DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Heart, Lung, and Blood Institute

RESEARCH AGENDA ON COMPLICATIONS OF HEMOPHILIA AND OTHER BLEEDING DISORDERS

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EXECUTIVE SUMMARY

The House Committee on Appropriations in its Report 105-635 urged the National Heart, Lung, and Blood Institute (NHLBI) to develop a research action plan, working with the National Institute of Allergy and Infectious Diseases (NIAID) and the hemophilia scientific and medical community, to address complications of hemophilia and other bleeding disorders. In developing the plan, the Committee requested that the NHLBI work collaboratively with the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) on how to improve hepatitis treatment options for persons with hemophilia. The Senate Committee on Appropriations in its Report 105-300 urged the NHLBI to develop a collaborative research plan for development of promising hemophilia gene therapy technologies with the NIDDK, the National Human Genome Research Institute (NHGRI), and the hemophilia scientific and medical community. Both the House and Senate requested a report on the steps taken by March 31, 1999.

The major complications of hemophilia include hemorrhage; inability of the blood to form clots; development of arthritis in joints that incur hemorrhages; development of pseudo tumors that can damage adjacent muscle, nerve, and bone; and infection with human immunodeficiency virus (HIV), hepatitis virus, and other blood-borne agents. Among other inherited bleeding disorders, the most common is von Willebrand disease (vWD). Severe vWD has complications similar to those of hemophilia.

The National Institutes of Health (NIH) supports a broad program of research relevant to hemophilia and other bleeding disorders. Overarching research goals are to (1) develop effective replacement products to address complications of hemophilia and other bleeding disorders, (2) assure the safety of the blood supply against transfusion-transmitted agents, (3) develop strategies and therapies to treat patients infected by transfusion-transmitted agents, and (4) find the means to cure bleeding disorders. Areas of research include studies of the mechanisms of bleeding and clotting; strategies to avoid formation of antibodies to blood coagulation factors; improvement of approaches to gene therapy; and therapeutic interventions for HIV/AIDS, hepatitis, and other transfusion-transmitted infections. Blood safety issues are of the highest priority and include continuous monitoring of the blood supply for infectious blood-borne agents and efforts to improve methods for detecting and inactivating them.

Research on all aspects of hemophilia and other bleeding disorders will remain a high NIH priority in the years ahead. For example, expanded efforts are being

planned that will lead to better understanding of factors that affect the progression of HCV infection in hemophilia patients and other frequently transfused populations, development of safer and more effective vectors for gene transfer, and induction of immune tolerance to factor VIII.

The federal government recognizes blood safety, an issue of extreme importance to patients with bleeding disorders, as one of its most important health priorities. Federal blood safety activities are coordinated at several levels throughout the government. Key committees include the DHHS Advisory Committee on Blood Safety and Availability, the Public Health Service Blood Safety Committee, the Trans-Agency Hepatitis Working Group, and the Trans-NIH Hepatitis C Virus Working Group.

RESEARCH AGENDA ON COMPLICATIONS OF HEMOPHILIA AND OTHER BLEEDING DISORDERS

INTRODUCTION

In its report on the fiscal year 1999 budget for the Department of Health and Human Services (DHHS), the House Committee on Appropriations stated:

> "The Committee remains supportive of NHLBI's hemophilia gene therapy research program and urges renewal and expanded research emphasis in this critical area. In light of the research opportunities in hemophilia gene therapy, the Committee urges the Institute to develop a research action plan, working with NIAID and the hemophilia scientific and medical community, that fully addresses complications of hemophilia and other bleeding disorders. In developing such a plan, NHLBI also should work collaboratively with NIDDK on how to improve hepatitis treatment options for persons with hemophilia. The Committee requests a report by March 31, 1999 on the status of these efforts." (House Report Number 105-635, pages 66-67).
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> "Last year the Committee encouraged NIAID, working with the national hemophilia leadership, to determine further research steps to address the complications of hemophilia, including treatment for HIV/AIDS and viral hepatitis. The Committee urges NIAID to develop a research action plan, working with the hemophilia scientific and medical community, that fully addresses the complications of hemophilia and other bleeding disorders. In developing such a plan, NIAID should work collaboratively with NIDDK on how to improve hepatitis treatment options for persons with hemophilia." (House Report Number 105-635, page 77).

The Senate Committee on Appropriations included similar language in its report on the fiscal year 1999 budget for the DHHS:

> "The Committee remains supportive of NHLBI's hemophilia gene therapy research program and encourages expanded research emphasis in this critical area. In light of research opportunities in hemophilia gene therapy, the Committee urges NHLBI to develop a collaborative research plan with NIDDK, the National Human Genome Research Institute, and the hemophilia scientific and

> medical community for the development of promising hemophilia gene therapy technologies. The Committee requests a report on the steps taken by March 31, 1999. (Senate Report Number 105-300, page 94).
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> "Last year the Committee encouraged NIAID, working with the national hemophilia organizations, to determine further research steps to address the complications of hemophilia, including treatment for HIV/AIDS and vimi [viral?] hepatitis. The Committee urges NIAID to develop a research action plan, working with the hemophilia scientific and medical community, that fully addresses the complications of hemophilia and other bleeding disorders. The Committee further urges that in developing such a plan, NIAID should work collaboratively with NIDDK on how to improve hepatitis treatment options for persons with hemophilia. The Committee requests a report by March 31, 1999, on the status of these efforts." (Senate Report Number 105-300, page 104-105).

In response to this request, the following agenda has been prepared by the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH), DHHS, in cooperation with the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Human Genome Research Institute (NHGRI), and the NIH Clinical Center Hematology Service. The agenda was also submitted for review by the National Hemophilia Foundation and members of their Medical and Scientific Advisory Council.

BACKGROUND

Treatment of Hemophilia and Other Bleeding Disorders

Transfusion as a treatment for hemophilia was first reported in 1840, but rest, pressure dressings, immobilization, ice, and cauterization remained the mainstays of treatment until about 100 years later. In 1911, it was shown that a globulin fraction in normal plasma could correct the hemophilic defect. In the 1950s, fresh-frozen plasma, as well as concentrates containing antihemophilic factors (AHF), could be prepared.

In 1958, Swedish clinicians began treating patients prophylactically with AHF to prevent joint damage. The success of their efforts supported t/he concept of prophylaxis, which remains the treatment of choice today. In 1965, NIH-

supported researchers developed an important technique that allowed the plasma component (now called factor VIII) to be made by precipitation in the cold (cryoprecipitate). Lysine analogues were also available to treat mucosal bleeding and for use during dental extractions. The hormone desmopressin (DDAVP) was found in 1977 to elevate factor VIII levels. It continues in use today to treat mild hemophilia and Type 1 von Willebrand disease (vWD) and some Type 2 variants. During the 1970s, freeze-dried, intermediate-purity factor VIII and IX concentrates were prepared from pools of over 2000 donors. Such innovations allowed home treatment of hemophilia patients, improved their quality of life, and increased their life expectancy from 11 years in 1931 to 60 years in 1980.

Among other inherited bleeding disorders, the most common one is vWD, which was first described in 1926. Although vWD is estimated to affect one to three percent of the United States population, it is often overlooked in women with bruisability, heavy menstrual flow, or postpartum bleeding. The disorder is caused by either a quantitative or a qualitative deficiency of von Willebrand factor (vWF), which functions in platelet adhesion and as a carrier for factor VIII. Treatment varies with the type of vWD and clinical condition. Mild symptoms often can be treated with a nasal spray of DDAVP that releases stored vWF. For the 10 to 15 percent of vWD patients who are moderately to severely affected, infusion of virally inactivated plasma products that contain vWF may be required.

Improvements in Blood Safety

In the early 1980s, use of large donor pools to prepare factor concentrates and lack of specific tests for infectious agents led to frequent infection by blood-borne viruses. At one time, up to 95 percent of those treated with unheated and dry heat-treated factor concentrates became infected with hepatitis C (HCV). About 90 percent of the hemophilia patient population was infected with HIV-1 by 1985. The AIDS crisis spurred development of better tests for blood-borne infectious agents which led to purer material that was free of viral contamination. The next generation of replacement products, produced by affinity chromatography with monoclonal antibodies, significantly reduced transmission of infectious agents.

In the late 1970s and early 1980s, various studies including the NHLBI-sponsored Transfusion-Transmitted Viruses (TTV) Study, proved that an emerging form of hepatitis that was neither hepatitis A nor hepatitis B was transmitted by blood transfusions. It is now clear that at least 90 percent of the nonA-nonB infections were due to HCV. HCV could not be detected directly. However, use of a surrogate marker (a liver enzyme that becomes elevated in cases of infectious hepatitis) to screen donors reduced the incidence of post-transfusion hepatitis. The first-generation single- antigen anti-HCV assay was introduced in 1990. Surrogate testing reduced the per-unit risk of HCV transmission to 0.19 percent.

After second-generation HCV testing was implemented, the per-unit risk dropped to 0.03 percent. A third generation multi antigen assay introduced this past year has reduced the per-unit risk still further, to less than 0.001 percent.

Mandatory testing was initiated to screen blood donors for hepatitis B (HBV) in 1971, for HIV-1 in 1985, for HCV in 1990, and for HIV-2 in 1992. In addition, blood could be frozen and quarantined until the donor was re-tested after the window period for seroconversion. Lipid-enveloped viruses -- HIV-1, HBV, and HCV -- also could be inactivated by solvent-detergent treatment of plasma. HBV vaccine became available in 1982. Since 1986, no cases of HIV transmission from factor concentrates have occurred, although transmission of HCV is sometimes reported.

To make hemophilia treatment safer for hemophilia patients, the factor VIII gene was cloned in 1984 and used to make recombinant factor VIII commercially. Two recombinant products have now been licensed by the Food and Drug Administration (FDA) as Recombinate® and Kogenate®. The factor IX gene is smaller and was cloned earlier, but its recombinant product was not approved by the FDA until 1997. The two factors are very pure, but are currently being made even safer by excluding carrier proteins that might harbor infectious agents from human plasma.

The steps taken to achieve purer products that remove risk of infection have substantially increased their cost. As a result, use of transgenic animals, notably sheep and pigs that produce large quantities of coagulation factors in their milk, is being explored. Animal products may soon be able to meet FDA approval requirements.

Complications of Hemophilia

Major complications range from the psychological impact of a chronic disease on children, adolescents, and their families to life-threatening cerebral hemorrhage and infection with deadly viruses such as HIV. In addition, many hemophilia patients develop antibodies (inhibitors) to the coagulation factors used to prevent bleeding. In the absence of prophylactic therapy, now recommended to begin at one to two years of age, potentially disabling arthritis (hemarthrosis) occurs in joints that have experienced hemorrhage. Pseudo tumors -- cysts that arise from hemorrhage in muscle or the covering of the bone which then damage adjacent muscle, nerve, and bone -- also occur and must be excised completely to avoid recurrence. There are also life-long concerns about availability, cost, and purity of replacement factor products.

Complications of Other Bleeding Disorders

Complications of severe vWD are similar to those of hemophilia, but hemorrhages into joints appear to be less frequent. Women, whom the disorder affects disproportionally , may also suffer problems with heavy menstrual flow and postpartum bleeding. Mucosal bleeding from the nose, mouth, or GI tract can occur, and major injury or surgery creates a risk of prolonged bleeding.

Finding a Cure

Although purer factor replacement products have significantly reduced the risk of disease transmission, researchers are actively seeking a cure for hemophilia. Liver transplantation does cure hemophilia, but carries its own risks. Further, if the patient already has hepatitis, the transplanted liver or liver cells are themselves subject to infection. Currently, the most likely route to a cure is thought to be through gene therapy.

RESEARCH ON COMPLICATIONS OF HEMOPHILIA

The NIH supports a broad program of research on hemophilia and other bleeding disorders. NIH institutes with large research portfolios relevant to hemophilia and other bleeding disorders include the NHLBI, the NIAID, the NIDDK, and the NHGRI. NHLBI research focuses on ensuring the safety and adequacy of the blood supply, while both the NHLBI and the NIH Clinical Center support research on the basic mechanisms of bleeding and clotting. The NIAID directs its research toward prevention of HIV infection and its complications, as well as discovery, development, and evaluation of therapeutic strategies and interventions for HIV/AIDS and its complications. The NIAID also pursues basic and clinical research on HCV infection. The NIDDK has an extensive intramural and extramural research program on HCV infection in persons both with and without hemophilia. The NHGRI supports a strong intramural gene therapy research program that includes gene therapy for hemophilia and for patients who develop inhibitors to coagulation factors used to prevent bleeding. In addition, the NHGRI is involved in development of a non-human primate model for use in hemophilia gene therapy studies. A summary of NIH-supported research follows.

Mechanisms of Bleeding and Clotting

Bleeding, or hemorrhage, is part of the natural course of hemophilia; internal hemorrhages can be severe in the brain, abdominal cavity, and throat, and resultant

compression of vital organs and nerves can be life-threatening or severely disabling.

Current Research

Researchers have identified the components of the coagulation system and the mechanisms that regulate formation and dissolution of blood clots. NHLBI- and Clinical Center-supported research has improved understanding of how clot formation is inhibited in bleeding disorders, as well as of how the unwanted clots are formed that cause heart attacks, stroke, and pulmonary embolism.

Basic studies that include cutting-edge research on factors VIII and IX will almost certainly continue to improve treatment for patients with hemophilia. Based on genetic, protein biochemistry, and functional information, factor VIII and IX molecules are being modified to improve stability, promote higher activity, reduce immunogenicity, and increase expression levels. Although further testing is needed in animal models, they have the potential to improve the effectiveness and lower the cost of future treatment with recombinant proteins. In addition to factors VIII and IX, deficiencies or mutations that can also result in bleeding have been identified in other coagulation factors such as vWF and factors XI, X, and VII.

Physicians who treat hemophilia have noted with concern an increase in bleeding in hemophilia patients with AIDS who have been treated with protease inhibitors. The NHLBI, NIDDK, NIAID, and National Cancer Institute (NCI) issued a Program Announcement (PA) in 1996 and again in 1998 inviting applications for research on hematologic abnormalities in AIDS. The hemophilia research community is invited to take advantage of this currently available mechanism to elucidate the pathophysiology of the increased bleeding and to develop a therapeutic approach.

Basic vWD research supported by the NHLBI and the NIH Clinical Center Hematology Service has led to in-depth understanding of the role that vWF plays in clotting and bleeding and its interrelationship with factor VIII, and has elucidated the molecular abnormalities underlying vWD variants.

Thrombocytopenia, a condition in which a low number of platelets results in risk of hemorrhage into the brain and elsewhere, is of considerable interest to the NHLBI and the Clinical Center Hematology Service. In 1992, the Institute released a Request for Applications (RFA) on *Thrombocytenias in Women and Neonates* to encourage research to characterize antiplatelet antibodies in immune thrombocytopenia. The most common antigen associated with thrombocytopenia, the PlA antigen, was cloned and its polymorphism defined. Key outcomes of the research included development of assays for screening pregnant women and

creation of a mouse model of heritable thrombocytopenia. In 1998, a new RFA on *Thrombocytopenia: Pathogenesis and Treatment* was released that emphasized HIV-related thrombocytopenia. Each RFA encouraged both basic and clinical research.

Future Plans

The NIH will continue its strong support of investigator-initiated basic research into the mechanisms of bleeding and clotting. Applications for research on increased bleeding in HIV-infected hemophilia patients treated with protease inhibitors are being encouraged actively, as are applications for studies that focus on the pathogenesis and treatment of thrombocytopenia. Investigators supported under the 1998 RFA on *Thrombocytopenia: Pathogenesis and Treatment* will be convened annually to encourage collaborative studies and information sharing.

Diagnosis of vWD, particularly Type 2 vWD, is currently complex and labor-intensive. The Clinical Center Hematology Service is developing more easily performed tests for vWD and the NHLBI is considering a research initiative to develop better diagnostic tests for vWD variants. Since it would be critical to move new tests to market as soon as possible, the program may target the small business community.

The Hematology Service will continue its active clinical referral service for studies, including molecular diagnostic studies, of patients with vWD and other coagulation factor deficiencies. The resulting information is expected to provide a clinical base for future pilot studies for gene therapy.

Antibody/Inhibitor Formation

Fifteen to 35 percent of patients with hemophilia A and one to four percent of those with factor IX deficiency (hemophilia B) develop antibodies to the coagulation factors used to prevent bleeding. In 60 to 80 percent of patients, antibodies can be suppressed by one of several drug regimens; however, costs of such treatment can exceed $1 million per year. High levels of antibodies occur less frequently with the use of recombinant product.

Current Research

In November 1993, the NHLBI sponsored the *Second International Symposium on Inhibitors to Coagulation Factors*, organized by the University of North Carolina. The workshop highlighted scientific advances in both basic research and treatment over the previous 10 years. The Institute, in collaboration with the NIH Office of Rare Diseases, held a workshop in June 1997 on *Immunogenetics of*

Inhibitor Formation in Hemophilia that focused on understanding the immune response in inhibitor formation. As a result, an RFA with the same title was released in 1998. Six new grants were awarded recently under the RFA to investigate the role of genetic factors in risk of inhibitor development, the feasibility of specific immunosuppressive treatments to block inhibitor formation, the potential of blocking antibodies to neutralize inhibitors, and the immune response to replacement factor or gene therapy in animal models.

NHGRI scientists report induction of immune tolerance in factor VIII-deficient mice following genetic modification of donor bone marrow cells with a retroviral vector encoding human factor VIII. This model system will prove useful for evaluation of genetic therapies for factor VIII immuno-modulation in patients. Induction of clotting factor tolerance by the gut epithelium is also being explored in studies using orally administering vectors containing genes for factors VIII and IX.

Future Plans

NHGRI scientists plan to extend studies of induction of immune tolerance in factor VIII-deficient mice to include evaluation of genetic therapies for factor VIII immuno-modulation in human patients. They will continue to study induction of clotting factor tolerance by gene therapy using the gut epithelium.

The NHGRI is considering an initiative in which hemophilia A and B will be the first genetic diseases systematically genotyped in every affected individual in the United States. With this information, it may ultimately be possible to identify individuals at risk for inhibitor formation.

The six grantees supported as a result of the NHLBI RFA on *Immunogenetics of Inhibitor Formation in Hemophilia* will meet annually to share data and establish collaborative studies.

Gene Therapy for Hemophilia

The often life-long reliance of patients with hemophilia or other bleeding disorders on replacement products will always be fraught with problems. Life-threatening bleeds and progressive joint destruction continue to be problems. Product availability and cost, as well as disruption of the lives of patients and their families due to a serious chronic, genetic disease, are additional concerns. If seriously ill patients could, themselves, produce only one percent of normal factor levels, their illness could be transformed to a mild form of the disease. Thus, transfer of a corrected gene to a patient, so that the patient's own body could produce the factor, potentially constitutes a cure. For a number of reasons, hemophilia is an

ideal disease to target as the first to be cured by gene therapy. Low levels of factor production would alleviate the most severe symptoms and almost entirely eliminate dependence on replacement products. Factor VIII and IX production need not be tightly regulated, because the precise amount produced is not a critical issue. Moreover, effectiveness of the corrected gene product is not dependent on other gene products as is the case, for example, with hemoglobinopathies.

Current Research

Recommendations from a March 1992 *International Workshop on Gene Therapy for Hemophilia* urged the NHLBI to proceed rapidly to develop gene therapy for hemophilia, not only because of the relative genetic simplicity of the disease but also because it could serve as a model system for other gene therapy efforts. The workshop led to a 1994 RFA on *Gene Therapy for Hemophilia A and B* that supported research on many viral and non-viral gene delivery systems and different target cells for gene expression. Study findings have contributed significantly to our understanding of events that regulate hemophilia gene expression. Approaches -- including use of lentiviruses, retroviruses, adenoviruses, adeno-associated viruses (AAV), and non-viral means of gene transfection -- are being developed to repair endogenous factor VIII and IX genes or to introduce new ones into cells, and to stimulate expression of sufficient functional protein. Hemophilic mouse and dog models, developed and maintained with NHLBI grant support, have shown that the vectors used to insert functional genes for factors VIII and IX often elicit an immune response themselves. Thus, not only do researchers need to develop an efficient system for transferring genes to patients, but they must also be certain that the patient does not produce antibodies to either the vector or the new gene product. Related NHLBI activities have included co-sponsorship of the *Hemophilia 1996: Research for a Cure Workshop* organized by the National Hemophilia Foundation and the *International Symposium on Gene Therapy for Hemophilia* organized by the University of North Carolina at Chapel Hill. The Institute also sponsors an annual RFA grantees' meeting to foster scientific collaboration.

The NHGRI has an active intramural hemophilia research unit that focuses on development of gene therapy for hemophilia A and B. Gene therapy initiatives include establishment of a CRADA (Cooperative Research and Development Agreement) to develop AAV vector-mediated gene transfer technology as a potential treatment for both factor VIII and factor IX deficiency. Plans are in place to investigate lentiviral vector systems as a new gene transfer system in preclinical studies. Lentiviral vectors offer significant advantages over existing retroviral vectors. Oral delivery to the intestinal ephilelium of vectors containing functional factor VIII and IX genes is also being explored. Several NHGRI

laboratories are developing whole new classes of gene transfer vectors including human artificial chromosomes, modified adenoviral vectors, and viral-based gene transfer vectors, including chimeric viral vectors. Some of these new approaches may be applicable to hemophilia gene therapy.

In addition to research directed specifically to hemophilia, the NIH supports a number of related activities that have significant potential application for hemophilia gene therapy. For example, the NHLBI program of *Specialized Centers of Research in Gene Transfer Principles for Heart, Lung and Blood Diseases,* established in 1997, is fostering research in gene transfer technology and somatic gene transfer. The NHLBI also provides support for the National Gene Vector Laboratories that help qualified investigators develop and produce clinical-grade gene vectors for human gene therapy trials. Plans are under way to expand their scope to include preclinical toxicity testing as well. In addition, under the leadership of the NIH Office of Rare Diseases, several NIH institutes and the FDA are cooperating to identify special needs in the development of gene therapeutics for treatment of rare monogenic diseases**.**

Future Plans

The need for targeted support of preclinical and clinical studies of specific hemophilia gene therapy approaches is being evaluated to determine how best to move gene therapy to clinical use. Interest is high not only in providing a cure for hemophilia but also in applying the successful technology to other more complex diseases. Thus, hemophilia gene therapy will continue to be a high priority research area for the NIH.

NHGRI scientists plan to enter into a CRADA to further develop and apply a new experimental strategy to correct mutations in genomic DNA in order to repair point mutations in hemophilia B. In order to determine the efficacy of any gene therapy strategies prior to clinical testing, it will be important to evaluate them in animals that closely resemble humans.

The NHLBI extramural program and NHGRI intramural scientists will continue to support substantial research to develop safe, effective gene therapy for hemophilia A and B. The variety of approaches under study increases the likelihood that some of them will be applicable to gene therapy in humans. A second-generation version of the NHLBI RFA on gene therapy for hemophilia is being planned, that will focus on facilitating the transition from pre-clinical testing to testing in humans. National Gene Vector Laboratory support will continue to be used to produce clinical-grade gene vectors for human gene therapy trials.

Blood-Borne Infectious Agents

Although acquisition of blood-borne infectious agents is not a complication of hemophilia *per se*, it constitutes a significant complication in hemophilia patients who received blood products in the past. Today, approximately 20 percent of adult hemophilia patients in the United States are HIV-infected; about 56 percent and 89 percent, respectively, are infected with HBV and HCV. The percentages are substantially lower for children. HIV remains the most common cause of death among hemophilia patients; of the 400 who die each year, roughly 75 percent die as a result of HIV infection.

Because of their previous reliance on repeated factor concentrate infusions, hemophilia patients were exposed to HCV and many other blood-borne viral agents such as HBV, HIV, and cytomegalovirus (CMV). Although new anti-viral drugs may prolong the lives of HIV-infected hemophilia patients, bleeding and liver damage are possible side effects. Hemophilia patients with the misfortune of being infected with both HIV and HCV have particular problems, as co-infection may cause HCV to worsen. Further, liver failure resulting from HCV cannot be treated with transplantation in AIDS patients because of the risk of opportunistic infections resulting from post-transplant immunosuppressive regimens.

Human Immunodeficiency Virus (HIV)

Current Research

The NIAID devotes substantial resources to discovery, development, and evaluation of innovative therapeutic strategies and interventions for HIV/AIDS and its complications. In addition to therapeutic research, the NIAID supports research on prevention of HIV infection and its complications.

The NIAID supports three large clinical trial networks -- the Adult AIDS Clinical Trials Group (AACTG), the Pediatric AIDS Clinical Trials Group (PACTG), and the Community Program for Clinical Research on AIDS (CPCRA). The major goals of the networks are to:

- Elucidate the pathogenesis of HIV-1 infection by identifying and evaluating viral and host factors that determine disease progression and response to antiretroviral therapies;

- Conduct clinical trials of novel antiretroviral compounds or combinations to achieve maximal, long-term viral suppression or eradication;

- Develop strategies to preserve, restore, and enhance both HIV-specific and opportunistic infection (OI)-specific immune responses;

- Elucidate the immunopathogenesis of OIs in HIV/AIDS clinical studies;

- Delineate the relationships between various OIs and HIV; and

- Develop improved therapeutics for OIs.

The AACTG and CPCRA have formed working groups to develop a research agenda to address hepatitis and HIV co-infection. The AACTG recently implemented a pilot study to determine the dynamics of HCV viral infection in HIV-infected individuals on highly active antiretroviral treatment. The interaction between the two viruses may influence ability to treat either virus. Information from the pilot study will assist in designing other HCV clinical trials.

HIV-positive persons with hemophilia have the opportunity to participate in the clinical trials through the three clinical trial networks. At present, approximately 50 AACTG, 8 CPCRA, and 25 PACTG protocols are open to enrollment. The AIDS Clinical Trials Service (telephone: 800 HIV-0440) is a resource for learning about clinical trials for HIV-infected individuals and the participating clinics.

Future Plans

The three NIAID clinical trial networks noted above focus on the pathogenesis of HIV, therapeutic antiretroviral agents, and OIs in persons with HIV. HIV-infected hemophilia patients, as well as patients with HIV alone, will continue to be included in these trials. In addition, the NIAID is planning an FY 1999 workshop to review and identify the scientific needs of the HIV-infected hemophilia population. Proposed attendees will include representatives from the NIAID and other NIH institutes, leading researchers, and hemophilia patients infected with HIV.

Hepatitis C Virus (HCV)

Current Research

A multi-institute RFA, *Hepatitis C: Natural History, Pathogenesis, and Therapy* was issued to support research to define the natural history of HCV infection in specific populations that have received, and continue to receive, frequent transfusions. Persons with hematologic disorders, such as hemophilia, are

participating in studies on the long-term morbidity and mortality of chronic HCV infection, including factors contributing to cirrhosis and hepatocellular carcinoma.

The NHLBI is collaborating with the NIAID to elucidate the role of T cells in disease progression. Researchers are studying a well-characterized population of hemophilia patients to compare the HCV-specific T cell responses in patients who have recovered from HCV infection with the responses of patients who have persistent chronic HCV infection.

Intramural NIDDK scientists have developed a system that uses insect cells for efficient assembly of HCV structural proteins into HCV-like particles. The noninfectious particles, in contrast to recombinant subunit vaccines, present viral proteins that mimic the native virus and may, therefore, be superior in eliciting a protective humoral and cellular immune response. The NIDDK and the NHLBI are collaborating to evaluate the immunogenicity of the HCV-like particles as a candidate vaccine. If developed, the vaccine could be of value for use in conjunction with HCV hyperimmune globulin to treat or modify the clinical manifestations of chronic HCV infection.

The NIAID *Framework for Progress on HCV* identifies key research areas and tools needed to accelerate the drug development process, including tissue culture and animal model systems with which to perform preclinical evaluation and closer examination of viral and host interactions. The NIAID emphasizes basic and clinical research on HCV infection and disease which could be extended to treat HCV infection in hemophilia patients who are chronic HCV carriers. Basic research on viral replication, persistence, pathogenesis, and natural history in non-hemophilic patients is ongoing especially through the Hepatitis C Cooperative Research Centers that began in 1996. Such research may lead to development of new therapies that can be evaluated in, and eventually used to treat, hemophilia patients who are chronic HCV carriers. The Collaborative Antiviral Study Group conducts clinical trials to evaluate candidate therapies for HCV and combined HIV/HCV infections.

Future Plans

Studies are being planned to define the long-term morbidity and mortality of chronic HCV infection and the role of T cells in disease progression. An eight-year NIDDK clinical study is being planned to elucidate how the virus causes liver damage and to develop noninvasive techniques to measure and predict progression. The multi-center study will direct attention to long-term treatment (up to four years) of HCV-infected persons who did not respond to initial conventional treatment. Several ancillary studies will be included aimed at understanding, among other issues, how the virus causes liver damage and defining

means to predict and measure progression using non-invasive techniques. These activities will be highly relevant for HCV-infected persons with hemophilia.

A trial to assess a newly developed HCV immune globulin is planned and studies to evaluate HCV-like particles as candidate vaccines will continue. A vaccine might be used in conjunction with HCV hyper immune globulin to treat or ameliorate the clinical manifestations of chronic HCV infection. The Hepatitis C Cooperative Research Centers supported by the NIAID are carrying out both basic and clinical research to develop new therapies to treat hemophilia patients who are chronic HCV carriers.

The NHLBI and the NIDDK are currently preparing an initiative to support a multi-center study to evaluate the acquisition, infection rate, extent of viral co-infection, pathogenesis, natural history, risk factors for progression, and treatment of HCV in persons with hemophilia. Development of fibrosis, cirrhosis, and hepatocellular carcinoma, as well as the frequency of occurrence of manifestations of HCV infection other than in the liver, will be studied to determine if these outcomes are related to viral, host, or environmental factors.

Some hemophilia patients are chronic carriers of HCV, and the sickest may need liver transplants. One goal of research is to find a way to immunize against HCV. Passive immunization (HBV-specific immune globulin) already exists for hepatitis B and has been used to prevent or delay reinfection after liver transplants. This approach may also be useful in HCV-infected patients who need liver transplants, but has not been proven. Together with other institutes, the NHLBI is considering a proposal from a pharmaceutical firm to co-sponsor a trial to assess a newly developed HCV immune globulin.

The NHLBI supports a colony of chimpanzees for use in non-destructive experiments to advance hepatitis or AIDS research. Since the chimpanzee is the only animal susceptible to HCV infection, a major focus of the NHLBI colony will be to test the safety and efficacy of therapeutic agents and candidate HCV vaccines prior to human use.

Blood Safety

Much hemophilia research is intimately related to the safety of the blood supply. NIH blood safety research related to HIV and HCV is described below, as are efforts to assess the danger to transfusion recipients of transmissible spongiform encephalopathy (TSE) agents such as Creutzfeldt-Jakob disease (CJD). Also described are ongoing general efforts to continuously monitor the blood supply.

HIV and Hepatitis

Current Research

Efforts to develop a nucleic acid amplification detection system for HIV-1, HIV-2, HBV, and HCV in blood donors are being supported by the NHLBI through a contract. The resulting technology will reduce the "window period" between the time of HIV-1 infection and the ability to detect it from 16 days to 5 days. Significant reductions in the window periods of HBV and HCV detection also will be realized through the technology.

In the mid 1980s, the NHLBI supported research that led to development of a solvent-detergent technique for inactivating viruses in plasma products. The procedure is very effective against lipoprotein-enveloped viruses such as HIV, HBV, and HCV. However, non-enveloped viruses such as hepatitis A virus and parvovirus B-19 are resistant. The NHLBI is now supporting research on use of photochemical virucidal methods to inactivate infectious agents that are resistant to solvent-detergent treatment.

Future Plans

Research to increase the accuracy of detection and decrease the "window period" between the time of infection and ability to detect viruses in blood donors is on-going and will continue. Since viruses may still enter the blood supply, development of technologies to inactivate infectious agents while maintaining the efficacy of blood products will continue to be a priority.

Creutzfeldt-Jakob Disease (CJD)

Current Research

CJD is a slow-moving disease of the central nervous system characterized by degeneration of the brain, progressive dementia, and motor dysfunction. The disease, which is rare and invariably fatal, is due to a transmissible agent and is classified as one of the TSEs. CJD is related to bovine spongiform encephalopathy (BSE or "mad cow disease") in England. Concern about its transmissibility by blood was heightened when a new variant of CJD that was found in over 25 people was possibly linked to the livestock epidemic and following reports of 37 people who donated gallons of blood between 1983 and 1997 before they were diagnosed with the disease.

Since hemophilia patients are exposed to thousands of donors through pooled factor VIII concentrate, they are considered at risk of contracting CJD through the

blood supply. Recent research published in *Transfusion* (September 1998) showed CJD infectivity in cellular blood components, plasma, and certain plasma fractions of blood collected from mice clinically ill with a strain of human CJD that had been adapted to become more virulent in mice. Infectivity was demonstrated by intracerebral inoculation into susceptible mice. The research suggests a potential risk to humans of acquiring CJD from transfusion therapy. However, the intracerebral inoculation used in the animal model is not analogous to intravenous infusion of blood components and plasma derivatives in humans undergoing transfusion therapy. Hence, a second experimental protocol has been initiated with mouse-adapted CJD in which infectivity assays are also done by the intravenous route to simulate blood transfusion. In addition, two methods for removing the CJD agent from blood are being evaluated. This study, now in its final phase, should be completed early in 1999.

To date, no cases of CJD transmission by blood products have been reported, suggesting that the risk of acquiring CJD from blood products, even if it exists, is very small. The Centers for Disease Control and Prevention (CDC) has an ongoing surveillance program including a unit monitoring for CJD among hemophilia patients. Thus far, no evidence of CJD has been found in persons with hemophilia, and the few cases of death due to progressive dementia were clearly associated with HIV infection.

The study of CJD transmission has been hampered by lack of a rapid assay system. The *Special Emphasis Panel on CJD and Blood Transfusion*, convened by the NHLBI, concluded that since "an unqualified and irreducible risk of exposure to CJD through blood and blood products does exist," a sensitive and specific test for the causative agent was needed to study and control CJD. Two laboratories have found monoclonal antibodies to distinguish between the "normal" CJD protein and an abnormal isoform, so an assay may be imminent. To expedite development of methods to detect preclinical CJD infection, the NHLBI announced a grant program in December 1998 with awards made in September 1999. The ultimate goals of the research are to devise a test to screen blood and tissue donors and to determine with certainty whether or not CJD is transmissible by blood and blood products. In addition, the research could lead to development of a diagnostic tool to detect preclinical disease.

It should be noted that other NIH institutes that are not part of this action plan, such as the National Institute of Neurological Disorders and Stroke and the National Institute on Aging, support other aspects of research related to TSEs and CJD.

Future Plans

The NHLBI is responsible for supporting research to ensure the safety of the blood supply. To that end, future NHLBI-supported research will focus on developing a test or tests to screen blood and tissue donors as well as to detect preclinical disease. The test would also be used to determine more precisely the transmissibility of CJD by blood and blood products. In 1999, the NHLBI will support research relevant to these goals through its CJD initiative.

Behavioral Research

Current Research

The NHLBI does not currently support any research on behavioral issues in patients with hemophilia. However, studies of pain management in sickle cell disease are being supported by the Institute. Other NIH Institutes, such as the National Institute of Mental Health, are documenting the effects of chronic diseases on patients and their families. Examples of such research include studies of adjustment of children and family members to chronic physical disorders; stress, social support, and depressive symptomology in children with congenital and acquired defects; and psychological maladjustment in chronically ill and handicapped children.

Future Plans

In November 1998, the NHLBI convened a working group to address ways of encouraging application of proven techniques in behavioral research to patients with genetic blood diseases such as hemophilia, vWD, sickle cell anemia, and Cooley's anemia. Topics identified for further research in the area of hemophilia include:

- Compliance with treatment, including both factor use and exercise;
- Behavioral methods of pain control;
- Barriers to educational achievement in the child with hemophilia and methods to overcome them;
- Facilitating adjustment to chronic illness and disability;
- Adolescent development; and
- Family dynamics.

The NHLBI is currently considering the working group recommendations.

MONITORING THE BLOOD SUPPLY

The CDC and the FDA are responsible for monitoring the blood supply for infectious agents that threaten its safety, while the NHLBI supports research to improve the safety and availability of blood and blood products. Although the United States blood supply is safer than ever, concerns continue to arise about new infectious agents such as human herpes virus-8 (HHV-8, associated with Kaposi's sarcoma), Borna virus, variants of HIV-1, a new variant of the CJD agent, and a virus called TTV that may be associated with hepatitis. Wide-ranging travel from one continent to another, from rainforests to industrial cities, has made the world a "global village" in which an emerging infectious disease anywhere can represent a potential threat to the blood supply of the United States.

Three major questions arise when an agent is suspected of being transmitted by transfusion:

- Does the agent cause disease in all recipients?
- What is the prevalence of the agent among blood donors? (Incidence is also important when there are window-period transmissions.)
- Is the agent transmitted by blood and/or blood products?

To answer these questions, reliable screening and confirmatory tests of donor-recipient paired specimens, or at least pre-and post-transfusion recipient specimens, are needed.

The NHLBI *Retroviral Epidemiology Donor Study (REDS),* initiated in 1989, includes a sample repository and database that have facilitated investigations of human retroviruses in volunteer blood donors. The repository and database allow a rapid analysis of critical questions about the safety of the blood supply. For example, prevalence and incidence of newly discovered infectious agents can be estimated rapidly, the characteristics of populations at risk can be evaluated, and the impact of new screening methods can be assessed. The REDS program includes epidemiological, laboratory, and clinical investigations, and thus provides a comprehensive framework for monitoring blood donations for new or known infectious agents. REDS is recognized widely for its important contributions to blood banking and transfusion safety. The program was extended recently for another five years to enlarge the donor-recipient repository.

Public Health Service (PHS) Blood Safety Committee

The PHS Blood Safety Committee (BSC), chaired by the Assistant Secretary for Health, is composed of senior PHS representatives including the Director, NIH; the Director, CDC; and the Commissioner, FDA. The BSC, as the highest level policy group regarding blood safety, is the direct advisor to the Secretary concerning blood safety issues.

DHHS Advisory Committee on Blood Safety and Availability (ACBSA)

The Secretary established the ACBSA in October 1996 in response to the Institute of Medicine report on *HIV and the Blood Supply: An Analysis of Crisis Decision Making.* The ACBSA advises the Secretary through the BSC. It addresses both scientific and societal issues (e.g., cost-benefit ratios, conflicting interests of patient groups, effects of decisions on product availability). At its first meeting in April 1997, the ACBSA considered such issues as the theoretical risk of blood transmission of CJD and direct notification of individuals who had received transfused blood from donors later testing positive for HCV, both of which concern hemophilia patients. Subsequent meetings considered product shortages, product recall policies, and preferential use of recombinant (as opposed to plasma-derived) proteins.

Trans-Agency Hepatitis Working Group

The Trans-Agency Hepatitis Working Group includes the NIH, the CDC, the Department of Defense, and the Veteran's Administration. Its goal is to facilitate or develop collaborative research activities in HCV and to develop uniform and consistent guidelines for screening and treatment.

Trans-NIH Hepatitis C Virus Working Group

Eight NIH institutes and centers[1] participate in the Trans-NIH Hepatitis C Virus Working Group. The charge of this group is to develop an integrated NIH-wide plan for research in HCV that addresses basic, translational, and clinical aspects of HCV infection aiming at the prevention and cure of the disease.

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[1]The NHLBI, NIAID, NIDDK, NCI, National Institute of Drug Abuse, National Institute on Alcohol Abuse and Alcoholism, National Center for Research Resources, and the NIH Center for Scientific Review.

Other Coordinating Groups

The PHS Interagency Working Group on Blood Safety and Availability, which functions through the BSC and is chaired by an FDA official, holds a monthly conference call. Federal agencies with an interest in blood safety issues, including the NIH and the CDC, are members of the Working Group. The telephone conferences provide an opportunity to exchange information among agencies and offer early warning regarding potential new threats to the blood supply. Participants discuss newly identified threats and methods for determining whether a new infectious agent is transmitted by blood, is detectable by a test, and produces disease. In addition, the NIH, the FDA, and the CDC often form ad hoc groups to study such issues further. The Working Group also follows up on tasks assigned to it by the BSC.

Additional collaborative opportunities are provided by two FDA advisory committees: the Blood Products Advisory Committee, and the Transmissible Spongiform Encephalopathy Advisory Committee. NIH and CDC members play key roles on both of these committees.

CONCLUSION

Addressing the needs of patients with hemophilia and other bleeding disorders is an important NIH priority. Currently supported NIH research relevant to the many complications of these disorders includes studies to:

- Design improved, less costly coagulation factor replacement products;
- Develop strategies that avoid or ameliorate problems with antibody development;
- Reduce the window period for detection of HIV, HBV, and HCV and to identify TSEs more rapidly;
- Improve understanding of newly identified agents such as HHV8 and the Borna virus;
- Develop treatments for patients already infected by transfusion-transmitted agents, especially HIV;
- Develop immune strategies to avoid or modify HCV infection through a vaccine program and testing of immune globulins; and

- Develop a cure through gene therapy for hemophilia and other bleeding disorders.

The NIH fully intends to continue and expand work in these areas. The NIH institutes are, for example, planning new research efforts for the coming year that will address such issues as factors affecting the progression of HCV infection in hemophilia patients and other frequently transfused populations, development of safer and more effective vectors for gene transfer, and induction of immune tolerance to factor VIII. The intermediate goal is to prevent, reduce, or eliminate the many complications that afflict patients with hemophilia and other bleeding disorders so that they can lead normal, healthy lives. The ultimate goal is to cure the disorders themselves.