conducting of reviews, including the exchange of information about the results of reviews; and acceptance of good manufacturing practices as the standard for inspections. The Bureau of Biologics and Radiopharmaceuticals must, however, retain the authority to make the licensing decisions for Canada. It must also retain the authority and the ability to conduct its own inspections and lot-by-lot reviews of biological drugs, particularly blood products.

45 It is recommended that international audits of the Bureau of Biologics and Radiopharmaceuticals be conducted every five years.

The insight of persons with international regulatory experience is valuable to the Bureau of Biologics and Radiopharmaceuticals. Through them, it will learn about shortcomings in its performance that it might not otherwise recognize. International audits will also reveal whether the bureau has adequate resources. The reports of the international audit should be made public.

PUBLIC HEALTH

46 It is recommended that provincial and territorial ministries of health require that the reports of cases of diseases that can be transmitted by blood specify the means of transmission.

47 It is recommended that the governing bodies of physicians and surgeons in the provinces and territories enforce the standard of practice that requires physicians to report notifiable diseases.

One of the most important roles that the public health system plays in contributing to the safety of the blood supply is the surveillance of infectious diseases transmitted by blood components and blood products. Satisfactory surveillance is impossible unless physicians report incidences of reportable infectious diseases to public health authorities.

There is, as there always has been, a chronic and serious underreporting of reportable diseases. Although it is a standard of practice for physicians in Canada that they comply with legal duties, including the reporting of infectious diseases, this legal duty to report is often ignored. Governing bodies of physicians and surgeons in the provinces and territories should stress the importance of reporting infectious diseases, and should enforce this requirement on their members.

The national blood service must learn of cases in which infectious diseases are transmitted by blood components and blood products so it can defer the implicated donor or donors, notify other recipients, and, if appropriate, withdraw the suspect blood components or blood products. Reports to public health authorities of cases of infectious diseases do not routinely include information about the route of transmission. In particular, they do not state whether the disease resulted from the use of blood components or blood products when that is the case. Accordingly, the regulations with respect to the reporting of infectious diseases in the provinces and territories should be amended to require the inclusion of information about the means of transmission for those infectious diseases that are transmissible by blood.

48 It is recommended that the governing bodies of physicians and surgeons in the provinces and territories make it a standard of practice that physicians report adverse reactions from the transfusion of blood components to the national blood service, and adverse reactions from the infusion of blood products to the national blood service and the manufacturers of blood products.

One of the most important aspects of post-market surveillance of blood components and blood products is the reporting of adverse reactions, and greater efforts must be made to encourage physicians to do so. The governing bodies of physicians and surgeons in the provinces and territories should make it a standard of practice that physicians must report adverse reactions.

49 It is recommended that the provincial and territorial ministers of health provide sufficient resources for public health services.

Public health departments in many parts of Canada do not have sufficient resources to carry out their duties. They must have sufficient personnel and resources to conduct adequate surveillance of infectious diseases, to develop and implement measures to control the spread of infectious diseases, including those that are blood borne, and to communicate with other public health authorities at both the federal and the provincial-territorial levels.

Continued chronic underfunding of public health departments is a disservice to the Canadian public. Moreover, it threatens the safety of the blood supply.

50 It is recommended that the conference of ministers of health create incentives to encourage the practice of transfusion medicine.

The field of transfusion medicine is a vital aspect of the practice of medicine. Unfortunately, few young physicians are entering this field. Although there may now be a sufficient number of physicians practising transfusion medicine, a shortage is inevitable if no measures are taken to prevent it.

Afterword

It is right to end with a reminder of a few assessments made in the Interim Report. There it was said that, to the question whether the tragedy of the 1980s could happen again with a different contaminating agent, the answer was yes. However, the blood and blood products used in Canada when necessary are as safe as blood and blood products used elsewhere in developed countries. Because safety implies the absence of risk and because risk is inherent in the use of blood and blood products, it can never be said that their use is absolutely without risk and therefore perfectly safe. But it should be borne in mind that, when their use is truly necessary, the risk of harm is significantly higher from the failure to use them appropriately than it is from the blood and blood products themselves.

To the extent that we have indeed learned the lessons from the tragedy of the 1980s and reform the system as recommended in this Report, the likelihood that the tragedy will happen again will be markedly reduced. Low as the risk may be of infection with HIV and the hepatitis C virus from today's blood supply, it is almost certain that infection will occur. When it does, the few members of our society to whom the risk accrues and to whom the harm results must be treated more compassionately than their predecessors were, and they must be given suitable compensation without the necessity of proving fault.