Food and Drug Administration Responses to the Challenges of AIDS

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THE APPEARANCE OF INCREASING NUMBERS of cases of acquired immune deficiency syndrome (AIDS) over the past few years has raised a number of issues relevant to responsibilities of the Food and Drug Administration (FDA) beyond its general responsibility for coordinating with other components of the Public Health Service on important health issues.

- The epidemiology of AIDS suggests that it is probably caused by an infectious agent transmitted in a manner analogous to transmission of the hepatitis B virus. As a result, concerns have been raised regarding the safety of blood products and of vaccines derived from them.
- If AIDS is caused by a virus, what we learn about how the putative AIDS agent causes immune deficiency will be relevant to understanding the immunity to viruses induced by vaccines and the antiviral effects of other drugs and biologics.
- A variety of experimental biologics and antiviral drugs are being or will be tested as possible treatments or prophylaxis for AIDS, and an understanding of any specific beneficial effects that occur, and the mechanisms by which these effects are achieved, will be needed.

FDA has initiated a number of actions to meet these varied needs, including making policy changes to increase assurance of the safety of blood products and conducting basic and clinical research on AIDS. The status of these initiatives is summarized in this report.

Safety of Blood and Plasma Derivatives

Regulatory activities. On March 24, 1983, memoranda were sent by the Director, Office of Biologics, FDA, to all establishments collecting source plasma, all establishments collecting human blood for transfusion, and all licensed manufacturers of plasma derivatives, describing those steps to be taken in order to decrease the risk of blood or plasma donation by individuals who might be at increased risk of transmitting AIDS. Establishments collecting source plasma or blood for transfusion were advised that:

- Educational programs should be established to inform persons at increased risk of contracting AIDS that until more information on the disease and its diagnosis becomes available, they should refrain from donation.
- Personnel responsible for donor screening should be reeducated, with special attention given to recognition of the early signs and symptoms of AIDS. Questioning of potential donors about medical history should include specific points designed to detect possible AIDS symptoms or exposure to patients with AIDS. Standard operating procedures should be revised to include questions that elicit any history of night sweats, unexplained fevers, unexpected weight loss, lymphadenopathy, or evidence of Kaposi's sarcoma.
- All plasma donors should be examined for lymphadenopathy—at the initial and annual physical examination, by a physician, and on each day of donation, by an adequately trained individual. Records of weight for plasma donors should also be maintained. If significant decrease in weight occurs, the donor should be referred to a physician for reevaluation, and any plasma in storage previously collected from the donor should be quarantined until the physician's evaluation is completed.

The biomedical and lay communities were made aware of these measures through a press release (Mar. 25, 1983) and a report published in the Centers for Disease Control's Morbidity and Mortality Weekly Report (*1*).

Analysis of death statistics for hemophiliacs. As of June 29, 1983, AIDS had been diagnosed in 13 hemophiliacs (0.8 percent of total AIDS cases) receiving intravenous clotting factor (antihemophilic factor) therapy. In this lifesaving therapy, hemophiliacs receive large amounts of pooled plasma antigens from literally thousands of plasma donors at each treatment and, as a result, are exposed to viruses such as the hepatitis B virus and the agent(s)

of non-A, non-B hepatitis. For this reason, before the appearance of AIDS in high-risk groups in the United States, FDA had obtained from the National Center for Health Statistics the causes of death among hemophiliacs during 1979.

In 1979, 101 hemophiliacs died. Causes of death included one case of disseminated candidiasis, one case of cryptococcosis, five cases of pneumonia (nonspecific), one case of lymphoma, and one of lymphosarcoma.

Complete death data are now being obtained for this small group of patients to determine whether AIDS-like diseases in hemophiliacs predated the appearance of AIDS in high-risk groups or whether they began to appear at the same time AIDS cases appeared in the other groups.

Assays of plasma derivatives. In collaboration with scientists at the Centers for Disease Control, FDA scientists assayed 200 separate lots of antihemophilic factor (AHF) concentrate, manufactured by the four major U.S. manufacturers, for virus contamination. The materials tested are summarized here.

	Number of lots tested, by year of manufacture	
Manufacturer	*1977–79*	*1980–81*
Hyland	26	24
Cutter	24	26
Alpha	25	25
Armour	25	25

Each lot tested was chromatographed to recover virus particles. Each was inoculated into cell cultures, including human embryo kidney cells and T-cell and B-cell lymphocytes. To date, all cultures have been negative for virus.

Removing virus infectivity from plasma derivatives. Clotting factor concentrates such as AHF are known to contain viruses, including hepatitis B virus and the agent(s) of non-A, non-B hepatitis. Because of the labile nature of the clotting factors, until recently it was impossible to carry out procedures to inactivate, remove, or neutralize viruses without seriously affecting the clotting factors themselves. Research to develop ways to remove virus infectivity from these products has progressed over the past several years, stimulated by studies at the Office of Biologics of the Food and Drug Administration.

The risk of hepatitis B associated with plasma derivatives is reduced but not eliminated by screening of donors for hepatitis B surface antigen. Further decrease of the risk of hepatitis B associated with antihemophilic factor or factor IX complex, as well as with newer products such as AT-III, fibronectin, C-1 inactivator, and factor XIII, has recently been accomplished either by the combination of stabilization and heating or by ensuring that these products contain an excess of protective antibodies. For highly purified products with little residual immunoglobulin, it may be necessary to add protective antibodies. The addition of antibodies against non-A, non-B hepatitis agents, when they are identified, could prevent transmission of both forms of viral hepatitis by plasma derivatives. Methods of stabilizing and heating high-risk plasma derivatives to inactivate hepatitis viruses have the potential for removing hepatitis B and non-A, non-B hepatitis infectivity as well as other virus infectivity. Details of inactivation studies that have already been completed have been published (*2*).

To date one manufacturer has been licensed for a "heat treated" clotting factor concentrate, two others are near licensure for a heated product, and a fourth is near licensure for a combination of heat and antibody treatment.

Basic Research

Etiology of AIDS. The designation of AIDS as a syndrome, rather than a disease, recognizes that it is a complex of symptoms and is not necessarily the same disease, with the same etiology, in every person affected. Nevertheless, it seems likely that most cases have the same etiology and that few of the cases so far diagnosed are actually different diseases.

Acting on the premise that AIDS is a disease of singular etiology, researchers have attempted to identify an infectious agent that is common to all AIDS patients.

Two main possibilities exist regarding the nature of such an agent. One is that it may be a newly emerging pathogen—presumably a mutant of some previously existing organism—that has developed the capacity to cause a disease that did not previously exist. A possible example of such an event is the recent outbreak of fatal enteric infections caused by canine parvoviruses. Apparently a member of this family of viruses developed a new, genetically determined ability to infect the gastrointestinal tract of dogs.

In most cases in the past few decades in which a new infectious disease has been recognized, however, the offending agent has not been a new organism. Instead, a change in the ecology of a previ-

ously existing organism has enabled it to gain access to a niche in which it could cause disease that it had not caused previously. Recent examples of this phenomenon include toxic shock syndrome and Legionnaire's disease.

Regardless of which possibility might eventually prove to be correct—emergence of a new organism or change in the ecology of a known one—the preponderance of epidemiologic data suggests that AIDS is an infectious disease. Factors such as case clustering and apparent person-to-person spread favor this hypothesis. Other etiological possibilities such as drug toxicities have not proven to be consistently associated with AIDS.

Many infectious agents can induce immune deficiency, including *Mycobacterium tuberculosis* and *Coccidioides immitis*. The possibility that bacteria, fungi, or parasites may be involved in the etiology of AIDS cannot be fully discounted; however, greater effort has been expended toward isolation of viruses that may be involved. The epidemiology of AIDS closely resembles the epidemiology of hepatitis B and in general is more typical of viral infections than of other types of infections. Moreover, viruses are more often immunosuppressive than other microorganisms and are more likely to cause progressive infection in a setting of deficient cellular immunity. Almost every class of viruses has been considered as an etiologic possibility, including hepatitis viruses, because of the similarity between the epidemiology of AIDS and that of hepatitis B; parvoviruses, because a number of animal parvoviruses of different types induce diseases that have some features in common with AIDS; retroviruses, because of the frequent malignancies that occur in the syndrome and because they are found in T lymphocytes; and papovaviruses, because they can also be found in lymphocytes. Herpesviruses have been of interest because they are extremely prevalent in homosexual men, and two of them—cytomegalovirus (CMV) and Epstein-Barr virus (EBV)—are immunosuppressive and probably or definitely are lymphocyte associated. CMV has been linked with Kaposi's sarcoma and EBV has been linked with lymphoid malignancies, including Burkitt's lymphoma in immunodeficient homosexual men.

At FDA's National Center for Drugs and Biologics, efforts have been made to study the involvement of a number of viruses in AIDS, but the major emphasis has been on the herpesviruses (*3,4*). Laboratory studies have been performed on blood and tissues obtained from AIDS patients in collaborative efforts with National Institutes of Health researchers. Surprising results have been obtained: infections with both CMV and EBV have been found in every case that has been fully studied. CMV infections were of recent onset, although probably not primary, while EBV infections were apparently in all cases the result of reactivation of latent virus. These infections were regularly associated with active disease, and were progressive. Many immunological abnormalities considered typical of AIDS are also known to be common effects of infections with one or the other of these viruses and were observed in the patients included in this study. EBV and CMV antigens were found in lymph node and Kaposi's sarcoma biopsies and cell lines derived from the sarcoma tissue, further strengthening the possibility that these viruses may be involved in the etiology of AIDS. The findings with respect to EBV and CMV infections contrasted with those for infections with herpes simplex virus and varicella zoster viruses, which were seen only occasionally. This difference suggested that the high frequencies of CMV and EBV infections were not due only to reactivation resulting from immunosuppression. The possibility that these herpesviruses may somehow have developed new ecological niches or have developed variants that may cause AIDS is under study.

Immunology and pathogenesis of AIDS. Much has been made of certain immunological abnormalities that typify AIDS and indicate that its pathogenesis is different from that of other known immunodeficiency states. To define the cause of AIDS, it would be helpful to know what the initial immune defect is that results in the sequence of immunological events manifest as susceptibility to opportunistic infections. A search for an offending agent could then be focused toward possible causes of the initial insult. Conversely stated, any proposed cause of the syndrome would have to be capable of initiating the underlying immune defect of AIDS. In addition, elucidation of the reason for susceptibility to opportunistic infections might direct approaches to immune system modulation as therapy for AIDS.

As part of the collaborative studies already described, the National Center for Drugs and Biologics has performed extensive studies of the immunology of AIDS. These studies have defined a variety of defects in cytotoxic lymphocytes, interferon effects and function, and lymphokine production by accessory cells. The effects of various interferons and other lymphokines on certain defects that appear most important have been studied *in vitro,* and the data are being interpreted to determine the potential

for using these immune system modulators therapeutically.

Many of the defects that have been defined appear related to, and possibly result from, chronically elevated serum interferon levels in AIDS patients. The possibility that most of the defects measured may result directly or indirectly from chronically elevated interferon levels is under study. It is an intriguing possibility, since it would imply that an infectious agent or agents that could somehow escape elimination by the immune system and undergo chronic high-grade replication might be capable of inducing a chronic hyperinterferonemic state resulting in the immunosuppression that occurs in AIDS. An agent or agents capable of inducing such a state and causing transformation of endothelial cells into Kaposi's sarcoma—perhaps mixed infection with EBV and CMV—could be the cause of the syndrome. Further studies to clarify the unifying basis for the immune deficiencies of AIDS should improve the possibilities of defining the cause of AIDS and devising treatments for it.

Clinical Research

Interferons and other lymphokines as treatments. Immune system modulators, often referred to as biological response modifiers, have become the subject of increasing interest in recent years, in parallel with advances in immunology. A number of naturally occurring substances in this category have been purified to homogeneity, and their biological effects have been defined in moderate or great detail. The only purified lymphokines that have been used in extensive human clinical studies are interferons. The products that have been studied most widely include alpha interferons, produced from human leukocytes or lymphoblastoid cells or by recombinant DNA technology, and recently gamma interferons.

The National Center for Drugs and Biologics has performed *in vitro* laboratory studies of the effects of these and other lymphokines on immune functions of lymphocytes from AIDS patients and healthy individuals. These studies form a basis for understanding (*a*) possible beneficial effects of these substances in treatment of AIDS, and (*b*) the pathogenesis of the syndrome. Collaborative studies are being performed with other scientists who are using some of these lymphokines in efforts to treat AIDS patients. The effects of these treatments on various immune functions are being compared with the effects observed *in vitro* and will be correlated with any beneficial effects observed on the course of the disease. These studies should help clarify mechanisms of action of interferons and differences in the effects of varying types of interferons and other lymphokines.

Antiviral drugs. The suggestion that AIDS may have a viral etiology has raised interest in the use of antiviral drugs to treat the syndrome. Because of lack of knowledge of the specific etiology of AIDS and the availability of only a small number of antiviral drugs, each with a limited spectrum of activity, relatively little has been done in this area to date. Some patients in the studies described above were treated effectively for herpes simplex virus infections. These results indicate that viral infections in patients with AIDS might be effectively treated if appropriate drugs were available and should motivate evaluation of products now at the laboratory testing stage—products that may perhaps include a treatment for the etiologic agent of AIDS.

Summary

Rarely has a public health issue emerged that has had impact on so many aspects of the responsibilities of the Food and Drug Administration. In a curious sense, the emergence of AIDS as a national problem has been timely. Only a few years ago, the scientific basis did not exist for performing studies of the immunology and pathogenesis of the syndrome—studies that should be helpful in directing therapeutic and preventive measures. Many of the techniques for studying AIDS and for manufacturing products to treat it involve modern technology. Research and policy actions that FDA has initiated have been designed to ensure as fully as possible the safety and effectiveness of regulated products that are relevant to AIDS and to apply new technology to this important public health problem.

References

1. Centers for Disease Control, Food and Drug Administration, and National Institutes of Health: Prevention of acquired immune deficiency syndrome (AIDS): report of inter-agency recommendations. MMWR 32: 101–103 (1983).
2. Gerety, R. J., and Aronson, D. L.: Plasma derivatives and viral hepatitis. Transfusion 22: 347–351 (1982).
3. Rook, A. H., et al.: Interleukin-2 enhances the depressed natural killer and cytomegalovirus specific cytotoxic activities of lymphocytes from patients with the acquired immunodeficiency syndrome. J Clin Invest. In press.
4. Quinnan, G. V., and Rook, A. H.: Cell mediated immunity in cytomegalovirus infections. Proceedings of symposium, Pathogenesis and Prevention of Human CMV Disease, 1983. In press.