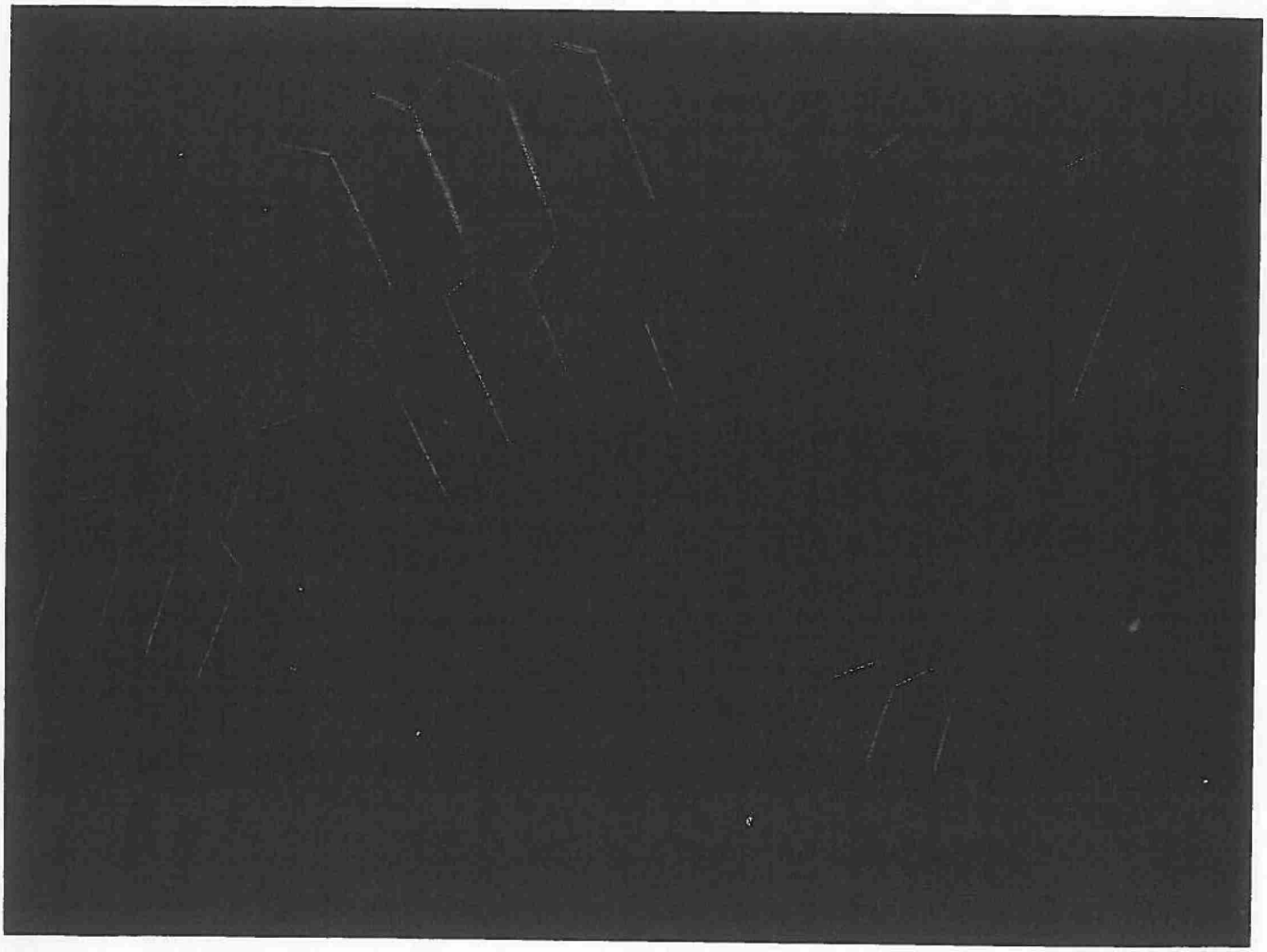
NIH Consensus Development Conference

# Impact of Routine HTLV-III Antibody Testing on Public Health



Program and Abstracts
July 7-9, 1986

# Impact of Routine HTLV-III Antibody Testing of Blood and Plasma Donors on Public Health

NIH Consensus Development Conference
July 7-9, 1986

Masur Auditorium
Warren Grant Magnuson Clinical Center
National Institutes of Health

Sponsored by the National Heart, Lung, and Blood Institute; the Centers for Disease Control; the Food and Drug Administration; the Clinical Center, NIH; the National Institute of Allergy and Infectious Diseases; the National Institute of Mental Health; and the NIH Office of Medical Applications of Research

# Contents

# Introduction

The identification of human T-lymphotropic virus type III (HTLV-III) as the causative agent of acquired immunodeficiency syndrome (AIDS) was facilitated by the development of serologic tests to detect antibodies to the virus. The finding that HTLV-III can be transmitted by blood, blood components, and blood products has stimulated the prompt use of such tests by the blood banking community. In March 1985, the first commercial antibody test kits were licensed; they are being used to screen blood and plasma donations in virtually every blood- and plasma-collecting facility in the United States.

Nationwide testing has had a profound impact on blood donors, on blood- and plasma-collecting facilities, on medical and surgical practice, and on the Nation's blood supply. Questions that have been raised as a result of the testing include: How effective is the test in identifying HTLV-III-contaminated units of blood? Has testing improved the safety of the blood supply? What are the medical, psychological, and social effects on donors found to have antibody to HTLV-III? Have problems arisen regarding confidentiality of information when a donor is antibody-positive? To address these and other questions, the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) and the NIH Office of Medical Applications of Research are sponsoring this Consensus Development Conference on the Impact of Routine HTLV-III Antibody Testing of Blood and Plasma Donors on Public Health. Other sponsors of the conference are the Centers for Disease Control; the Food and Drug Administration; the Clinical Center, NIH; the National Institute of Allergy and Infectious Diseases, NIH; and the National Institute of Mental Health. In this open forum, participants will evaluate more than a year's experience with routine HTLV-III antibody testing and try to analyze its impact on the public health of the Nation.

The conference will bring together biomedical investigators, blood bank specialists, clinicians, consumers, and representatives of public interest groups. Following 2 days of presentations by medical experts and discussion by the audience, a consensus panel will consider the scientific evidence. The panel members, drawn from the medical and behavioral areas of expertise, blood banking organizations, and lay persons, will formulate a draft statement responding to the following key questions:

- What tests are currently being used? What are their performance characteristics? How should these tests be used?
- What impact has testing had on transfusion medicine?
- What constitutes a positive test? How should a positive HTLV-III antibody test result be interpreted?
- How should positive test results be handled?
- What are the psychosocial ramifications for blood donors of knowledge of a positive test result?
- What research directions should be pursued?

On the final day of the meeting, the consensus panel chairman will read the draft statement to the conference audience and invite comments and questions.

## GENERAL INFORMATION

Conference sessions will take place in Masur Auditorium, Warren Grant Magnuson Clinical Center. The telephone number for messages is (301) 496-2520.

Speakers from the floor are asked to use the aisle microphones for their comments and to identify themselves by name and affiliation. A projectionist will be available to show slides. Speakers from the floor who intend to use slides are asked to complete the pink form in their packets and take it and their slides to the registration desk before the appropriate discussion period.

## CAFETERIA

The Clinical Center cafeteria is on the B-1 level, one floor below Masur Auditorium. The cafeteria offers coffee and snacks 24 hours a day. The grill and deli offer hot sandwiches and coldcuts at all hours except between 5:30 a.m. and 11:00 a.m. Regular meals are served at the following hours:

| | |
|---|---|
| 7:15 a.m. to 9:00 a.m. | Breakfast |
| 11:00 a.m. to 2:00 p.m. | Lunch |
| 4:45 p.m. to 8:30 p.m. | Dinner |

## CONTINUING EDUCATION CREDIT

The NIH is accredited by the Accreditation Council for Continuing Medical Education to sponsor continuing medical education for physicians. The NIH has certified this conference as meeting the criteria for 12 credit hours in Category 1 of the Physician's Recognition Award of the American Medical Association.

To request CEU's in nursing, individual nurses should send a completed consensus conference CME form and a copy of the conference agenda to their state nurses' association.

A CME form is included in the registration packet.

SPONSORS

This conference is sponsored by the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) and the NIH Office of Medical Applications of Research. Other sponsors of the conference are the Centers for Disease Control; the Food and Drug Administration; the Clinical Center, NIH; the National Institute of Allergy and Infectious Diseases, NIH; and the National Institute of Mental Health.

# Agenda

Monday, July 7

| | | |
|---|---|---|
| 8:30 a.m. | I. Introduction | |
| | Welcome | Amoz Chernoff, M.D.<br>Director<br>Division of Blood Diseases and Resources<br>National Heart, Lung, and Blood Institute |
| | Charge to the Panel | Itzhak Jacoby, Ph.D.<br>Acting Director<br>Office of Medical Applications of Research, NIH |
| 9:00 a.m. | II. Introductory Statement | |
| | Overview of Blood Banking and HTLV-III Antibody Testing | Joseph R. Bove |
| | III. Overview of Current Testing Technology | |
| 9:15 a.m. | Virologic Basis of Testing | Phillip D. Markham |
| 9:30 a.m. | Testing the Blood Supply for Antibodies to HTLV-III/LAV: The First Year Review of Currently Licensed and Prospective Tests | Thomas F. Zuck |
| 9:45 a.m. | Recent Experience in HTLV-III Antibody Testing: Characteristics of False Positive and False Negative Reactions | Judith A. Britz |
| 10:00 a.m. | Discussion | |

Monday, July 7 (continued)

IV. Epidemiologic Studies

| | | |
|---|---|---|
| 10:45 a.m. | Strategies for Screening Blood for HTLV-III/LAV Antibody: Use of A Decision Support System | J. Sanford Schwartz |
| 11:15 a.m. | Testing Blood Donors for HTLV-III Antibodies: The American Red Cross Experience | S. Gerald Sandler |
| 11:30 a.m. | Testing for HTLV-III at San Francisco's Irwin Memorial Blood Bank | Herbert A. Perkins |
| 11:40 a.m. | Transfusion-Transmitted HTLV-III | James W. Mosley |
| 11:50 a.m. | The Risk of HTLV-III/LAV Infection for Recipients of Blood From Donors Who Later Developed AIDS | John W. Ward |
| 11:55 a.m. | Transfusion-Transmitted HTLV-III: The Hemophilia Experience | Peter H. Levine |
| 12:05 p.m. | HTLV-III/LAV Infection in Blood Donors | James R. Allen |
| 12:15 p.m. | HTLV-III Infection in Asymptomatic Blood Donors | Harvey J. Alter |
| 12:25 p.m. | Discussion | |
| 1:00 p.m. | Lunch | |

V. Epidemiologic and Clinical Studies

| | | |
|---|---|---|
| 2:00 p.m. | Risks of Secondary HTLV-III Transmission | James J. Goedert |
| 2:10 p.m. | Risks of Secondary Transmission in Health Care and Laboratory Workers | David K. Henderson |
| 2:20 p.m. | The Medical Consequences of HTLV-III Infection | James J. Goedert |
| 2:30 p.m. | Outcome of HTLV-III/LAV Infection in a Cohort of Gay Men | Harold W. Jaffe |
| 2:40 p.m. | Discussion | |

Monday, July 7 (continued)

| | | |
|---|---|---|
| | VI. Operational Considerations | |
| 3:10 p.m. | HTLV-III Antibody Testing: Rights of the Individual | Christopher J. Collins |
| 3:25 p.m. | HTLV-III Antibody Testing: Rights of the Public | Karen Shoos Lipton |
| 3:40 p.m. | Discussion | |
| 4:05 p.m. | The Blood Donation Contract: Predonation Screening and Notification Policies | Johanna Pindyck |
| 4:20 p.m. | Plasma Donors | Robert W. Reilly |
| 4:30 p.m. | Issues Concerning Notification of Blood Donors Found HTLV-III Antibody-Positive | Jay E. Menitove |
| 4:40 p.m. | Effects of Notification | Robert W. Reilly |
| 4:50 p.m. | Effects of Notification on HTLV-III Antibody-Positive Donors: The California Experience | Steven Kleinman |
| 5:00 p.m. | Discussion | |
| 5:45 p.m. | Adjournment | |

Tuesday, July 8

| | | |
|---|---|---|
| | VII. Impact of Psychosocial Issues on the Individual | |
| 8:30 a.m. | Psychosocial Issues: Synthesis of Clinical Information | Jill G. Joseph |
| 8:45 a.m. | Causes and Consequences of Testing for HTLV-III Antibody: The Gay Community Experience | John L. Martin |
| 9:00 a.m. | Psychosocial Impact of Anti-HTLV-III Notification: The New York Experience | Johanna Pindyck |
| 9:15 a.m. | Psychosocial Impact of Anti-HTLV-III: The Hemophilia Experience | Peter H. Levine |
| 9:30 a.m. | Discussion | |

Tuesday, July 8 (continued)

VIII. Impact on Transfusion Medicine

| | | |
|---|---|---|
| 10:10 a.m. | The Impact of HTLV-III Antibody Testing on Donor Recruitment and Transfusion Practices | John L. Thornton |
| 10:20 a.m. | Impact of HTLV-III Antibody Testing on Transfusion Practice: An Overview | Douglas MacN. Surgenor |
| 10:35 a.m. | New Trends in Transfusion Medicine: Autologous Transfusions and Directed Donations | Margot S. Kruskall |
| 10:50 a.m. | Neonatal Transfusion Medicine: HTLV-III Implications | Naomi L. C. Luban |
| 11:05 a.m. | Discussion | |
| 11:40 a.m. | Adjournment | |

Wednesday, July 9

| | | |
|---|---|---|
| 8:30 a.m. | Presentation of the Consensus Statement | Thomas C. Chalmers<br>Panel and Conference Chairman |
| | Discussion | |
| 10:30 a.m. | Panel Meets in Executive Session | |
| 12:00 noon | Press Conference | |

## Consensus Panel

Thomas C. Chalmers, M.D.
Panel and Conference Chairperson
Distinguished Service Professor
Mount Sinai School of Medicine
New York, New York

Richard H. Aster, M.D.
President
Blood Center of Southeastern
Wisconsin
Clinical Professor of Medicine
and Pathology
Medical College of Wisconsin
Milwaukee, Wisconsin

Joan R. Bloom, Ph.D.
Professor
University of California
School of Public Health
Berkeley, California

John J. Collins, Jr., M.D.
Professor of Surgery
Harvard Medical School
Chief
Thoracic and Cardiac Surgery
Brigham and Women's Hospital
Boston, Massachusetts

Dale H. Cowan, M.D., J.D.
Clinical Professor of Environmental
Health Sciences
Case Western Reserve University
Director of Hematology and Oncology
Marymount Hospital
Cleveland, Ohio

Leon Gordis, M.D., Dr.P.H.
Professor and Chairman
Department of Epidemiology
Johns Hopkins University
School of Hygiene and Public Health
Baltimore, Maryland

Wolfgang K. Joklik, D.Phil.
Chairman
Department of Microbiology
and Immunology
Duke University Medical Center
Durham, North Carolina

Albert R. Jonsen, Ph.D.
Professor of Ethics in Medicine
University of California at
San Francisco School of Medicine
San Francisco, California

Lincoln E. Moses, Ph.D.
Professor of Statistics
Stanford University
School of Medicine
Stanford, California

Alvin Novick, M.D.
Professor of Biology
Department of Biology
Yale University
New Haven, Connecticut

Fred Rapp, Ph.D.
Professor and Chairman
Pennsylvania State University
College of Medicine
Hershey, Pennsylvania

Harold R. Roberts, M.D.
Professor of Medicine
Division of Hematology
University of North Carolina
School of Medicine
Chapel Hill, North Carolina

Marvin Stein, M.D.
Esther and Joseph Klingenstein
Professor and Chairman
Department of Psychiatry
Mount Sinai School of Medicine
New York, New York

## Speakers

James R. Allen, M.D., M.P.H.
Assistant Director for Medical Science
AIDS Program
Center for Infectious Diseases
Centers for Disease Control
Atlanta, Georgia

Harvey J. Alter, M.D.
Chief, Immunology Section
Department of Transfusion Medicine
Clinical Center
National Institutes of Health
Bethesda, Maryland

Joseph R. Bove, M.D.
Professor of Laboratory Medicine
Department of Laboratory Medicine
Yale University School of Medicine
Yale-New Haven Hospital
New Haven, Connecticut

Judith A. Britz, Ph.D.
Manager
Immunoassay Department
Electro-Nucleonics, Inc.
Columbia, Maryland

Christopher J. Collins, J.D.
Partner
Maione & Collins
Volunteer Cooperating Attorney
Lambda Legal Defense and Education Fund
New York, New York

James J. Goedert, M.D.
Cancer Expert
Environmental Epidemiology Branch
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

David K. Henderson, M.D.
Hospital Epidemiologist
Clinical Center
National Institutes of Health
Bethesda, Maryland

Harold W. Jaffe, M.D.
Chief
Epidemiology Branch
AIDS Program
Centers for Disease Control
Atlanta, Georgia

Jill G. Joseph, Ph.D., M.P.H.
Assistant Professor of Epidemiology
Department of Epidemiology
University of Michigan
School of Public Health
Ann Arbor, Michigan

Steven Kleinman, M.D.
Associate Medical Director
American Red Cross Blood Services
Los Angeles-Orange Counties Region
Los Angeles, California

Margot S. Kruskall, M.D.
Assistant Professor of Pathology
and Medicine
Harvard Medical School
Medical Director
Beth Israel Hospital Blood Bank
Boston, Massachusetts

Peter H. Levine, M.D.
Professor of Medicine
University of Massachusetts
Medical School
Director
New England Area Comprehensive
Hemophilia Center
Worcester Memorial Hospital
Worcester, Massachusetts

Karen Shoos Lipton, J.D.
Assistant General Counsel
Office of the General Counsel
American National Red Cross
Washington, D.C.

Naomi L.C. Luban, M.D.
Director
Hematology and Blood Bank Sections
Department of Laboratory Medicine
Professor
Children's Hospital National
Medical Center
Washington, D.C.

Phillip D. Markham, Ph.D.
Head
Tumor Biology Section
Department of Cell Biology
Bionetics Research, Inc.
Rockville, Maryland

John L. Martin, Ph.D., M.P.H.
Associate Research Scientist
Division of Sociomedical Sciences
Columbia University School of
Public Health
New York, New York

Jay E. Menitove, M.D.
Medical Director
Blood Center of Southeastern
Wisconsin, Inc.
Milwaukee, Wisconsin

James W. Mosley, M.D.
Professor of Medicine
University of Southern California
Los Angeles, California

Herbert A. Perkins, M.D.
Scientific Director
Irwin Memorial Blood Bank
San Francisco, California

Johanna Pindyck, M.D.
Senior Vice President
New York Blood Center
Director
Greater New York Blood Program
New York, New York

Robert W. Reilly
President
American Blood Resources Association
Annapolis, Maryland

S. Gerald Sandler, M.D.
Associate Vice President of
Medical Operations
National Headquarters
American Red Cross
Washington, D.C.

J. Sanford Schwartz, M.D.
Senior Fellow
Leonard Davis Institute of
Health Economics
University of Pennsylvania
Assistant Professor of Medicine
Section of General Medicine
Hospital of the University
of Pennsylvania
Philadelphia, Pennsylvania

Douglas MacN. Surgenor, Ph.D.
President
Center for Blood Research
Boston, Massachusetts

John L. Thornton, M.D.
President
American Blood Commission
Richmond, Virginia

John W. Ward, M.D.
Medical Epidemiologist
Epidemiology Section
AIDS Program
Center for Infectious Diseases
Centers for Disease Control
Atlanta, Georgia

Col. Thomas F. Zuck, M.D., MC
Director
Blood and Blood Products Division
Center for Drugs and Biologics
Food and Drug Administration
Bethesda, Maryland

## Planning Committee

Luiz H. Barbosa, D.V.M.
Planning Committee Chairperson
Health Scientist Administrator
Blood Resources Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

James R. Allen, M.D., M.P.H.
Assistant Director for Medical Science
AIDS Program
Centers for Disease Control
Center for Infectious Diseases
Atlanta, Georgia

Thomas C. Chalmers, M.D.
Panel Chairperson
Distinguished Service Professor
Mount Sinai School of Medicine
New York, New York

Roger Y. Dodd, Ph.D.
Head
Transmissible Diseases Laboratory
American Red Cross Biomedical Research and Development
Bethesda, Maryland

Jerry M. Elliott
OMAR Coordinator
Program Analyst
Office of Medical Applications of Research
National Institutes of Health
Bethesda, Maryland

James J. Goedert, M.D.
Cancer Expert
Environmental Epidemiology Branch
National Cancer Institute
National Institutes of Health
Bethesda, Maryland

James C. Hill, Ph.D.
Assistant to the Director
National Institute of Allergy and Infectious Diseases
National Institutes of Health
Bethesda, Maryland

Harvey G. Klein, M.D.
Chief
Department of Transfusion Medicine
Clinical Center
National Institutes of Health
Bethesda, Maryland

Gary B. McDonald
Executive Director
AIDS Action Council
Washington, D.C.

Christine T. Parker, Ph.D.
Health Program Specialist
Blood Resources Branch
National Heart, Lung, and Blood Institute
National Institutes of Health
Bethesda, Maryland

Barbara Silver, Ph.D.
Special Assistant to the Director
National Institute of Mental Health
Rockville, Maryland

Douglas MacN. Surgenor, Ph.D.
President
Center for Blood Research
Boston, Massachusetts

Col. Thomas F. Zuck, M.D., MC
Director
Blood and Blood Products Division
Center for Drugs and Biologics
Food and Drug Administration
Bethesda, Maryland

---

Michael J. Bernstein
Director of Communications
Office of Medical Applications
of Research
National Institutes of Health
Bethesda, Maryland

Carol M. Florance
Writer/Editor
Public Inquiries and Reports Branch
National Heart, Lung, and
Blood Institute
National Institutes of Health
Bethesda, Maryland

# Abstracts

The following are the abstracts of presentations to the Consensus Development Conference on the Impact of Routine HTLV-III Antibody Testing on Public Health. They are designed for the use of panelists and participants in the conference and as a reference document pertinent to the conference for anyone interested in the conference deliberations. We are grateful to the authors, who have summarized their material and made it available in a timely fashion.

Luiz H. Barbosa, D.V.M.
Health Scientist Administrator
Blood Resources Branch
National Heart, Lung, and
Blood Institute
National Institutes of Health

Christine T. Parker, Ph.D.
Health Program Specialist
Blood Resources Branch
National Heart, Lung, and
Blood Institute
National Institutes of Health

Jerry M. Elliott
Program Analyst
Office of Medical Applications
of Research
National Institutes of Health

# Overview of Blood Banking and HTLV-III Antibody Testing

Joseph R. Bove

On January 4, 1983, blood bankers, epidemiologists, virologists, medical policymakers, the CDC, the FDA, the NIH, and a whole host of representatives from concerned groups met at the CDC headquarters in Atlanta. The topic was the possibility that AIDS was being transmitted by blood and blood products. The setting was hardly conducive to discussion or decisionmaking. It was rather more like a media event, with those who shouldered responsibility for the nation's blood supply exposed and vulnerable. But there was discussion, if not decision, and from the meeting came a very clear message that the risk of transfusion-transmitted AIDS was perceived as a serious threat.

Since that day nothing in blood banking has been the same. The consequences of the AIDS epidemic have been far-reaching and their full impact on blood banking is still unknown. But one thing is clear. Every move, every decision, and every word from the blood bankers has become fair game for an aggressive press and a concerned public. In a disease where there are more questions than answers, basic biologists, virologists, epidemiologists, and blood bankers have struggled to come to grips with a number of new and serious problems. In this disease, no discovery, no new information, and no new comment, whether scientific, medical, or social, has been without myriad consequences, most of which were unanticipated. For the next 2 days we will examine the consequences of one of the discoveries which has been central to our understanding of the disease. I mean, of course, the identification of the etiologic agent of AIDS, and the development, evaluation, and implementation of a test for antibodies to it.

I cannot move on without a word of tribute and respect to the many scientists who--in a very short time--identified the virus and developed the test that is the subject of our conference. This meeting is not the place to discuss priority, but two things should be part of the record. First, the discovery of HTLV-III and its relationship to AIDS rested squarely on the previous work of Dr. Gallo and his group. Without their years of research in retrovirology we could not, today, be talking about the test. And second, the American public--and indeed the world--has been well served by the nation's longstanding investment in basic research. Without this investment, the struggle to understand the virology of AIDS would still be in its infancy.

For the next 2 days we will address the impact of anti-HTLV-III testing on blood banking, transfusion practices, and the American public. It is remarkable that in a relatively short time the scientific community identified the etiologic agent, developed the test, validated its relation to the disease, mass-produced and tested the reagent kits, and applied this new and immature test at a rate of over 20 million a year. There have been problems and it is these that are the agenda of our conference. But there have been positive features as well. Because of testing, the blood supply is safer and that was the goal of the test. But it is the problems that we have assembled to hear about. They have arisen partly because of the very important social and emotional aspects of AIDS, partly because of the magnitude of the testing program, partly because of the test itself, and partly because of our still incomplete understanding of the disease and its epidemiology.

As background let me say a few words about blood and plasma collection in the United States today. All of the nation's blood and blood components are collected from volunteer donors. The same is true of about 20 percent of the plasma that is used for further processing into derivatives such as albumin, plasma protein fraction, and the various clotting proteins. The remaining 80 percent of the plasma comes via plasmapheresis of paid donors. In the voluntary sector, the American Red Cross Blood Program collects about 6.2 million units a year, members of the American Association of Blood Banks, about 3 million units a year, and members of the Council of Community Blood Centers, about 2.6 million units yearly. These numbers have been corrected for the overlap introduced because some blood banks belong to more than one organization. According to the American Blood Resources Association--the organization that represents the commercial plasmapheresis operations--its 100 corporate members harvest about 6 million liters of plasma each year from about 10 million collections. All collectors--whether volunteer or commercial--operate under Federal regulations and maintain high standards. When the test for anti-HTLV-III became available in late spring of 1985 both the volunteer and commercial sector immediately implemented testing of all donors. There is still no requirment for testing, but there is also--to the best of my knowledge-no blood bank or plasma center that is not testing. We are doing over 20 million tests a year or about 80,000 tests every working day. At that level problems--and there are some--soon become evident.

## WHAT CONSTITUTES A POSITIVE TEST AND HOW SHOULD A POSITIVE RESULT BE INTERPRETED?

Throughout the conference we will hear, again and again, questions about the meaning of a positive test. At the outset the Food and Drug Administration (FDA) recognized the lack of knowledge in this area and reacted to it by avoiding the term "positive." Rather, the FDA coined a new set of words, "repeatedly reactive," to indicate only a laboratory result. The correlation of that laboratory finding with a clinical state or with a medical prognosis is less than perfect at present. We need to

examine what data we have and to decide, if we can, what a repeatedly reactive test result means. There is reason to believe that all repeatedly reactive results do not have the same clinical significance. In particular, there has been concern about those repeatedly reactive results where the ratio of sample reactivity to an arbitrarily determined "cut-off" value is low. These are suspected of being falsely positive, but we lack the criteria to establish the validity of this concept. At the current rate of testing and if the early experience continues unchanged, each year about 17,000 of the volunteer blood donors will be identified as having a repeatedly reactive test. But of these, only about 4,000 will have a positive reaction when tested by Western blot, a test thought to be more specific. (These estimates are for the volunteer sector only.) We need to know more about both sets of donors--those with and those without a positive Western blot test. We desperately need a confirmatory test so that we can establish the significance of the "repeatedly reactive" test in those donors who are ELISA positive, Western blot negative. The massive testing program has produced its desired result--blood is safer. But it has produced, as well, a large number of individuals whose serologic and clinical state is in doubt. We need to know what to tell these people.

HOW SHOULD POSITIVE TEST RESULTS BE HANDLED?

The burden of a positive test for anti-HTLV-III is a heavy one to place on the shoulders of anyone, and all the more so on a healthy low-risk individual. We are not yet comfortable that many of the positive test results we are finding mean infection or infectivity. We are so uncomfortable, in fact, that we do not tell donors who have a positive ELISA test unconfirmed by Western blot that their test is positive and their donation discarded. We do, however, place their names on a list of donors whose further donations are not to be used. We are in the unacceptable and intolerable position of having collected a group of individuals--now numbering perhaps as many as 20,000--who may continue to donate although we know in advance that we do not plan to use their blood. They have not been notified of previous findings and many continue to donate. There is every reason to believe that many of these persons are healthy and that their isolated laboratory test was an anomaly. We need criteria for deciding who should be told that they are possibly infected and who should be told nothing and returned to the donor lists.

WHAT RESEARCH DIRECTIONS SHOULD BE PURSUED?

The panel has been charged to reach consensus on research directions to be pursued. The goal is admirable, but almost unattainable. There is so much to do. Even the limited charge implied by the title of this conference--research related to antibody testing of blood and plasma donors--leaves myriad fertile areas for investigation. Do we need more sensitive and specific tests? Do we need long-term epidemiological studies of low-

risk donors who have a positive test? Should we mount a major campaign to find, test, and counsel all recipients of blood components donated by persons who now test positive? Are we in need of an antigen test or is antibody testing, as currently used, adequate? Should we prepare a major research thrust aimed at inactivating the HTLV-III virus in all blood products, or should we assume the safety of antibody-negative donors? Just how common is the antibody-negative, culture-positive state? Do we need additional, and perhaps surrogate, tests? Who should seek out, inform, council, and follow the donors who are antibody-positive? And how should this be done?

Finally, perhaps as a question for "research directions to be pursued," we need to understand how to go about regaining public confidence in the blood bank system. The U. S. voluntary blood program is a good one, but physicians, patients, and donors seem to have lost faith in it. We need to get that faith back, and perhaps we need some research into how to go about it.

Nothing about the AIDS epidemic has been easy. Not for the research community, not for the government, not for physicians, not for the blood banks, not for members of high-risk groups, and certainly not for the patients. We look to this conference for answers to a few of the many troublesome problems that remain.

# Testing the Blood Supply for Antibodies to HTLV-III/LAV: The First Year Review of Currently Licensed and Prospective Tests

Thomas F. Zuck

About 2 percent of acquired immune deficiency syndrome (AIDS) cases occur following blood transfusions and the causative human T cell lymphotropic virus, type III/lymphadenopathy-associated virus (HTLV-III/LAV), is known to be transmitted by blood. The spread of infection by transfusion creates particular concern because recipients usually cannot modify their behavior to avoid transmission in this manner. To reduce the prevalence of infected blood, collecting establishments in the United States began testing for HTLV-III/LAV antibody in the spring of 1985. All blood and plasma donations were screened with one of three commercial enzyme immunoassay (EIA) test kits licensed initially. Testing also became available to people at increased risk for HTLV-III/LAV infection at alternative test sites established in many communities; these people previously had been asked not to donate blood or plasma. Perspectives gained from testing millions of people during this first year may be helpful in charting tasks to improve the safety of the blood supply in the future.

The evidence suggests that available EIA test kits are highly sensitive for detecting HTLV-III/LAV antibodies in donated blood and plasma, but the expected penalty for nonspecificity has been high. Rates of nonspecific reactions vary among test kits from different manufacturers and among different lots of test kits from the same manufacturer. With test kits of the initial five companies licensed by the government up to 75 percent of initially reactive tests cannot be confirmed by a second test performed in duplicate on the same sample. If either of these repeat tests is reactive, in blood banking practice the sample is considered repeatably reactive, the donated unit of blood or plasma is discarded, and the donor is deferred permanently. The number of repeatably reactive samples confirmed to have antibody by additional testing--usually Western blotting--also is variable. With some tests this confirmation rate of repeatably reactive tests is less than 20 percent. However, for all HTLV-III/LAV-antibody EIA test kits the probability of nonspecificity is related inversely to the optical density of the EIA, that is, the more strongly reactive the sample, the more likely that it will be confirmed.

Although nonspecific reactions have been accepted in order to provide maximum protection of the blood supply, they have caused difficulties.

First, because the interpretation of repeatably reactive test which cannot be validated by an additional test remains in doubt, volunteer blood donors generally are not notified about repeatably reactive test results unless the presence of antibody is confirmed by an additional test, usually Western blotting. Since these donors have been deferred permanently, their future donations are accepted but discarded. It is estimated that 25,000 donors may be in this awkward, deferred status.

Further, because of the high rate of nonspecific reactions, the HTLV-III/LAV-antibody EIA must be used with great care for other than screening units of blood and plasma. Although a repeatably reactive EIA on a serum obtained from a person at increased risk of HTLV-III/LAV infection is highly predictive of the presence of HTLV-III/LAV antibody, and thus probable infectivity, the predictive value of a reactive EIA is very poor in persons of unknown or low risk for infection. For this reason, the presence of the antibody in these people cannot be inferred solely from a reactive EIA. Testing should include an additional, more specific test, such as Western blotting, and, if the presence of antibody is confirmed, medical evaluation and counseling should be provided.

Experience during the first year of testing also suggests that people who are at increased risk of HTLV-III/LAV infection continue to donate blood and plasma. The ratio of male-to-female blood and plasma donors with repeatably reactive sera is approximately one-to-one; however, of those donors whose sera have antibody confirmed, usually by Western blotting, over 90 percent have been men. One study of recent donations suggests this male predominance may have dropped to 72 percent. The presence of antibody in donors, which can be confirmed by additional testing in about 0.04 percent, itself indicates that risk factors for HTLV-III/LAV infection were present in these people when they donated. During counseling of blood donors with antibody to HTLV-III/LAV recognized by Western blot, many were found to have risk factors for HTLV-III/LAV infection but did not consider themselves at increased risk. Other donors admitted risk factors but feared loss of anonymity about their lifestyles if they failed to donate. In two studies, over 70 percent of donors with confirmed antibody had helper-to-suppressor T cell ratios of less than one, suggesting established infection. There is a time lapse between a defined exposure to HTLV-III/LAV and the appearance of detectable antibody in an exposed person's serum. However, the risk to patients receiving blood donated by people at increased risk for HTLV-III/LAV infection without detectable antibody in their sera is not known. Because of the sensitivity of the EIA and the brief interval between exposure and antibody seroconversion, the risk probably is extremely small.

Experience during the first year of testing suggests future tasks; two come to mind readily. First, tests to confirm the presence or absence of antibody to HTLV-III/LAV quickly, reliably, and economically are under development. Their availability should preclude most problems of nonspecificity. Although it probably would not well serve the safety of the blood supply to decrease EIA sensitivity by increasing specificity, it

may be possible to improve both through new test configurations. As additional licensed tests become available, uniform methods of validating reliability and surveying performance will be required. These tasks should be completed through cooperative efforts of the Government and the private sector. International coordination would be desirable.

Second, the number of persons at increased risk for HTLV-III/LAV infection who continue to donate must be reduced. More effective donor education and screening, as well as more subtle strategies for confidential self-exclusion, must be developed. Little attention is now focused on increasing the understanding of AIDS by the estimated 60 million Americans of marginal literacy through video presentations or other improved educational techniques. Research should be undertaken to develop approaches that would be more effective than those now is use.

In summary, it seems clear that testing for HTLV-III/LAV antibody in blood and plasma has increased the safety of the blood supply in the United States. The experience of the first year has defined tasks to improve that safety even further. It also seems clear that, despite our needs, no biological system can be completely without risk. Therefore, increased caution and adherence to more rigorous criteria for transfusing blood must be the cornerstone on which to base self-exclusion and HTLV-III/LAV antibody testing. Vigorous educational efforts in this area are indicated.

# Recent Experience in HTLV-III Antibody Testing: Characteristics of False Positive and False Negative Reactions

Judith A. Britz

The discovery of HTLV-III/LAV as the etiological agent of AIDS mandated the development of a highly sensitive antibody screening test to eliminate potentially infectious units from use in blood transfusions.[1] The requirement for maximum sensitivity has had an impact on test specificity, especially since the prevalence of HTLV-III infection among random blood donors is low.[2] Based on a projected prevalence rate of 0.1 percent in the donor population, the false positive rate of repeatably reactive ELISA tests for the seven licensed manufacturers is estimated between 68 and 90 percent.

Additional evidence of a false positive problem in screening of low-risk populations is obtained by a closer examination of the repeatably reactive samples: (1) The majority of these are low-level ELISA reactors which fall in the tail of the normal distribution; (2) the sex distribution of these reactives is close to 50:50--a fact inconsistent with the epidemiology of AIDS where 94 percent of its victims are men; and (3) less than 50 percent of these repeatably reactive results can be confirmed by Western blot.

The types of false positives encountered in HTLV-III ELISA testing fall into two categories: technical and biological. A comparison of initial and repeat reactive rates for several manufacturers demonstrates that a large proportion of initially reactive samples cannot be repeated. These nonrepeatable reactives are likely to arise from slight differences in sample dilution, time or temperature of incubation, and washing efficiency. Sample quality is also important. Bacterial contamination, repeated freeze-thawing, and heat treatments are known to increase the number of false positive results. These types of technical problems are common to all ELISA assays and are not unique to the HTLV-III ELISA test.

The sources of biological false positives in HTLV-III testing are more elusive. Six of the seven manufacturers utilize the same HTLV-III isolate propagated in the H9 cell line. The seventh manufacturer uses LAV grown in the CEM line. Given that maturation of the HTLV-III/LAV virus is achieved by the budding of virus particles from the cell surface and that purification of the virus by buoyant density in sucrose is uniformly used by the licensed manufacturers, it is not surprising that human cellular antigens copurify with viral antigens.

In spite of similarities in the cell line and method of purification, the subpopulations of false positives for the various manufacturers usually do not overlap.[3] An increased rate of false positives, however, has been identified in multiparous women as well as individuals with autoimmune disorders (systemic lupus erythematosus, rheumatoid arthritis, and connective tissue diseases). Anti-HLA antibodies of both Class I and II specificities have been implicated in sera from multiparous women.[4] The presence of antinuclear, antimitochondrial, and anti-T cell antibodies has been correlated with higher repeat reactive rates on the HTLV-III ELISA.[5] For reasons not yet identified but presumably related to the methods of antigen purification, these samples present problems of varying degrees for the seven licensed tests, whether the H9 or CEM cell line has been used for propagation of the virus.

Finally, since the sensitivity of all HTLV-III ELISA kits exceeds 99 percent, false negative results occur with extremely low frequency. However, all of the current HTLV-III ELISA assays are designed to detect HTLV-III antibody only. Therefore, carriers of the HTLV-III antigen who have not yet mounted an antibody response will not be detected. In addition, if the levels of HTLV-III antibodies or their affinity or avidity are sufficiently low, they may fall below the detection limits of some assays. Some false negatives result from differences between manufacturers in the relative proportions of p24 to gp41 or gp110 to 120 HTLV-III-specific proteins. Lastly, inability to detect IgM or other immunoglobulin subclasses as efficiently as IgG may account for a very small percentage of false negative results.

The overall performance of the seven licensed HTLV-III ELISA assays indicates a high degree of both sensitivity and specificity for a first generation test, especially when compared with similar ELISA assays for rubella antibodies or hepatitis surface antigen. Nonetheless, the populations of samples that react falsely (either positively or negatively) appear to be unique for each of the licensed screening tests.

REFERENCES


1. Gallo RC, Salahuddin SZ, Popovic M et al. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. Science 1984;244:500-3

2. Schorr JB, Berkowitz A, Cumming DP et al. Prevalence of HTLV-III antibody in American blood donors. N Engl J Med 1985;34:1-5

3. Fang CT, Darr F, Kleinman S, Wehling RH, Dodd RY. Relative specificity of enzyme-linked immunosorbent assays for antibodies to human T-lymphotropic virus, type III, and their relationship to Western blotting. Transfusion 1986;26(2):208-9

4. Kuhnl P, Seidl S, Holzberger G. HLA dry antibodies cause positive HTLV-III antibody ELISA results. Lancet 1985;May 25:1222-3

5. Britz JA, Zimmerman DH, Mundon FK, O'Connor T, Bush G. The HTLV-III ELISA: a sensitive and specific test for the detection of antibodies to human T lymphotropic virus. In: The International Symposium on Virology, Anaheim, California, Luiz de la Maza (ed), Hillsdale, New Jersey: Lawrence Erlbaum Associates, 1986 (in press)

# Testing Blood Donors for HTLV-III Antibodies: The American Red Cross Experience

S. Gerald Sandler

By July 1986, American Red Cross regional blood services will have tested 7,500,000 units of blood for HTLV-III antibodies using Abbott Laboratories' enzyme immunoassay test kits (EIA). As of February 1986, test results on 5,500,000 donor units showed 65,000 (1.19 percent) to be EIA initially reactive; 18,000 (0.33 percent) to be EIA repeatedly reactive; and 1,675 (0.031 percent) to be Western-blot-positive. An increase in repeatedly reactive EIA results from 0.14 percent (April 1985) to 0.44 percent (February 1986) has been attributed to a rise in false positive reactions, because the percentage of Western-blot-confirmed test results remained constant or decreased during this same period. Also during this period, 30 percent of all donor samples testing EIA repeatedly reactive, Western-blot-negative in regional blood centers were found to be EIA nonreactive when retested by the manufacturer, Abbott Laboratories. Of specimens found in Red Cross centers to be EIA repeatedly reactive with sample/cutoff (S/C) ratios of two or less, 40 percent were found to be EIA nonreactive when retested by the manufacturer. Of 6,000 EIA repeatedly reactive donor specimens retested by the Abbott EIA at Red Cross national headquarters, 50 percent were nonreactive.

Using current criteria for interpreting Western blot tests, none of 2,928 EIA repeatedly reactive specimens drawn in 1986 was found to be Western-blot-positive by Abbott Laboratories if the EIA S/C ratio was two or less.

When 222 Western-blot-negative donors with EIA S/C ratios of two or less were retested more than 6 weeks later, 162 (73 percent) were found to be EIA nonreactive. The remaining 60 donors (27 percent) were still EIA repeatedly reactive but clinically well and Western-blot-negative.

Blood units found to be repeatedly reactive were not transfused. Donors were notified that their blood tested positive for HTLV-III antibodies only if Western blot test results unequivocably showed the presence of HTLV-III antibodies.

Red Cross donors were first notified of Western-blot-positive test results in July 1985. Additional health history information obtained during subsequent notification interviews indicated that more than 75 percent of these Western-blot-positive donors actually had risk factors

for HTLV-III exposure, although they had not identified themselves as individuals in high-risk groups at the time of donation. Demographics of Western-blot-positive donors resemble those of AIDS cases when compared for gender, geographic distribution, and prevalence of hepatitis B surface antigen.

# Testing for HTLV-III at San Francisco's Irwin Memorial Blood Bank

Herbert A. Perkins

## ROUTINE VOLUNTEER BLOOD DONORS

Starting on March 6, 1985, Irwin has tested approximately 100,000 blood donors. Using the Abbott EIA test, the frequency of repeat reactors has been 3 in 1,000. The frequency of Western-blot-confirmed reactors has been 1 in 1,000. Western blot testing has been done by an experienced university-based laboratory. Almost all of the Western-blot-positive donors, when confonted with the test results, admitted exposures which classified them in a risk group for AIDS, but they had donated and had not answered the donor questions accurately on the mistaken belief that they could not possibly be at risk. Several Western-blot-positive donors had been exposed through prior blood transfusions. There were two donors, however, for whom all risk factors were denied. In retrospect our referral laboratory now believes the results should have been reported as equivocal rather than positive. In both cases the patterns consisted of a weak p25 and a very weak gp41. In one of these cases, repeated tests suggested that either a labile factor had caused false-positive results or test reagents had varied in sensitivity (table 1).

Irwin was involved in field-testing a number of commercial kits preliminary to licensing, and had the usual experience of very poor agreement between EIA-reactives when the Western blot was negative. In a recent comparison of two licensed tests, we were disturbed to find several Western-blot-confirmed sera which had been detected by one licensed EIA test but missed by the other.

## DONORS TO RECIPIENTS WHO DEVELOP AIDS

Twenty-eight cases of AIDS have been attributed to prior transfusions with blood from Irwin. In seven of these cases, one of their donors has subsequently developed AIDS. In all other cases at least one antibody-positive donor from a high-risk group has been found, except for those cases for which the investigation is still incomplete.

RECIPIENTS OF DONORS WHO LATER DEVELOP AIDS

Approximately 1,800 cases of AIDS have been reported in San Francisco city and county alone, and Irwin provides blood in seven other counties as well. It is thus not surprising that, as of the end of 1985, 61 previous Irwin donors with AIDS had been identified. Nearly all of these were ascertained by comparison of county lists of AIDS victims with the blood bank donor files, and were not reported through routine surveillance activities.

Blood components from these 61 donors given since January 1, 1979, had been transfused into 257 recipients. Of these 257 recipients, 160 were dead (primarily of the condition for which they were transfused) and 72 were alive. The remainder had not yet been contacted. Of the 232 recipients whose fate is known, six had developed AIDS.

We have tested 53 of the recipients for antibody. The results are on table 2.

Of the six AIDS cases, only four had confirmed antibody. One would normally be considered a false positive, since both IFA and Western blot were negative. One was negative on Western blot and not tested by other methods. The less than 100 percent confirmed positivity is consistent with other reports that antibody may disappear at the stage of advanced immunodeficiency which characterizes CDC-defined AIDS.

Of the 47 remaining recipients, 27 (57 percent) had antibody confirmed by both IFA and Western blot, although it is noteworthy that two of these were missed by EIA. Again one case would appear by usual standards to be a false positive, since the reactive EIA was not confirmed by either IFA or Western blot. Finally, we have one case in which the IFA and Western blot (done in different referral laboratories) did not agree. This discrepancy still needs to be confirmed by repetition. On initial testing, there were four other conflicting results between IFA and Western blots, but these were clarified by multiple repetitions using blinded samples. The errors had occurred on both IFA and Western blot testing. Although clerical errors may have been the cause of some of the discrepancies, there were multiple instances where a request to the reference laboratory to reread the original pattern resulted in a different interpretation.

CONCLUSIONS

The EIA screening test has performed better than expected, but does require specificity confirmation when dealing with a population at low risk for AIDS, such as blood donors and recipients. Numerous problems remain, however, and the need for improved tests is obvious.

The currently licensed EIA tests appear to miss occasional samples that have specific antibody as defined by IFA and Western blot. The frequency of these false negatives is not known, and there are no figures available now to make any kind of reasonable estimate. However, one false negative test on a blood donor is one too many, since it is highly likely to result in infection of the recipient.

The false positive problem is much more common. The frequency of false positives may be less with some of the more recently licensed EIA tests and other modifications undergoing testing. False positive reactions may be caused by inclusion of cell membrane antigens in the viral extract used as target for the test, and we have confirmed that antisera with anti-HLA-DR4 uniformly react in some of these EIA tests. This problem should be solved with second generation screening tests using recombinant DNA-manufactured viral proteins. The genetically engineered materials, however, may still cause false positives because of antibodies induced by other viruses or other materials that crossreact with AIDS virus proteins. A completely reliable specificity test for confirmation is not in sight at this point.

Our experiences with conflicting and nonreproducible interpretations of IFA and Western blot tests have convinced us that a test with a subjective endpoint is not acceptable. We need machine-readable endpoints and we need some way to standardize the tests so that there will not be lot-to-lot variation in sensitivity, nor decay in sensitivity on storage.

Table 1

| Sample | Irwin | Lab 2 | Lab 3 | Lab 4 |
|---|---|---|---|---|
| No. 1 | EIA+ | EIA+ | IFA+,WB+ | EIA-,WB- |
| No. 2 | | | | EIA-,WB- |
| No. 1 | EIA- | | | |

EIA = enzyme immunoassay
IFA = immune fluorescence assay
WB = Western blot

Table 2

| AIDS CASES | EIA | IFA | WB | No. Cases |
|---|---|---|---|---|
| | + | + | + | 3 |
| | + | + | NT | 1 |
| | + | - | - | 1 |
| | NT | NT | - | 1 |
| OTHERS | + | + | + | 25 |
| | - | + | + | 2 |
| | + | - | - | 1 |
| | + | - | + | 1 |
| | - | - | - | 18 |

NT = not tested (insufficient sample available)

# The Risk of HTLV-III/LAV Infection for Recipients of Blood from Donors Who Later Developed AIDS

John W. Ward

To assess the risk of human immunodeficiency virus (HIV) transmission by blood transfusion, we identified recipients of blood components from donors who later developed the acquired immunodeficiency syndrome (AIDS). Of 59 living recipients, 39 (66 percent) were positive for HIV antibody. The virus was isolated from 5 of 20 seropositive recipients. On average, seropositive recipients had received blood within 29 months of the donors' AIDS diagnosis compared with 46 months for seronegative recipients. All 11 recipients who received blood within 23 months of the diagnosis of AIDS in the donor became infected. In the seven instances of split donations, both recipients were infected. After the first transmission of HIV to a recipient, all later recipients from the same donor became infected. If a donor's blood was infectious, HIV transmission occurred regardless of the blood component received. These findings suggest that HIV-infected donors have a well-defined period of infectivity during which recipients will become infected with HIV.

# Transfusion-Transmitted HTLV-III: The Hemophilia Experience

Peter H. Levine

There are an estimated 20,000 persons with hemophilia A or B in the United States. Of this group, approximately half are severely affected; such patients have hemorrhagic episodes which require blood product therapy about once a week, on the average.

HTLV-III antibody testing of samples from serum banks established in hemophilia centers has shown that: (1) no patients were seropositive before 1978, (2) there was a sharp increase in the subsequent rates of seropositivity during the period between 1981 and 1983, (3) severely affected patients were more likely to be seropositive than were patients with moderate or mild disease, (4) hemophilia A patients were more often seropositive than were hemophilia B patients, and (5) patients treated with commercial concentrate were more often seropositive than were patients treated with nonpooled blood products (much of this difference may be due to the fact that most of the latter group had mild disease or received little therapy). As of now, cohorts of patients with hemophilia demonstrate an overall rate of seropositivity of approximately two-thirds, with severely affected patients showing seropositivity in more than 90 percent of these studied.

Applying HTLV-III testing to study groups of persons with hemophilia has allowed a number of important findings and conclusions. Some arbitrarily selected examples follow.

1. Although an estimated 10,000 persons with hemophilia were infected with HTLV-III (predominantly between 1981 and 1983) the attack rate of AIDS appears to be reaching a plateau; with 158 cases now reported, the AIDS rate is lower than for other risk groups.

2. With a screening test as accurate as 99.5 percent applied to the donor pool, and even if the issue of culture-positive but antibody-negative persons is ignored, the application of HTLV-III testing to factor VIII concentrate donors will greatly reduce the titer of virus in the product, but will not be likely to fully eliminate it.

3. No "clean" case of seroconversion attributable to heat-treated factor VIII or IX concentrate has yet been reported. A few cases will certainly occur, sooner or later.

4. Not all of the immune abnormalities found in treated hemophiliacs are attributable to HTLV-III infection.

5. Family members of seropositive persons with hemophilia are at very low risk for HTLV-III infection (more than 650 studied; zero seroconverters) with the exception of heterosexual partners, who may have a risk of seroconversion approximating 1 percent per year.

6. HTLV-III testing is of importance in family planning, since seropositive women have high likelihood of producing infected and ill offspring.

7. The identification of cohorts of seropositive persons with hemophilia will allow us to study the natural history of HTLV-III infection and to seek to understand associated risk factors as well as effects of therapeutic interventions in this highly motivated and compliant population.

8. The large discrepancy between seropositive and culture-positive persons needs further study.

9. The many instances of disclosure of HTLV-III seropositivity which have occurred have led to numerous episodes of expulsion, exclusion, quarantine, and the like for persons with hemophilia.

# HTLV-III/LAV Infection in Blood Donors

James R. Allen

## BLOOD DONORS TO PEOPLE WITH TRANSFUSION-ASSOCIATED AIDS

Epidemiologic investigations of donors to the first cases of transfusion-associated AIDS unequivocally demonstrated that for each case at least one donor could be found who was at high risk for AIDS or who had immunologic deficiency characteristic of people with AIDS. Subsequent evaluation of the antibody status of many of these donors confirmed that a high proportion (85 percent) of those with a risk factor by history or with immunologic abnormality had antibody to the human immunodeficiency virus (HIV or HTLV-III/LAV) or enzyme immunoassay (EIA) and Western blot. In contrast, donors who did not have a risk factor and who were immunologically normal did not have antibody.

Lymphocyte specimens from 27 high-risk donors to 24 cases of transfusion-associated AIDS were available for viral culture. Two specimens were from donors who were asymptomatic, had a normal lymphocyte count, and a negative test for antibody to HIV; both had a negative culture for HIV. Two other specimens were from donors with antibody to HIV, one of whom had a normal lymphocyte count but did have lymphadenopathy; the results of the cultures could not be evaluated because of technical problems. Of the 23 specimens from donors with antibody to HIV in which the cultures could be evaluated, 22 (95.7 percent) were positive for HIV. The 22 donors with HIV on culture included 20 with an abnormally low ratio of T-helper to T-suppressor lymphocytes and two with normal lymphocyte counts. The antibody-positive donors had been clinically evaluated and specimens obtained 12 to 52 months (mean, 28 months) after they had given the unit of blood transfused to the patient who subsequently had AIDS. At evaluation, 15 (68.2 percent) donors were asymptomatic, 5 (22.7 percent) had lymphadenopathy, and 2 (9.1 percent) had been diagnosed with AIDS. The single antibody-positive, culture-negative donor was asymptomatic and had a normal lymphocyte count 24 months after the donation. All the donors who had a positive culture for HIV had antibody to HIV detectable by available screening tests.

## EVALUATION OF BLOOD DONORS WITH A LICENSED HIV ANTIBODY EIA TEST

Although the retrospective study of blood donors epidemiologically implicated in transfusion-associated AIDS cases showed that donors at risk of AIDS were highly likely to have HIV antibody and to be culture-positive, many people were not convinced the HIV-antibody screening tests

that were licensed in 1985 would actually detect infected blood or plasma donors. In addition, because of the low prevalence of infected persons that was expected in the blood donor population, there was concern that a large number of the tests would be false positive. To determine the validity of these concerns and to evaluate the performance of a licensed production-lot EIA test for HIV antibody in a blood donor population, the Centers for Disease Control (CDC) and the American Red Cross Blood Services (ARCBS), Atlanta Region, initiated a cooperative study in March 1985.

Over the 18-week study period from March 25 through July 31, all potential donors at ARCBS continued to be given information about AIDS and HIV infection, including the need for those with a risk factor for infection to self-defer. In addition, they were told that donated blood would be screened for antibody to HIV; that alternative test sites were available for people with a risk factor who wished to be tested anonymously; that additional tests may be performed on their blood specimens at CDC; and that donors with positive tests would be informed and counseling provided. An additional 27 ml of blood for extra studies was obtained during phlebotomy from people accepted as donors.

All units of blood collected were processed by the ARCBS central laboratory. Blood was screened for antibody to HIV using the Abbott HTLV-III EIA.* Units with an initially reactive test had two repeat EIA tests performed in accord with the manufacturer's instructions. Specimens of blood from units with initially reactive EIA tests and from a random sample of those with negative EIA tests were transferred to the CDC for additional studies that included repeat testing with the Abbott HTLV-III EIA, Western blot testing, and culture of peripheral lymphocytes for HIV.

During the study, 67,190 sequentially collected units of blood were screened by the ARCBS. Of these, 569 (0.85 percent) units had an initially reactive EIA test; only 171 units (0.25 percent of all donations or 30.1 percent of initially reactive units) had a repeatedly reactive EIA test. Specimens were sent to the CDC from 150 units that were repeatedly reactive, 628 units that were EIA-negative, and 306 units that were reactive on initial EIA but negative on repeat testing (table 1). None of the EIA-negative or initially reactive specimens were either Western-blot-positive or culture-positive, although approximately 1 percent did have a repeatedly reactive EIA test at the CDC; all these EIA results were weakly reactive (absorbance value < 3.0 times the cutoff value).

Of the 150 specimens repeatedly reactive by EIA that were further evaluated at the CDC, 86 (57.3 percent) were defined as weakly reactive,

*Use of trade names is for identification only and does not imply endorsement by the U.S. Public Service, the Centers for Disease Control, or the American Red Cross.

19 (12.7 percent) were moderately reactive (absorbance value $\geq$ 3.0 but < 6.0 times the cutoff value), and 45 (30.0 percent) were highly reactive (absorbance value $\geq$ 6.0 times the cutoff value). Both Western blot assay and culture for HIV correlated strongly with degree of EIA test reactivity (table 2). For all specimens that were repeatedly reactive by EIA, 26.0 percent were Western-blot-positive and 16.7 percent were culture-positive. Only 1.0 percent of the weakly or moderately reactive specimens were Western-blot-positive and 1.9 percent were culture-positive, while 84.4 percent of the highly reactive specimens were Western-blot-positive and 51.1 percent were culture-positive.

Blood donors whose specimens were weakly or moderately reactive on EIA were significantly more likely than other donors to be older and women. In contrast, donors whose specimens were highly reactive were almost exclusively men. Twenty-nine of the donors with highly reactive EIA specimens were interviewed; 25 (86.2 percent) had a risk factor for HIV infection. Two of these donors who did not acknowledge a risk factor had positive HIV cultures. Of 75 donors whose specimens were weakly or moderately reactive by EIA (and negative by Western blot and culture), only 1 had a risk factor.

## SUMMARY

In this study, approximately 28 percent of blood donors who had a repeatedly reactive EIA test for antibody to HIV probably were infected with the virus as judged by a positive Western blot test or isolation of the virus on culture. Most of these people had a risk factor for infection. The estimated prevalence of HIV infection in this selected population was 7.0 per 10,000.

If a positive Western blot test or isolation of HIV by culture or both, is used as the standard of infection, the calculated specificity of a repeatedly reactive EIA test was 99.8 percent and the predictive value in the population studied was 27.5 percent. The predictive value of a single reactive test by EIA was much lower, only 8.3 percent. For specimens that gave repeatedly reactive results, the predictive value varied markedly by degree of EIA reactivity: a weakly or moderately reactive test had a predictive value of 1.9 percent while a strongly reactive test had a predictive value of 86.7 percent. Most of the weakly and moderately reactive test results probably are caused by nonspecific reactivity or cross-reactivity to other human cellular antigens present in the test.

The sensitivity of the EIA test could not be determined in this study since it was not possible to perform Western blot or culture on even a large sample of the donors screened by EIA. The failure to find any infected people in this study among those with a negative or only an initially reactive EIA test and the performance of the same test in a population of gay men at high risk of infection suggest that the lower limits of confidence for test sensitivity is > 97 percent.

## AREAS OF FUTURE STUDY

Most important, a standard of HIV infection needs to be established against which all tests can be evaluated uniformly. The pattern of specific antibody response to infection should be clarified to determine which antigens may be most useful to incorporate into future generations of tests.

Additional studies should explore the reasons for and significance of discrepancies in test results, e.g., those donors who are strongly EIA-reactive but Western-blot- and culture-negative and those who are EIA- and culture-positive but Western-blot-negative. The reasons for and significance of discrepancies in results from tests that are considered "confirmatory" (e.g., Western blot, radioimmunoprecipitation assay, fluorescent antibody, competitive inhibition assays using purified antigens or recombinant or synthesized antigens) should also be determined.

Finally, the frequency of culture-positive infection in asymptomatic, seronegative people should be determined using antigen detection systems or DNA probes. The utility of these procedures as screening tests in blood and plasma centers should be evaluated.

Table 1

Results of Western Blot Assay and HIV Culture of Specimens From Blood Donors With One or More Reactive EIA Tests and a Random Sample of Blood Donors With Negative EIA Tests

| | Western Blot | | | | Totals | |
|---|---|---|---|---|---|---|
| | Positive | | Negative | | | |
| EIA Negative | | | | | | |
| Culture-Positive | 0 | | 0 | | 0 | ( 0.0%) |
| Culture-Negative | 0 | | 50 | | 50 | ( 8.0%) |
| Culture Not Done | 0 | | 578 | | 578 | (92.0%) |
| Total | 0 | | 628 | | 628 | (100.0%) |
| EIA Initially Reactive Only | | | | | | |
| Culture-Positive | 0 | | 0 | | 0 | ( 0.0%) |
| Culture-Negative | 0 | | 227[a] | | 227 | (74.2%) |
| Culture Not Done | 0 | | 79 | | 79 | (25.8%) |
| Total | 0 | | 306 | | 306 | (100.0%) |
| EIA Repeatedly Reactive | | | | | | |
| Culture-Positive | 23 | (59.0%)[b] | 2 | ( 1.8%)[b] | 25 | (16.7%) |
| Culture-Negative | 13 | (33.3%) | 96 | (86.5%) | 109 | (72.7%) |
| Culture Not Done/ Contaminated | 3 | ( 7.7%) | 13 | (11.7%) | 16 | (10.7%) |
| Total | 39 | (26.0%)[c] | 111 | (74.0%)[c] | 150 | (100.0%) |

[a] One specimen had an initially equivocal Western blot test (p24 band only) that was subsequently negative on repeat blinded testing.

[b] Percent of column total.

[c] Percent of row total.

Table 2

Results of Western Blot Assay and HIV Culture of Specimens From Antibody-Positive Blood Donors

| | Western Blot: Positive | | Western Blot: Negative | | Totals | |
|---|---|---|---|---|---|---|
| EIA Weakly/Moderately Reactive[c] | | | | | | |
| Culture-Positive | 1 | (100.0%)[a] | 1 | ( 1.0%)[a] | 2 | ( 1.9%) |
| Culture-Negative | 0 | ( 0.0%) | 92 | (88.5%) | 92 | ( 87.6%) |
| Culture Not Done/Contaminated | 0 | ( 0.0%) | 11 | (10.6%) | 11 | ( 10.5%) |
| Total | 1 | ( 1.0%)[b] | 104 | (99.0%)[b] | 105 | (100.0%) |
| EIA Highly Reactive Only[c] | | | | | | |
| Culture-Positive | 22 | (57.9%)[a] | 1 | (14.3%)[a] | 23 | ( 51.1%) |
| Culture-Negative | 13 | (34.2%) | 4 | (57.1%) | 17 | ( 37.8%) |
| Culture Not Done/Contaminated | 3 | ( 7.9%) | 2 | (28.6%) | 5 | ( 11.1%) |
| Total | 38 | (84.4%)[b] | 7 | (15.6%)[b] | 45 | (100.0%) |

[a] Percent of column total.

[b] Percent of row total.

[c] EIA reactivity: weakly/moderately reactive, absorbance < 6.0 times cutoff value; highly reactive, absorbance $\geq$ 6.0 times cutoff value.

# HTLV-III Infection in Asymptomatic Blood Donors

Harvey J. Alter, Juan Esteban

Although preventive measures currently in effect are most likely to greatly reduce, if not eradicate, the occurrence of transfusion-associated HTLV-III infection, there are still some unresolved issues that need to be addressed: (1) identification and evaluation of those transfusion recipients who were infected before the implementation of anti-HTLV-III testing; (2) mechanisms to detect the apparently rare seronegative HTLV-III-infectious blood donor; and (3) the evaluation and management of asymptomatic anti-HTLV-III-positive blood donors.

Since March 1985, the Department of Transfusion Medicine, Clinical Center, NIH, in collaboration with the Washington Chapter of the American Red Cross has been conducting a prospective, long-term followup of asymptomatic anti-HTLV-III-positive donors. This study is intended to assess the disease risk to these donors and to identify possible cofactors associated with development of disease as well as potential prognostic markers of clinical outcome.

In the study, blood donors found repeatedly reactive for anti-HTLV-III by EIA are divided into two groups based on the result of Western blot (WB) confirmation testing. Both WB-positive (WB+) and WB-negative (WB-) donors are subjected to a thorough evaluation of risk factors, and an assessment of their physical, immunologic, and virologic status.

As of May 1986, 100 donors have completed the initial evaluation (63 WB+ and 37 WB-) and 29 of the WB+ group have been reevaluated at 6 months. The analysis of demographic data shows that the WB+ donors tend to be younger than those in the control group (WB-), are mostly males (89 percent), and include a higher proportion of blacks. None of the donors in the control group had risk factors, whereas 88 percent of those in the WB+ group had a risk factor for HTLV-III infection, homosexual or bisexual behavior being the most common (76 percent). This high proportion of homosexuals offers additional evidence that screening measures based on self-deferral of members of high-risk groups are clearly insufficient. The reasons for this lack of self-deferral seem to be related to the relatively low promiscuity of the homosexuals in our study population and their feeling that they were not at risk for transmitting AIDS virus infection. In addition, they often felt that antibody screening would identify any infectious unit and hence that self-deferral was relatively unimportant.

None of the WB+ donors evaluated thus far has constitutional symptoms or AIDS-related diseases, although at the time of the initial visit 44 percent had various degrees of significant lymphadenopathy of unknown duration. Hence, over 50 percent would be in the CDC group II and the remainder either in group II or III depending on the persistence of their lymphadenopathy.

Laboratory evaluation showed significant differences between WB+ and WB- groups. Mean values for WBC, $T_4$ cells and $T_4/T_8$ ratios were significantly lower in the WB+ group as compared to the control group. Similarly, the mean number of suppressor T cells and mean levels of serum IgG were significantly higher in the WB+ group. Overall, 84 percent of donors in these groups had decreased $T_4$ and $T_4/T_8$ ratio and almost 70 percent had IgG levels above 1,600 ug/dl. Approximately 1/3 of WB+ donors had a diminished in vitro response to mitogens (PWM) or to soluble antigen (tetanus toxoid); since almost 10 percent of the subjects in the control group also had an abnormal mitogen response, the meaning of these tests as indicators of subclinical immunologic dysfunction must be interpreted cautiously.

The HTLV-III virus could be isolated in only 8 of 63 WB+ donors (12 percent) and in none of the ELISA+/WB- donors in the control group. This contrasts with the figures reported from other laboratories in which the virus has been recovered from over 60 percent of asymptomatic anti-HTLV-III-positive blood donors. Our low rate of virus recovery could be due to an unacceptably low sensitivity of our culture techniques or it might reflect a real difference in the proportion of viremic patients in our donor population as compared to other cohorts studied.

Reevaluation of a subgroup of 29 WB+ donors at 6 months revealed no major changes in their clinical or immunologic status with respect to the initial visit, although 5 patients in this group (17 percent) developed lymphadenopathy during this period of time. Despite some individual variations, mean values for T cell subsets were not significantly different at 6 months. The major change occurred in the lymphocyte response to mitogens which became abnormal in a substantial proportion of patients. However, this was also observed in the control group, again reflecting the relative nonspecificity of these tests.

These preliminary results suggest:

1. That individuals from high-risk groups are still donating blood, thus making imperative a reinforcement of educational programs to improve self-deferral mechanisms.

2. That current homosexual blood donors might represent a separate subset of less promiscuous individuals for which the disease incidence encountered in other cohorts of homosexuals might not be directly applicable. It is theoretically possible that less repeated exposure to HTLV-III and less exposure to other

viruses or agents which might serve as cofactors could ameliorate the progression from HTLV-III infection to fully expressed AIDS. This, however, is very speculative since there is now no evidence that disease outcome is related to lifestyle.

3. That most asymptomatic Western-blot-positive donors have some evidence of immunologic derangement, the most consistently found abnormalities being a low number of T4 cells, an inverted $T_4/T_8$ ratio, and a high serum level of IgG.

4. That long-term followup will be necessary to define prognostic markers and associated cofactors and to assess the disease risk for this cohort of HTLV-III-infected blood donors.

5. That ELISA-positive donors who are not confirmed by Western blot show no clinical, immunologic, or virologic evidence of HTLV-III infection. This provides clinical support to the premise that most, if not all, such donors present false positive ELISA reactions.

# Risks of Secondary HTLV-III Transmission

James J. Goedert

The primary mode of transmission of HTLV-III is sexual intercourse, either homosexual or heterosexual. The secondary modes are by transfusion, transplantation, or parenteral inoculation of infected blood or tissue and by in utero or perinatal exposure to infected women. Except for the possible effect of breast feeding, tertiary modes such as intimate kissing or exposure of mucous membranes or open sores to infected fluids are only rarely linked to seroconversion. In contrast, several carefully done studies have shown that HTLV-III seropositivity is closely correlated with frequent receptive anal intercourse with numerous homosexual partners in areas at high risk of AIDS.

In most instances, HTLV-III antibody seroconversion probably occurs within 6 weeks of infection, and the HTLV-III antibody assays are sensitive and specific tools for assessing transmission risks. It is possible, however, that antibody-negative HTLV-III infection may be present in a few individuals or at very low levels for periods ranging from months to years. The tools for assessing the "pre-antibody" period are currently too insensitive or nonspecific to completely quantitate either the prevalence or natural history of antibody-negative HTLV-III infection.

Even in the presence of antibody, the efficiency of HTLV-III transmission has been hard to quantify because of multiple or repeated exposures or because the number of exposed persons is unknown. In a few situations, however, transmission efficiency can be estimated. Health care workers with needle-stick injuries or similar percutaneous exposure to the blood of AIDS patients have about a 1.0 percent risk of developing HTLV-III antibodies (2 of 378 and 1 of 42 in two studies), although the risk may be somewhat higher with deep puncture injuries and gross contamination of the instrument with blood. The risk of seroconversion following transfusion with HTLV-III-infected blood (Western-blot-positive) is probably much higher (two out of two in a posttransfusion hepatitis study). In a different situation, four (50 percent) of eight women developed HTLV-III antibodies after artificial insemination from an HTLV-III seropositive donor.

The risks of HTLV-III seroconversion attributed to heterosexual transmission range from 10 percent in the wives of hemophiliacs to 60 percent or more in the spouses of drug users or Haitians with AIDS or in East African female prostitutes. This discrepancy probably has to do

with types or frequencies of sexual activities, with the presence or absence of coincident genital infections, or, less likely, with differences in the biology of virus strains or host immune responses. It is very clear, however, that bidirectional heterosexual transmission during vaginal intercourse is efficient enough to be detected in cross-sectional HTLV-III seroprevalence surveys of at-risk persons who deny anal intercourse and other risk factors.

Two studies suggest that the risk of HTLV-III seropositivity in the babies born to seropositive mothers is probably very high. In one study 11 of 12 (92 percent) children born to seropositive mothers had HTLV-III antibodies, although this study may have been biased by selecting clinically ill children for evaluation. In the second study of 20 infants born to HTLV-III-infected mothers who had already delivered one infant with AIDS, 13 (65 percent) had serologic or clinical evidence of HTLV-III infection several months after birth. Many of the mothers in that study developed AIDS, and it is possible that the risks may be lower in the offspring of healthier mothers or when HTLV-III transmission to an older sibling has not been demonstrated. This latter hypothesis is supported by one study in which none of the three children born to the women infected with HTLV-III by artificial insemination had antibodies. It has also been suggested that the risk to the offspring of seropositive mothers may be lower with Cesarean section (0 of 5 seropositive) than with vaginal delivery (3 of 7 seropositive). Broader studies that are representative of the population of seropositive pregnant women are needed to better define the rate of in utero or perinatal transmission.

With regard to tertiary modes of transmission, there is one well-documented case of HTLV-III seroconversion in a mother who provided nursing care to her infected baby that involved extensive unprotected exposure to the child's blood and body secretions and excretions during a 4- to 5-month period. In a second case, AIDS developed in a woman with no known risk factors who provided home health care to a man who died of AIDS. The care involved prolonged and frequent contact with his secretions and excretions, and she recalled having some small cuts on her hands and an exacerbation of chronic eczema. In contrast to these two cases, there is a strong case against transmission of HTLV-III within households during routing nonsexual activities. Except for vertical transmission from mother to fetus or newborn, not even one HTLV-III infection has been identified in more than 500 family members of patients with AIDS, related conditions, or asymptomatic HTLV-III infection. These data include studies in Africa and Haiti, and among drug users, hemophiliacs, and transfusion-acquired cases in the United States or Europe. These family members were typically exposed within their households for several years, and the types of non-sexual contact included sharing of household items (razors, toothbrushes, nail clippers, combs, towels, clothes, eating utensils, plates, drinking glasses), sharing of household facilities (bed, toilet, bath or shower, kitchen), washing items used by the patient (dishes, toilet, bath, clothes), and interacting with the patient (helping to bathe, helping to dress, helping to eat, hugging, kissing on the cheek, kissing on the lips). With

occupational exposure to AIDS patients, their specimens, or HTLV-III-infected laboratory materials, none of more than 1500 workers has developed HTLV-III infection except from the needle sticks mentioned above. Many of these workers have prolonged exposures to aerosolized secretions or materials, and at least 96 have documented exposure of their mucous membranes or open wounds to the blood or other body fluids of AIDS patients.

Finally, two unique case reports of possible tertiary modes of transmission deserve mention, although quantification may never be possible. In the first, HTLV-III infection acquired by a woman from a postpartum blood transfusion appears to have been transmitted to her baby by breast feeding. Prospective studies of infants who are apparently uninfected at birth but who are breast-fed by antibody-positive mothers are clearly needed, although the caution against this situation is appropriate. In spite of the fact that transmission by oral-genital contact has not been demonstrated, transmission by breast-feeding is very plausible because of the high concentration of lymphocytes in breast milk, the immaturity of the neonatal gastrointestinal tract, and the documentation of this route of transmission for HTLV-I, a less infectious human retrovirus. There is also an anecdotal case report of one HTLV-III-positive saliva culture, in the absence of HTLV-III serum antibodies, in which intimate kissing may have been the only exposure.

In summary, HTLV-III is efficiently transmitted by anal or vaginal intercourse, although the factors that increase or decrease efficiency are unknown. HTLV-III is probably transmitted efficiently by transfusion of blood, blood components, and untreated plasma products, although the relative efficiency of each of these has not been evaluated. Transmission occurs with relatively high efficiency with artificial insemination and probably with organ transplantation, and all organs and tissues must be considered potentially infectious. With small inoculations, such as occur in needle-stick injuries and probably in needle-sharing among drug users, transmission efficiency may be 1 percent or less. This is much less than occurs with hepatitis B virus and is probably attributable to the low levels of HTLV-III in the circulation. Babies exposed in utero to HTLV-III are often but not inevitably infected, and the possible benefits of Cesarean section and bottle-feeding must be evaluated. Infection with HTLV-III by other types of exposure are probably extremely rare, and appear never to occur as a consequence of routine household or occupational activities. To buttress this conclusion, continued large, careful studies are needed, as are new assays to quantify the prevalence and natural history of the preantibody period of HTLV-III infection.

# Risks of Secondary Transmission in Health Care and Laboratory Workers

David K. Henderson

In November 1982, the Centers for Disease Control (CDC) published precautions for clinical and laboratory health care workers in caring for patients with AIDS or in processing specimens from these patients.[1] These precautions emphasized the remarkable similarity between the epidemiologies of AIDS and hepatitis B. Because of these early similarities, health care workers across the country became concerned about the risk of transmission of the human T cell lymphotropic retrovirus, Type III/lymphadenopathy-associated virus (HTLV-III/LAV). Early studies, such as those by Hirsch and coworkers,[2] and Weiss et al.[3] suggested that there might be significant differences between the community and nosocomial epidemiologies of HTLV-III/LAV infection.

In September 1983, we began a prospective study of the risk of transmission of HTLV-III/LAV to health care workers and scientists involved in the care of patients with this infection, in the processing of specimens from these patients, and in the scientific evaluation of patients and the virus.

As of June 1, 1986, a total of 900 employees of the National Institutes of Health had been enrolled in the study. Two hundred and three instances of either percutaneous or mucous membrane exposures to blood or body fluids from a patient with HTLV-III/LAV infection have occurred during the evaluation, treatment, and study of more than 400 such patients since 1981.

All employees have been evaluated for serologic evidence of exposure to HTLV-III/LAV by enzyme-linked immunosorbent assay (ELISA). Serum samples found to be positive or borderline by ELISA were also evaluated by immunoblotting. Employees who sustained either percutaneous or mucous membrane exposures were also offered virus cultures and immunologic studies. Results of the study through May 1986 are summarized in table 1.

In summary, four individuals known to be in risk-group populations were found to have serologic evidence of exposure to HTLV-III/LAV. Of the more than 200 employees who sustained either percutaneous or mucous membrane exposure to blood or body fluids from a patient with HTLV-III/LAV infection, none has serologic evidence of exposure or infection with HTLV-III/LAV.

Results from this study coupled with the results from the studies of Hirsch,[2] Weiss,[3,4] McCray,[5] Gerberding,[6] and Shanson[7] provide evidence that the risk of nosocomial transmission of HTLV-III/LAV is low; and, specifically, that the rate of HTLV-III seroconversion following nosocomial percutaneous or mucous membrane exposure to blood or body fluids from a patient with HTLV-III/LAV infection is less than 4 per 1,000 exposures. Such studies also demonstrate that the precautions that were empirically recommended by the CDC appear to be adequate to minimize the risk for nosocomial transmission of HTLV-III/LAV

REFERENCES


1. Centers for Disease Control. Acquired immune deficiency syndrome (AIDS): precautions for clinical and laboratory staffs. MMWR 1982;31:577-80

2. Hirsch MS, Wormser GP, Schooley RT et al. Risk of nosocomial infection with human T-cell lymphotropic virus III (HTLV-III). N Engl J Med 1985;312:1-4

3. Weiss SH, Goedert JJ, Sarngadharan MG, Bodner AJ, Gallo RC, Blattner WA. Screening test for HTLV-III (AIDS agent) antibodies: specificity, sensitivity, and applications. JAMA 1985;253:221-5

4. Weiss SH, Saxinger WC, Rechtman D et al. HTLV-III infection among health care workers: association with needle-stick injuries. JAMA 1985;254:2089-93

5. McCray E and the Cooperative Needlestick Surveillance Group. Occupational risk of the acquired immunodeficiency syndrome among health care workers. N Engl J Med 1986;314:1127-32

6. Gerberding JL, Moss AR, Bryant CE, Levy J, Sande MA. Risk of acquired immune deficiency syndrome (AIDS) virus transmission to health care workers (HCW) [Abstract]. In: Program and Abstracts of the Twenty-Fifth Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, D.C.: American Society for Microbiology, 1985:131

7. Shanson DC, Evans R, Lai L. Incidence and risk of transmission of HTLV-III infections to staff at a London hospital 1982-85. J Hosp Infect 1985;6:(suppl C):15-22

Table 1

Results of ELISA Testing of Current Employee and Control Specimens

| Study Groups | Data Sera Collected | Seropositivity By ELISA # Subjects +/ # Subjects Tested | # Specimens Tested |
|---|---|---|---|
| CC Employees Total | 1981-1986 | 6/890 | 2763 |
| NS Exposures | | 0/108 | 0/181 |
| Mucous Membrane Exposures | | 0/134 | 0/267 |
| Positive Controls (AIDS Patients) | 1981-1986 | 50/50 | 103 |
| Negative Controls (Healthy Hetero-sexuals) | 1981-1986 | 0/69 | 94 |

# The Medical Consequences of HTLV-III Infection

James J. Goedert

HTLV-III infection is associated with various manifestations that range from asymptomatic laboratory abnormalities, to mild illnesses, to fully lethal conditions such as AIDS. An acute syndrome associated with seroconversion has been noted in some individuals but is probably relatively uncommon. This syndrome resembles acute mononucleosis but may also include skin rash and acute neurologic complications such as encephalitis, aseptic meningitis, and peripheral neuritis. There may be transient lymphopenia, mild thrombocytopenia, relative monocytosis, and the presence of atypical mononuclear cells in the circulation. Following both symptomatic and asymptomatic seroconversions there is a decrease in the ratio of T4:T8 (helper:suppressor) lymphocytes due exclusively to a rise in the total number of T8 cells. In both homosexual men and hemophiliacs, T8 cells remain high for at least 2 years after seroconversion. Meanwhile there is a slow, steady decrease in the number of T4 cells that is evident 2 or more years after seroconversion. The early increase in T8 cells and later decrease in T4 cells are so universal that by 3 to 4 years after seroconversion approximately 90 percent of homosexual men and hemophiliacs have clearly low T4:T8 ratios (< 1.0). Lymphadenopathy can occur both as a short-term and a long-term manifestation, having been noted in 25 to 29 percent of seropositive homosexual men and, with lengthy (> 3 years) HTLV-III infections, in up to 70 percent of hemophiliacs. Three relatively mild conditions--diarrhea, oral candidiasis, and herpes zoster--are clearly associated with long-term seropositivity; and one or more of these may occur in fully 50 percent of homosexual men who are seropositive for more than 29 months.

Most estimates of the cumulative risk of developing a lethal condition, such as AIDS, following HTLV-III infection have one or more of the following weaknesses: very poor estimates of the number of persons at risk (infected), assumptions that persons lost to followup are alive and well, or short duration of followup. Of 176 HTLV-III seropositive individuals in five cohorts followed for 3+ years, 176 have had crude AIDS rates ranging from 31.8 percent (14 of 44) among homosexual men in Manhattan to 7.7 percent (2 of 26) among homosexual men in Denmark. Crude AIDS rates have been intermediate among homosexual men in Washington, D.C. (16.7 percent, 7 of 42), hemophiliacs in Hershey, Pennsylvania, (15 percent, 6 of 40), drug abusers in Queens, New York (8.3 percent, 2 of 24), and other reported cohorts. Actuarial estimates of AIDS risk with 3 years of followup tend to be slightly higher because "lost" persons are not counted beyond

the time they are last known to be AIDS-free. By Kaplan-Meier technique, 276 seropositive individuals in the five cohorts described above have had 3-year AIDS incidence rates of 34.2 percent in Manhattan homosexuals, 25 percent in Queens drug users, 17.2 percent in Washington homosexuals, 12.8 percent in Hershey hemophiliacs, and 8 percent in Denmark homosexuals (figure 1). The gradient in these cumulative incidence rates is likely to be related to two factors--the duration of HTLV-III infection (longest in Manhattan, shortest in Denmark, intermediate in the others) and more frequent Kaposi's sarcoma in Manhattan (seven cases) than in the other cohorts (two cases). Data from the estimated date of HTLV-III seroconversion to AIDS in a defined population are beginning to accumulate. Incident HTLV-III seroconversion has been demonstrated in 117 subjects in the five cohorts described above. In 51 hemophiliacs, with a mean and median followup of 53 months, 5 cases of AIDS occurred 28 to 62 months after the estimated dates of seroconversion, for a cumulative AIDS incidence of 14.9 percent ($\pm$ 6.8 percent) (figure 2). However, the standard error of this incidence is very large (> 10 percent) beyond 6 years after seroconversion (figure 2). Among the 66 homosexual men and drug users in the other four cohorts with incident HTLV-III seroconversions, none has developed AIDS; but the mean followup period has been only 17 months (maximum 32 months) after the estimated dates of seroconversion.

Potential markers or cofactors that might modify the risk of AIDS, Kaposi's sarcoma, or pneumocystis pneumonia have been evaluated in the 86 initially seropositive homosexual men in the Manhattan and Washington cohorts. Risk of AIDS was strongly related to the T4 (helper) cell count at initial enrollment, being 12.87 times more likely to develop with 0 to 299 T4 cells/mm3 than in seropositive men with > 549 T4 cells/mm3. Intermediate T4 counts had intermediate relative hazards ($p$ for trend $< 0.001$). There was no trend between the T8 (suppressor/cytotoxic) count and subsequent AIDS, but AIDS risk was extremely high in the two men who reported fever and the four men who reported unintentional weight loss ($p < 0.001$ for both). AIDS with Kaposi's sarcoma tended to be more common in Manhattan ($p = 0.08$) than in Washington ($p = 0.03$) (seven cases compared to one). AIDS also appeared to be more common among men with many homosexual partners ($p = 0.08$), suggesting that repeated HTLV-III infection or repeated antigenic stimulation with foreign semen might be involved. However, it should be noted that increased risks associated with Manhattan and with exposure to many homosexual partners both could indicate earlier HTLV-III infection, and the risk may be higher simply on this basis. The use of nitrite inhalants has been suggested as a possible cofactor for Kaposi's sarcoma, but this association was not noted in the Manhattan and Washington cohorts. Several of 40 potential cofactors defined ex post facto, but no one factor, suggested that some aspects of homosexual lifestyle may be related to Kaposi's sarcoma.

In summary, HTLV-III infection causes a wide spectrum of conditions, and most infected individuals will have one or more manifestations. The cumulative risk of AIDS is approximately 15 percent among hemophiliacs after 5 to 6 years of seropositivity and can be more than 30 percent in

some cohorts. The likelihood of AIDS during the subsequent 2- to 3-year period can be clearly predicted by the T4 count, and cofactors do not appear to have a strong modifying effect on AIDS incidence. Every effort must be made to prevent HTLV-III transmission and to intervene at an early stage of infection with antiretroviral and immunomodulating drugs.

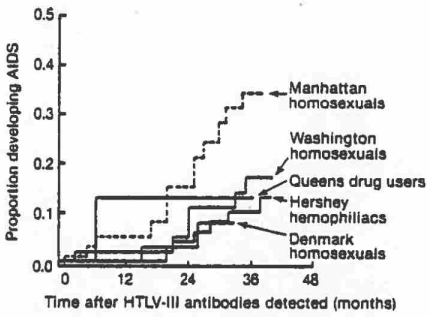



Fig. 1. Actuarial incidence of AIDS among all 276 HTLV-III seropositive study subjects in five different cohorts. Data are computed by the Kaplan-Meier survival technique, with the first seropositive specimen (or September 1982 for hemophiliacs with positive historic specimens, see text) being used as time 0. The cohort of Manhattan homosexual men has a significantly higher incidence of AIDS ( $^2$ = 10.48, $P$ = 0.001) than the other cohorts combined. Cumulative AIDS incidence in the Queens drug users was 25 percent with an additional case reported at followup.

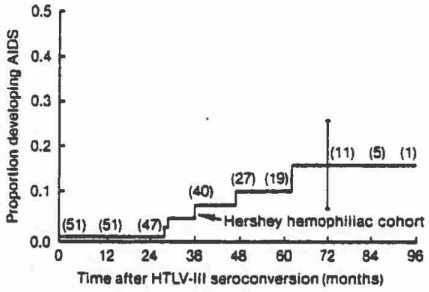



Fig. 2. Actuarial incidence of AIDS among 51 hemophiliacs developing antibodies to HTLV-III. Data are computed by the Kaplan-Meier survival technique, with each individual patient's seroconversion date (the midpoint in time between the last seronegative and first seropositive specimens) being used as time 0 [for actual calendar dates, see (7)]. Numbers in parentheses indicate the number of persons still being followed at each 12-month interval after seroconversion. Vertical bars at 72 months indicate ± 1 standard error.

# Outcome of HTLV-III/LAV Infection in a Cohort of Gay Men

Harold W. Jaffe, Paul M. O'Malley, William W. Darrow, George Rutherford, Charles A. Schable, Paul M. Feorino, Robert H. Byers, and Dean F. Echenberg

Between 1978 and 1980, a cohort of 6,717 homosexual and bisexual (gay) men treated for sexually transmitted diseases at San Francisco City Clinic were enrolled in a series of studies of hepatitis B virus infections.[1,2] At the time of enrollment, basic demographic data and a blood specimen were obtained from each participant; sera were frozen and stored.

In 1984, the San Francisco Department of Public Health and the Centers for Disease Control began a study of AIDS in this cohort of gay men.[3] A representative sample of cohort members, as well as all other cohort members with AIDS not included in the sample, were asked to participate. Participants were interviewed, examined for signs of AIDS or related conditions, and blood specimens were obtained from them. Serum samples from the participant's initial blood specimen, collected between 1978 and 1980, and followup specimens collected between 1984 and 1985 were tested for antibodies to HTLV-III/LAV by an enzyme immunoassay (EIA). Lymphocytes, obtained from selected participants in 1984, were cultured to isolate HTLV-III/LAV.[4]

As of mid-April 1986, 380 (6 percent) of the men in the cohort were reported to have AIDS. Although the first AIDS case in the cohort was not diagnosed until 1981, members of the cohort were, in retrospect, infected with HTLV-III/LAV as early as 1978 and the prevalence of infection has increased rapidly since then (table 1). Of the estimated 4,700 cohort members who have been infected, approximately 8 percent now have AIDS.

Among a group of 44 randomly selected men who were seropositive on entry to the cohort or seroconverted within 12 months of a negative antibody test, 6 (14 percent) developed AIDS and 18 (41 percent) developed AIDS-related conditions (ARC) from 22 to 84 months (median = 65 months) after their estimated date of seroconversion. Estimated incubation periods for AIDS ranged from 40 to 72 months.

Among a group of 46 randomly selected men who were seropositive and asymptomatic in 1984, 9 of 29 (31 percent) with HTLV-III/LAV viremia in 1984 developed AIDS or ARC over a median followup of 16 months as compared with 1 of 18 (6 percent) whose lymphocytes were culture-negative ($p < .05$). Once these culture results were entered into a logistic regression model,

immunodeficiency, as measured by a low $T_4/T_8$ ratio, was not associated with the development of AIDS or ARC.

Preliminary analyses have been done to examine risk factors for illness in persons with HTLV-III/LAV infection and for determinants of specific disease outcomes in those who develop AIDS. Thus far, the major determinant of illness in those infected appears to be duration of infection. Among persons with AIDS, no behavioral risk factors have been shown to distinguish those with Kaposi's sarcoma from those with opportunistic infections.

Conclusions from the San Francisco cohort study thus far include the following:

1. The epidemic of AIDS was preceded by an unrecognized epidemic of HTLV-III/LAV infections.

2. Gay men have a low risk for AIDS within the first few years following HTLV-III/LAV infection. This risk subsequently increases and persists for at least 6 years.

3. HTLV-III/LAV viremia in asymptomatically infected gay men is associated with an increased risk of development of illness in these men.

4. Behavioral risk factors for development of illness in infected gay men have not yet been identified.

REFERENCES


1. Schreeder MT, Thompson SE, Hadler SC et al. Hepatitis B in homosexual men: prevalence of infection and factors related to transmission. J Infect Dis 1982;146:7-15

2. Francis DP, Hadler SC, Thompson SE et al. The prevention of hepatitis B with vaccine: report of the Centers for Disease Control multicenter efficacy trial among homosexual men. Ann Intern Med 1982; 97:362-9

3. Jaffe HW, Darrow WW, Echenberg DF et al. The acquired immunodeficiency syndrome in a cohort of homosexual men. A six-year followup study. Ann Intern Med 1985;103:210-4

4. Jaffe HW, Feorino PM, Darrow WW et al. Persistent infection with human T-lymphotropic virus type III/lymphadenopathy-associated virus in apparently healthy homosexual men. Ann Intern Med 1985;104:627-8

Table 1

Prevalence of HTLV-III/LAV Antibody in Randomly Selected Gay Men, San Francisco Cohort Study, 1978-85

| Year of Specimen Collection | Proportion of Specimens with HTLV-III/LAV Antibody |
|---|---|
| 1978 | 5% |
| 1979 | 13% |
| 1980 | 24% |
| 1984 | 67% |
| 1985 | 70% (approx.) |

# HTLV-III Antibody Testing: Rights of the Individual

Christopher J. Collins

BACKGROUND

The HTLV-III antibody test was originally designed to protect the Nation's blood supply and to screen those units of blood that tested positive. This test was made available last summer and has been implemented for the past year.

At the time that the test was initially licensed, many organizations from around the country, including Lambda Legal Defense and Education Fund and the National Gay and Lesbian Task Force, approached the Public Health Service and the Food and Drug Administration warning of potential misuses of the test. Accordingly, labeling of the test was restricted so it would not be used as a diagnostic test for AIDS for the purposes of screening certain at-risk groups. However, since then, reports of widespread misuse of the test have been received from around the country. Insurance companies have been attempting to obtain use of the test and its results for purposes of disqualifying applicants from purchasing health or life insurance. Employers are seeking to use the test for screening applicants and terminating employees who test positive for HTLV-III antibody. In short, every conceivable use for the test has been attempted and suggested. William Buckley, in a recent column in the New York Times, has gone so far to suggest that those who are positive for the HTLV-III antibody test, which he referred to as the "AIDS test," should be tattooed. More recently, state health departments in some jurisdictions have required the reporting of test results. These departments have suggested or implemented mechanisms for contact-tracing and followup of infected sexual partners and partners of needle-sharing individuals who demonstrate positive test results. What impact, if any, has this had on public health?

While it is difficult to document, it is my belief that the impact on public health has been negative. The test has taken on a life of its own and those who are at risk for developing AIDS are fearful that the results of the test will be misused. Consequently, those who are most likely to seek testing are refraining from doing so in the absence of a clear legislative mandate prohibiting the misuse of test results.

USE OF THE TEST

How does the test affect the rights of individuals and are they consistent with the rights of society? Civil liberties and good public health are not mutually exclusive. Sound public health policy regarding the use of the test must address the protection of those who test positive. Because a positive test result is perceived as the equivalent of the disease AIDS, both AIDS and the test for the HTLV-III antibody have been stigmatized. Because of the fear, hysteria, and panic that surround the disease, AIDS cannot be treated like any other sexually transmitted disease. Therefore, it is my belief that the following four conditions must be present when an individual is tested for HTLV-III antibody:

1. The person to be tested must not be identified.

2. The test must be voluntary.

3. The informed consent of the individual to be tested must be obtained.

4. There must be counseling and education both before and after the test is performed.

Recently, several state legislatures and health departments have required the reporting of HTLV-III antibody test results. Their justification for doing so is:

- To alert responsible health agencies to the presence of persons likely to be infected with the dangerous virus.

- To allow responsible health agencies to ensure that such persons are properly counseled as to the significance of their laboratory tests and as to what they need to do to prevent transmission of the virus.

- To allow responsible health agencies to monitor the occurrence and spread of infection with this virus in the population of a particular state.

- To allow responsible health agencies to identify and contact persons with likely or proven HTLV-III infection when specific antiviral treatment becomes available.

It is submitted that the collection of names of individuals who test positive is not necessary under any of the four criteria listed above. Inasmuch as there is no cure for AIDS, the question must be asked why is collecting names necessary. The skepticism with which high-risk groups perceive the test emanates from what use will be made of the identity of

someone who is infected. For example, recent attempts have been made in Colorado to permit the local health department to detain, isolate, and quarantine those individuals who are merely suspected of being HTLV-III antibody-positive without appropriate due process safeguards. This only serves to heighten the mistrust of the authorities by high-risk groups. The second justification is to enable health agencies to counsel those who test positive; however, effective counseling can be done without revealing the name of the person being counseled. Moreover, counseling and education should be done before the test is performed because once an individual receives news of a positive test result the counseling and education will have little impact. That individual will be so overwhelmed by the news of his or her test result that immediate posttest education and counseling will be futile.

The third reason given for reporting of positive test results is to monitor the occurrence and spread of infection. Incidence of disease can be measured by numbers and the identity of individuals is irrelevant. Overlapping of duplicate test results will occur; however, whether or not names are obtained, that overlapping will occur because of people moving from one jurisdiction to another. The fourth and last reason given to identify individuals is to permit health authorities to notify individuals should a treatment or cure develop. Obviously, this is the least likely scenario of events.

The rights of the individual to maintain his or her privacy and to have control of the information obtained as a result of a positive test are paramount. They are consistent with good, sound public health. Confidentiality standards are helpful but not convincing. Without a specific legislative mandate to prohibit the misuse of the information gathered by a positive test result, the only effective means for testing high-risk groups is to do so anonymously.

Under no situation should a policy be set requiring compulsory testing. All testing must be voluntary and a pursuant to true informed consent. The individual should be warned of the risks and implications of both a positive and negative test result. Informed consent should be obtained specifically for the HTLV-III antibody test and not as part of a generalized overall medical informed consent.

## PUBLIC HEALTH BY REFERENDUM

Recent attempts in California to set public health by referendum are not only dangerous, but misguided. The Federal government has an obligation to speak out against such attempts and to develop an overall strategy prohibiting the misuse of test results. Failure to do so will result in additional local initiatives, thereby complicating the public health process. Each state has a different approach to the AIDS problem

and to the development and implementation of the HTLV-III antibody test. This has led to confusion with various reporting requirements, alternative sites, and legislation regarding the test. New, creative public health initiatives must be implemented to protect the rights of the individual who is tested. Anonymous testing is the only appropriate procedure. Where local jurisdictions attempt to set public health policy by referendum to require not only the reporting of HTLV-III antibody results, but the quarantining of people with AIDS, there is an obvious disincentive for cooperation by the affected risk groups. It should be noted that the number of risk groups has grown since 1981 and with the inclusion of sexual partners of any people in a risk group, the list may continue to grow. The potential for harm to these individuals is significant and their willingness to cooperate will no doubt be affected by the restrictive legislation and curtailment of their civil liberties and rights to a job, housing, insurance, etc. In short, the list of individuals who are potentially affected by restrictive measures will continue to grow.

## HTLV-III ANTIBODY TEST: EMPLOYMENT AND INSURANCE

### Employment

It is my opinion that HTLV-III infection does constitute a disability within the meaning of section 504 of the Rehabilitation Act of 1973. In addition, many state laws have legislation prohibiting discrimination against those who are disabled. These statutes may cover AIDS, AIDS-Related Complex and HTLV-III infections. Although the U.S. Supreme Court is presently considering the applicability of section 504 of the Rehabilitation Act to contagious diseases, it is not yet clear how that case will be resolved and whether and to what extent it will be applicable to AIDS. However, at the present time, employers who test for HTLV-III antibody and make employment decisions regarding a person on the basis of HTLV-III antibody status are likely to be faced with a lawsuit charging, inter alia, violation of section 504 of the act (assuming that employers are a Federal contractor or Federal agency) and/or one or more local state statutes. Disability laws have been effectively used to prohibit discrimination against those people who have a handicap, but who are otherwise qualified to perform their job. A recent decision in the State of Florida, Shuttleworth v. Broward County Office of Management and Budget Policy, Florida Commission on Human Relations, FCHR No. 85-0624, (12/17/85) has found that Broward County Office of Management and Budget Policy unfairly discriminated against an individual who had AIDS in violation of the Florida Human Rights statute. A New York judge has found that an individual school child with AIDS should be permitted to attend school and that the failure to admit the pupil would be a violation of section 504 of the Rehabilitation Act of 1973. See, District 27 Community School Board, et al. versus Board of Education of the City of New York, et al. Index No. 14940/85, Hyman, J. (Queens Co. Sup. Ct. 2/11/85).

The Centers for Disease Control (CDC) has issued guidelines with respect to AIDS in the workplace which essentially found that people with AIDS but without an ongoing active opportunistic infection should be qualified to participate in nearly every type of employment. (MMWR November 15, 1985, Vol. 34/No. 45.) Accordingly, the use of the HTLV-III antibody test by employers should be prohibited in most states. In addition, employers who believe that they can use the test to exclude employees on the theory that the cost of health and disability insurance will increase may not do so because that may be in violation of the Employee Retirement Income Security Act of 1974 (ERISA), 29 U.S.C. §1001 et seq.

Insurance

Insurance provides yet another area of concern. Insurance companies have sought the use of the test to deny or terminate coverage for both health and life insurance of an individual who tests positive. The position of many of the gay rights organizations has been that there is no predictive value to the HTLV-III antibody test. Nevertheless, the overall position is that we as a country have made a determination to leave health insurance to the private sector. Consequently, the Government has an inherent right to control and restrict the availability of this test to insurance companies. Otherwise, the Government will be faced with the overriding burden of paying for medical costs associated with the development of AIDS. In addition, the Government will be burdened with paying the health care costs for other illnesses not associated with AIDS, but which occur in an individual who is HTLV-III antibody-positive, but not longer has insurance. The larger question is if insurance companies are permitted to continue to exclude certain illnesses, soon there will no longer be anyone left to insure.

Several states, most notably California and the District of Columbia, have enacted legislation that specifically prohibits the use of the HTLV-III antibody test by insurance companies. Obviously such legislation demonstrates a concern by the government for protecting atrisk groups. The resultant cooperation of the at-risk groups with those jurisdictions has been significant and no doubt will continue.

CONCLUSION

The rights of the individual are directly affected by the HTLV-III antibody test. An individual's right to be free from harassment and misuse of the test must be secure. Othewise, those most affected by the disease will fail to cooperate and the disease will be driven underground. Public health policy set by referendum is guided by hysteria, prejudice, and fear and not by an intelligent and rational understanding of the complex elements surrounding the disease. It will lead inevitably to a proliferation of the very disease it seeks to eradicate.

# HTLV-III Antibody Testing: Rights of the Public

Karen Shoos Lipton

The most significant "public right" at issue in the performance of HTLV-III antibody testing is protection of the public health. Blood collecting organizations assist in protecting the public health by ensuring an adequate and safe supply of blood and blood components to all who require them. Maintaining the confidentiality of donor information helps achieve these twin goals by ensuring that donors will feel completely free to be honest about their health histories and by ensuring that donors will not be deterred from donating because of the possibility that their health histories will be disclosed.

Although blood collecting organizations require confidentiality to fulfill their public health obligations, a donor's expectation of privacy can be honored only when that expectation does not interfere with the need to provide a safe and adequate supply of blood or with the blood collecting organization's legal obligations to report information to the public health department. From a blood collecting organization perspective, the tension between the need to maintain the safety of the blood supply and the need to preserve the confidentiality of donor information surfaces most often in the management of information about the seropositive donor, specifically in the maintenance of donor deferral registries (DDR's) and the reportability of test results to public health agencies.

The HTLV-III antibody test was developed specifically for use by blood collecting organizations to reduce the risk of transmission of HTLV-III/LAV through blood and blood products. Package inserts for these tests confirm that it is inappropriate to use this test as a screen for AIDS or as a screen for members of groups at increased risk for AIDS in the general population. To date, testing has been governmentally mandated only in the blood banking context. (General Biological Products Standards, Additional Standards for Human Blood and Blood Products, 51 Fed. Reg. 6362, February 21, 1986).

Experience with the HTLV-III antibody test, however, has demonstrated the significance of repeatedly reactive enzyme-linked immunosorbent assays (ELISA's) that are confirmed by more specific tests (e.g., Western blot, immunofluorescent assay). Individuals who have both repeatedly reactive tests and a positive confirmatory test should be considered infectious for HTLV-III/LAV.

DDR's, and the ability of blood collecting organizations to maintain these registries are, thus, an essential layer in the multiple layers of donor screening built into the donation process. The rights of blood collecting organizations to maintain these registries is well-founded in legal and ethical principles.

The Supreme Court of the United States has determined that there is no Federal constitutional right to privacy of information, at least in situations where confidentiality protocols are observed. (Whalen versus Roe, 429 U.S. 589, 1977). Federal and state courts, however, continue to suggest that the public disclosure of confidential information at least raises constitutional issues. See, for example, United States versus Westinghouse Electric Corp., 638 F. 2d 570 (3d Cir. 1980).

Moreover, legal concerns that do not rise to the level of constitutional guarantees continue to create liability concerns over the disclosure of confidential information for blood collecting organizations. The right to privacy, however, is not absolute. To be actionable, a disclosure of private facts about an individual must be public and must be highly objectionable to a person of reasonable sensitivities. There is a privilege for disclosures of information that are in the public interest or with respect to which both the discloser and the person to whom the information is disclosed, have a legitimate interest.

Under these analyses, maintenance of a confidential DDR, which is essential to the safety of the blood supply, is a permissible use of confidential donor information. These same principles justify the disclosure of donor deferral information to other blood collecting organizations. American Red Cross regional blood services do not, as a matter of course, share their registries with other blood collecting organizations. They do cooperate with other blood collecting organizations by cross-checking individual identifying information through American Red Cross DDR's.

Disclosures of the name and test result information to state and local public health agencies have raised concerns among individuals concerned with the confidentiality of donor information. The implementation of HTLV-III antibody screening and, more recently, the notification of recipients of previous donations from donors who subsequently developed AIDS or who now have a verified positive test for HTLV-III antibody have severely strained blood collecting organizations' resources. Although blood collecting organizations, in an effort to prevent disclosure of confidential information, have been and will continue to make significant efforts to contact infectious donors and potentially infectious recipients, this notification cannot always be performed without the assistance and resources of public health authorities. The public health significance of this information, however, justifies the disclosure of this information to public health agencies. See, for example, Whalen versus Roe, 429 U.S. 589 (1977) ("Disclosures of private medical information to. . . public health agencies are often an essential of modern medical practice even when the disclosure may reflect unfavorably on the character of the patient.")

Each of these uses and disclosures should be accomplished with notice to the donor whenever possible. Presently, prospective blood donors are notified that their names may be reported to state and local public health agencies and that identifying information about their status may be placed into the DDR. These steps fairly balance the individual's right to privacy and the rights of the public to a safe and adequate supply of blood.

# The Blood Donation Contract: Predonation Screening and Notification Policies

Johanna Pindyck

The purpose of this presentation is to examine the responsibilities of the blood donor when giving blood and of the blood collection agency when collecting it. It will focus on those responsibilities which relate to prevention of HTLV-III infection transmission by blood transfusion, including predonation education and screening, consent for anti-HTLV-III testing, and notification of seropositive donors.

Because certain infectious diseases are transmissible by transfusion, including HTLV-III infection, blood collection agencies impose constraints on the public's freedom to give blood. Most of these restrictions are mandated in Federal, state, and local regulations. Persons wishing to donate blood are expected to abide by these restrictions and withhold donation if they fall outside accepted guidelines. Effective communication to the donor is an essential step in achieving compliance with established guidelines. In addition, the stigma attached to membership in many of the groups at risk of AIDS made it apparent that compliance with donor exclusion guidelines to prevent AIDS transmission would be difficult unless socially acceptable means to facilitate compliance were provided. Methods currently in use to accomplish this goal will be discussed.

The advent of anti-HTLV-III testing brought with it new challenges to blood donors and blood collection agencies. By agreeing to donate blood, donors give up the right not to be tested for antibody to HTLV-III. The blood collection agencies assumed the responsibility of telling people, before donation, that the blood would be tested and what this implies. For example, positive test results would be reported back to the donor and reporting to public health agencies might be required in the future. The following issues presented themselves with respect to handling test results: seropositive test results are not yet reportable to public health agencies in most states; they must be protected to preserve confidentiality; donors have a right to know of positive test results; the testing agency has a duty to tell them, for public health reasons. The policies which have been adopted to deal with these issues will be reviewed.

# Issues Concerning Notification of Blood Donors Found HTLV-III Antibody-Positive

Jay E. Menitove

Most blood centers notify only those donors testing positive for antibody to HTLV-III by both EIA and Western blot procedures. This approach was initially adopted because of the theoretically calculated greater-than-60-percent chance of mislabeling as positive an individual not in a risk group for AIDS on the basis of a repeatedly reactive EIA test result alone. The accumulating evidence indicates that the observed EIA "false positive" rate for these individuals may be as high as 95 percent when the Western blot result is used as a confirmatory test. Nevertheless, FDA guidelines and proposed rules require that previous, current, and future donations from EIA repeatedly reactive donors cannot be used for transfusion. These donors generally are not notified that their donation was not used and that future donations will also not be used.

## NOTIFICATION OF EIA-POSITIVE, WESTERN-BLOT-POSITIVE DONORS

Notification is accomplished by several methods depending upon logistic and staffing considerations. Personal notification allows a direct assessment of counseling needs. However, appropriate information can be transmitted by telephone or letter. Regardless of technique used, written information should be given to the donor that explains the test procedures used, the groups at risk for AIDS, the clinical spectrum resulting from infection with HTLV-III (asymptomatic carrier state to full-blown AIDS), methods for preventing further transmission, confidentiality considerations, lists of physicians knowledgeable and interested in seeing patients testing antibody-positive, lists of referral agencies that provide further counseling, and lists of sites where close contacts can be tested.

Donors testing EIA- and Western-blot-positive usually give a history of homosexual activity, although they perceive that these contacts have not placed them at risk for AIDS. Their reaction following notification varies from devastation to mild, acute anxiety. Invariably, these individuals want to know what a positive test result means and an estimate of their prognosis. Since a complete medical history, physical exam, and laboratory evaluation is not performed when notification is made, this question cannot be answered with certainty and the donor is advised to

seek followup medical care. Donors are usually informed, however, that only a minority of asymptomatic antibody-positive individuals develop AIDS.

Notification of individuals such as female heterosexual contacts of IV drug addicts, pose other problems. These individuals may understand how they became infected but suffer similar problems as those with known high-risk exposure. The problem is further exacerbated if there is a young child who may have been infected in utero.

## NOTIFICATION OF EIA-POSITIVE, WESTERN-NEGATIVE DONORS

Units collected from donors testing EIA-positive, Western-blot-negative are precluded from use. At issue is whether to inform these donors that their HTLV-III antibody test was reactive but represents a "false positive" result. Furthermore, the certainty that the reaction is "false" has been questioned by some since the Western blot test is reportedly more specific but less sensitive than the EIA.

On the basis of limited experience notifying donors that their test result gives a "false positive" reaction, it appears that most donors accept the explanation that a screening test was positive but a more specific second test was negative. These donors understand that their blood donation was not used and that, for the present time, future donations will also not be used for transfusion. A few donors complain they are being given a "mixed" message and question the certainty that the reaction was a "false positive." These donors appear to have experienced events that could have exposed them to the HTLV-III virus. Lengthy discussions are necessary to explain the routes of HTLV-III transmission and the type of information provided by ELISA and Western blot tests.

## NOTIFICATION OF RECIPIENTS OF BLOOD FROM DONORS FOUND TO BE WESTERN-BLOT-POSITIVE FOR HTLV-III ANTIBODY

Notification that an individual was transfused with a unit of blood from a donor subsequently found HTLV-III positive is appropriate on the basis of public health reasons. In addition, it will preclude these individuals from future blood donation.

## CURRENTLY UNRESOLVED ISSUES RELATED TO DONOR NOTIFICATION

- The prognosis of HTLV-III antibody-positive donors.
- Whether EIA-positive and confirmatory-negative (i.e., Western-blot-negative) donors are infectious for the HTLV-III virus.

- Improved methods for discouraging individuals at risk for HTLV-III infection from donating blood.

- An evaluation of the impact of notification on the lifestyle, social adjustment, etc., of donors found antibody-positive and recipients notified that they received blood from a donor later found positive for HTLV-III antibody.

- The effectiveness of notification by blood center personnel versus public health officials.

- Removing screening-test-positive, confirmatory-test-negative donors from deferral lists.

REFERENCES


1. Update: Acquired immune deficiency syndrome. United States:MMWR 1985;34:245-8

2. Hunter JB, Menitove JE. HLA antibodies detected by ELISA HTLV-III antibody kits. Lancet 1985;2:387

3. Schorr JB, Berkowitz A, Cumming PD, Katz AJ, Sandler SG. Prevalence of HTLV-III antibody in American blood donors. N Engl J Med 1985; 313:384-5

4. Peterman TA, Jaffe HW, Feorino PM, Getchell JP, Warfield DT, Haverkos HW, Stoneburner RL, Curran JW. Transfusion-associated acquired immunodeficiency syndrome in the United States. JAMA 1985;254:2913-7

5. Holland PV, Richards CA, Teghtmeyer JR, Douville CM. Anti-HTLV-III testing of blood donors: reproducibility and confirmability of commercial test kits. Transfusion 1985;25:395-7

6. Sayers MH, Beatty PG, Hansen JA. HLA antibodies as a cause of false-positive reactions in screening enzyme immunoassays for antibodies to human T-lymphotrophic virus type III. Transfusion 1986;26:113-5

7. Kuritsky JN, Rastogi SC, Faich GA, Schorr JB, Menitove JE, Reilly RW, Bove JR. Results of nationwide screening of blood and plasma for antibodies to human T-cell lymphotrophic III virus, type III. Transfusion 1986;26:205-7

8. Fang CT, Darr F, Kleinman S, Wehling RH, Dodd RY. Relative specificity of enzyme-linked immunosorbent assays for antibodies to human T-cell lymphotrophic virus, type III, and their relationship to Western blotting. Transfusion 1986;36:208-9

# Effects of Notification of HTLV-III Antibody-Positive Donors: The California Experience

Steven Kleinman, Lynda Fitzpatrick, Sally Sohner, and Diana Wilke

The notification policy of HTLV-III antibody-positive donors at the Los Angeles-Orange Counties Red Cross involves four major principles: (1) accurate transfer of information about test results and significance, (2) maintenance of confidentiality, (3) attempts to minimize donor anxiety, and (4) documentation for the record. Our notification method is the use of a certified, restricted-delivery letter which specifically informs a donor of his or her confirmed positive HTLV-III antibody test results. This mailing also includes the public health service recommendations for HTLV-III antibody-positive individuals, a release of medical information form allowing us to provide test results to private physicians, and a statement in the body of the letter urging individuals who desire more information about the meaning of their test results to call one of our trained team of nurse-counselors. We have recently begun a long-term followup study of such donors and are now including an invitation for participation in the research study in this initial mailing. As of April 15, 1985, we have seen 35 antibody-positive donors in person and have talked to an additional 31 by telephone. The primary questions of persons calling by telephone were: What does this mean? What should I do now? During the course of the interviews we were able to elicit more specific concerns from the donors; the two major questions were: Will I become ill? Can I transmit this infection to others, including my sexual partner, my children, and offspring of future pregnancies? Other concerns expressed by a smaller number of persons centered on the accuracy of the test results, the confidentiality of the information, and the ability to qualify for medical insurance.

We used a modification of the Overall and Gorham "Brief Psychiatric Rating Scale" to rate the subject on dimensions such as degree of anger or anxiety. We used a seven-point rating scale where 1 = not present and 7 = extremely severe.

Our ratings indicated that most callers had mild to moderate anxiety centered around concern over their uncertain future; only an occasional individual manifested extreme feelings of guilt, hostility, or anxiety. These telephone impressions have been confirmed and expanded during our interviews. The research setting has allowed us to form ongoing relationships with antibody-positive donors and to further elucidate their degree of concern.

Despite our advice to seek medical followup, we have learned that the majority of asymptomatic HTLV-III antibody-positive donors do not follow this advice. The primary deterrent to seeking medical care seems to be concern about the confidentiality of test results.

It appears that the donors who have the most difficulty adjusting to the news of their HTLV-III seropositivity are those who do not perceive themselves to have risk factors for HTLV-III infection. These include women, bisexual men, and monogamous or nearly monogamous gay men. In addition, bisexual men have voiced concerns over informing their female sexual partners or spouses of their HTLV-III seropositivity. Despite such problems, we have not encountered any situations in which we have assessed HTLV-III individuals as being psychotic or suicidal.

There are several questions of both a research and operational nature that remain unanswered. Although several methods of notifying donors are in use by blood centers, there are no controlled studies to evaluate if one method is superior either in successfully conveying the essential information to the donor or in minimizing the donor's anxiety or use of denial. Second, studies are needed to assess HTLV-III seropositive donors over a long-term followup period to measure the true effects of notification on both the psychological adaptation and behavioral changes of these individuals. Such studies may help to decide whether blood centers have the necessary resources to interact with these donors in a continuing long-term relationship.

# Psychosocial Issues: Synthesis of Clinical Information

Jill G. Joseph

This paper discusses the impact of HTLV-III antibody testing of blood donors from the perspective of social epidemiology. Particular attention will therefore be paid to transmission-relevant behaviors, although broader and interrelated psychosocial effects will also be considered. In order to do so, the HTLV-III antibody testing experience of blood donors and gay men will be compared in terms of a model used to predict health behaviors. This model, based on a recent review of more than a dozen separate approaches to the topic, is based on six core conceptual elements: (1) knowledge, (2) perceptions of vulnerability, (3) beliefs about the efficacy of change, (4) accessibility of barriers to relevant systems, or both, (5) social network characteristics, and (6) demographic characteristics. Each is considered below.

Previous research, for example, on changes in cardiovascular risk factors, has indicated the considerable importance of knowledge as a prerequisite for behavioral changes. Similarly, knowledge of risk reduction guidelines appears to be essential to HTLV-III antibody-positive individuals. Indeed, considerable attention has been paid by the Public Health Service to the development of appropriate information for the seropositive donor. Perceptions of vulnerability to disease might reasonably be expected to play a central role in behavior change and considerable evidence is already available linking such perceptions to other health-protective behaviors. Little is known, however, of how such perceptions originate and recent research suggests an optimistic bias or underestimation of risk characterizes beliefs about one's own vulnerability to illness. Such a bias may be particularly common when there are lingering public doubts about the adequacy of HTLV-III testing technology, when exposure resulted from infrequent previous behaviors, and when the consequences of accepting the sense of vulnerability are potentially extreme. Previous research on community health campaigns indicates that the decision to adopt a preventive health behavior is largely contingent on how effective the behavior is perceived to be in preventing the threatening illness or condition. In the case of HTLV-III infection, the situation is more complex as the seropositive individual has dual concerns: (1) preventing, in the absence of good information regarding how such prevention is achievable, the development of AIDS for himself or herself; and (2) preventing the transmission of HTLV-III to others. Current behavioral recommendations to seropositive donors focus on the latter aspect, which may be a small part of an individual's concern regarding antibody status. Access to health care or preventive

care is known to influence the likelihood that individuals will adopt a desired behavior. Traditionally, geographic and financial factors have affected a variety of health-related behaviors. In addition, several researchers have suggested that dispositional as well as material factors may need to be considered as they promote or provide barriers to behavioral changes. For the HTLV-III-seropositive donor, both may need to be taken into account depending upon the circumstances of the individual. For example, rural donors face special constraints, as does the seropositive donor who does not have a primary health care provider with whom he or she has already established a good relationship. Social networks have been defined in terms of social contact within and between population subgroups and in terms of social norms. Research has demonstrated that both the presence of a social network and behaviors and values within the network are likely to influence relevant health behaviors. The probable route of infection (intravenous drug use, sexual behavior, unknown) may suggest the network available to the donor and norms within it. Certainly, increased social isolation needs to be considered as a possible consequence of receiving HTLV-III serologic test results. Finally, the adoption of preventive health behaviors is consistently related to certain demographic characteristics. In general, those with more income, more education, or of higher social class are more likely to adopt preventive health behaviors. Although in large measure unmodifiable, such factors need to be taken into account in understanding the impact of HTLV-III antibody testing and in designing any intervention program.

In order to appropriately apply this model to the current epidemic, several additional factors need to be taken into account. (1) It is generally recognized that having AIDS leads to extreme threat, uncertainty, and stigmatization. Thus extrapolation from previous research dealing with less volatile issues needs to be examined cautiously. (2) The extent and salience of the recommended behavior change may have no parallel in the recent history of public health. Peculiarly enough, the success of biomedical technology in making available HTLV-III antibody testing has served to highlight anew the myriad cultural, social, psychological, and behavioral factors that need to be considered in adequately reducing the transmission of HTLV-III. (3) The probable interrelated behavioral and psychological effects of HTLV-III testing must be kept in mind. To focus on either alone is inadequate.

It should also be recognized that there are important differences between HTLV-III antibody testing of blood donors and of gay men. The anticipation and consequences of a positive test result need to be considered carefully in the two contexts. For the seropositive blood donor, testing is accepted but not sought out, while for the gay male the decision to seek such testing may be the result of a long process of debate and decisionmaking. Similarly, for the blood donor, a positive test result may constitute the abrupt intrusion of a crisis, while for the gay male it is more likely to be another (although dramatic) step in an evolving process of defining personal risk. Thus, the application of the model described above needs to be particularized in each of these cases.

Components of the model are reviewed as to both donors and gay men. This review suggests that there may be major weaknesses in our ability to facilitate appropriate behavioral changes in HTLV-III seropositive individuals. The features of AIDS reviewed above, the social and political climate within which HTLV-III serologic testing is occurring, our evolving but incomplete understanding of the relevant medical issues, and the difficulties in initiating and maintaining any behavioral changes suggest that it is imperative to develop a better informational base. Such data would focus on factors that promote both appropriate behavioral change and psychological well-being in the seropositive individual. Only when such information becomes available will it be possible to design appropriate and adequate interventions.

# Causes and Consequences of Testing for HTLV-III Antibody: The Gay Community Experience

John L. Martin

A sample of 745 gay men who did not have AIDS were enrolled in a prospective study of the social, psychological, and behavioral impact of the AIDS epidemic on the New York City gay community. Initial interviews were conducted in mid-1985. A longitudinal serologic/immunologic study was subsequently added to the psychosocial study to assess HTLV-III/LAV antibody status, various hematologic characteristics, and T cell phenotypes. Participants for this substudy were recruited from the cohort of 745 and were offered the option of finding out their antibody status. A total of 350 enrolled and initial baseline blood samples were drawn in early 1986. At the time each sample was taken participants were asked a variety of questions about their intention to seek test results, their anticipated antibody status, and their intentions regarding changes they expect to make based on their antibody status. Approximately 50 percent of those enrolled in the serologic study indicated that they intended to find out their antibody status. The remaining 50 percent either said they did not know whether they would seek this information or said they were determined to not seek their results.

At this time only a portion of the data are available for analysis. Thus, results described here must be regarded as preliminary and are subject to change when analyses are conducted on the complete data set. Three main questions can be addressed at this time: (1) What factors lead gay men to avoid antibody testing? (2) What are the characteristics of gay men who seek testing? (3) What is the impact of knowing one's antibody status on mental health and sexual behavior?

In order to determine factors associated with avoiding testing, reasons for refusing to enroll in the serologic study were analyzed for content and classified into four mutually exclusive categories. The most common reason for refusing (40 percent of all reasons) was concern over confidentiality of test results. In spite of the fact that this study employs a system which assures anonymity many respondents felt that if government agencies or insurance companies decide to compile lists of antibody-positive individuals no method of protecting confidentiality could be considered 100 percent effective. The second most common reason for refusing to participate (20 percent of all reasons) was concern over personal psychological well-being. Although respondents were given the option of participating in the serologic study for research purposes

only, without having to be informed of their antibody status, a number of men expressed concern that they would not be able to resist knowing the result if it were available. Many respondents said they simply felt overwhelmed by AIDS-related issues and could not cope with the additional stress associated with testing. The third most common reason for refusing (12 percent of all reasons) was simply distrust in the accuracy and reliability of the test. (This reason was given in spite of the fact that Western blot confirmation following two positive readings based on the ELISA assay are required in order to be classified as antibody-positive.) The remaining reasons for refusing to participate varied widely and included dislike of the study itself, general opposition to all blood testing, and fear of needles.

To address the question of what type of gay man is most likely to seek antibody testing, two groups were compared: (1) men who enrolled in the serologic study specifically to find out their antibody status, (seekers, N = 97), and (2) men who enrolled for research purposes only or men who elected not to enroll at all, (nonseekers, N = 534). These two groups were compared on sets of variables measuring background and demographic characteristics, sexual behavior activity levels, involvements with persons with AIDS, and psychological distress. No differences between the two groups were found for age, education, income, ethnicity, lover status, or veteran status. Nor were any significant differences between the two groups found on variables representing the number of sexual partners, frequencies of engaging in specific sexual activities, or frequency of condom use, either before hearing about AIDS (1980-81) or in the year prior to the interview (1984-85).

Differences were found, however, in two other areas. A significantly larger proportion of those seeking their antibody status reported having a close friend or lover sick with AIDS (20 percent) compared with the group of nonseekers (11 percent; $p < .02$). In addition, significant differences were found on measures of subjective vulnerability to AIDS and psychological distress related to the fear of AIDS. Specifically, compared to nonseekers, seekers of antibody test results report lower levels of subjective threat of developing AIDS ($p < .02$) and lower levels of psychological distress symptoms involving intrusive and avoidant thoughts about AIDS, panic attacks, thoughts of dying, and dreams and nightmares about AIDS ($p < .04$).

These results indicate that the type of gay man most likely to seek HTLV-III antibody testing is more likely to be close to someone with AIDS and to be comparatively better defended, psychologically, against the threat of AIDS. The lack of significant differences between seekers and nonseekers on sexual behavior histories and background factors suggests that entry into testing programs by gay men is not influenced by the likelihood of being antibody-positive or antibody-negative.

The question of the impact of knowing one's antibody status on mental health and sexual behavior is the question least amenable to being

addressed with the available data. Two analytic approaches were taken to generate convergent evidence. The first approach involves content analyses of anticipated changes described by serological study participants. Of those men who intend to seek their antibody status, 39 percent plan to make changes in their lives should they be antibody-positive; 11 percent intend to make changes if they are antibody-negative. The changes the men intend to make if they are positive can be classified, in descending order of frequency, as follows: (1) more careful in sexual behavior, (2) more attentive to health behaviors and more frequent use of medical services for health monitoring, (3) initiation of financial arrangements for the future, execution of a will, and preparation for death, and (4) changes in psychological and philosophical approaches to life. It is important to note that 61 percent of those who intend to seek their antibody status said they do not intend to change anything about their lives. In most cases the reason for this is that they had changed all relevant aspects of their sexual behavior so that there was nothing left to change.

The second analytic approach taken to the question of knowledge impact involves comparing the following three groups: (1) men who knew they were antibody-positive at the time of the initial interview (N = 16), (2) men who knew they were antibody-negative at the time of the interview (N = 34), and (3) men who had not been tested at the time of the interview but who subsequently enrolled in the serologic study with the intention of knowing their antibody status (N = 97). The data were collected in a way that does not allow firm conclusions to be drawn from the lack of differences between these groups. The reason for this is that respondents who knew their antibody status at the time of the interview were informed of their status an average of 5 months prior to the interview (range--1 to 13 months). Since questions about mental health and current sexual behavior focused on the 12 months prior to the interview only a portion of the measured time period includes the time that these men knew their antibody status. Thus, the ability to detect differences due to knowledge of antibody status is diminished here because of our inability to separate time periods during which antibody status was known from the time period during which antibody status was not known. However, any significant differences that do emerge may be taken as suggestive of areas in which knowledge of antibody status will have an impact within a relatively brief time period.

The three groups were compared on the following three mental health measures: (1) demoralization, a measure which taps nonspecific psychological distress and depressive symptomatology, (2) subjective sense of vulnerability to contracting AIDS, and (3) AIDS-specific distress symptoms including intrusive and avoidant thoughts about AIDS, panic attacks, thoughts of death, and dreams and nightmares about AIDS. No significant difference among the three groups was found on demoralization. However, significant differences were found on measures of subjective vulnerability and AIDS-specific distress. Men who knew that they were antibody-positive report more intense feelings of vulnerability ($p < .04$) and more intense

distress symptoms ($p < .02$) compared to men who knew they were antibody-negative and men who were unaware of their antibody status. The last two groups do not differ from each other on either measure.

Comparisons among the three groups on measures of sexual behavior revealed no significant differences in number of partners, frequency of engaging in specific sexual activities, or tendency towards condom use. As noted above, the lack of differences associated with knowledge of antibody status may be due to methodological factors, and thus cannot be relied upon at this time.

In summary, these results suggest that within the New York City gay community men who are close to someone who is sick with AIDS and who have relatively good psychological defenses against the threat of AIDS will be the most likely men to seek testing. The issue of confidentiality of test results is the most frequent reason for avoiding testing followed by concern for one's ability to cope with the stress of anticipating the test result and dealing with the issues raised by it. The majority of those seeking their antibody status indicate that a positive result would not lead to behavioral changes since relevant changes have already been made, particularly with regard to sexual behavior. However, a substantial minority claims that they would change their behavior, given a positive result, and the main change would be towards more caution in sexual activity. Preliminary empirical results indicate that knowledge that one is antibody-positive leads to increased feelings of vulnerability to developing AIDS and increased psychological distress symptoms associated with this AIDS-related fear. Thus, while better psychological defenses characterize those who present for testing these defenses may be broken down by knowledge of being antibody-positive.

# Psychosocial Impact of Anti-HTLV-III Notification: The New York Experience

Johanna Pindyck

Through January 14, 1986, the New York Blood Center (NYBC) advised 221 blood donors that the results of a test on their recently donated blood were important to their health. Donors were asked to call for an appointment to discuss the test result. The letters were generated in response to laboratory determination that these donors had antibody to HTLV-III by Western blot testing. By January 31, 1986, 155 (70 percent) of these donors were personally notified and counseled by trained NYBC nurse-clinicians. If donors did not respond to the first letter, a second one was sent, again urging response. However, if none was received, a third mailing, containing test results and public health recommendations to prevent infection transmission, was sent. More than 90 percent of donors were seen after the second or third mailing.

Donors receiving information on anti-HTLV-III seropositivity are presented with a complex and anxiety-generating situation. They come from varied backgrounds, and have substantially different levels of information about the infection and its associated disease, AIDS. The presence or absence of risk factors for exposure, and the donor's awareness of these risk factors, is related to the amount of stress evidenced at notification.

To screen out donors at high risk of AIDS, the NYBC has all donors indicate in a confidential manner whether their blood may be used "for transfusion," or, because of the presence of risk factors, it must be used for "studies only." Testing of 330,651 "for transfusion" donors through December 31, 1986, revealed a prevalence of antibody positivity in 205,723 male donors of 0.09 percent, and in 124,926 female donors of 0.06 percent. During the same time interval, of 4,082 "studies only" male donors, 2.74 percent were seropositive and 0.33 percent of 2,101 female "studies only" donors were seropositive. Women comprise 28 percent of the seropositive "for transfusion" donors who must be notified, and 21 percent of the total seropositives.

The NYBC has implemented an intensive health education and support program for seropositive donors. Studies are in progress to evaluate the psychosocial impact of notification and the benefits of subsequent counseling to the mental and physical health of the donors. Early data

indicate that most donors (75 percent) do not anticipate receipt of information on positive test results, and are moderately to severely distressed when informed. They are concerned about the confidentiality of the information. Donors are seen again at 2 weeks after notification and counseling. Only 52 percent discussed the test finding with their spouse or lover at the time of revisit. Several who had done so report serious disruption in the relationship. Special counseling for a significant other (e.g., spouse, lover, mother) has been requested in 20 percent of cases and has been arranged. A description of the counseling program and results of studies in progress will be reported.

# Psychosocial Impact of Anti-HTLV-III: The Hemophilia Experience

Peter H. Levine

Persons with hemophilia have often experienced some form of discrimination related to their chronic handicapping condition. In addition, the difficult decisions surrounding family planning, the issue of maternal guilt, the parental stresses imposed by a chronically ill child, the financial burden and the educational/vocational problems associated with hemophilia all have combined to yield a high rate of psychosocial problems in affected families. To superimpose a partially understood, blood-borne, sexually transmitted, and sometimes lethal infection onto this substrate has had predictably dire psychosocial consequences.

Most (but not all) patients have been intensively educated by the cooperative efforts of the National Hemophilia Foundation, the network of federally funded hemophilia treatment centers, and local health care providers. Studies suggest that incomplete information or incorrect beliefs are commonplace, however. Further, many patients use denial as their primary defense mechanism. No studies of psychosocial intervention strategies concerning HTLV-III infection in persons with hemophilia have yet been carried out.

There will soon be supplemental grants for the provision and evaluation of enhanced psychosocial support via the federally funded network of hemophilia treatment centers. This effort will be vital to: (1) maintain the previous gains in normalizing the lives of persons with hemophilia; (2) assure compliance with strategies to minimize the spread of HTLV-III virus, and, (3) decrease the risk of inappropriate exclusion, expulsion, or quarantine of persons with hemophilia by uninformed members of lay or medical groups.

# The Impact of HTLV-III Antibody Testing on Donor Recruitment and Transfusion Practices

John L. Thornton

Few, if any, know the impact of HTLV-III antibody testing on volunteer donors or on donor recruitment. There is much conjecture and little analysis. It may be valid to consider in 1986 what Alvin Drake, Ph.D., said in the late 1970's: "Public attitudes and unwillingness to give are not the primary causes of the limited difficulties the blood collection and distribution system still experiences. . . Professionalism and coordination of the blood collecting organizations seem to be the critical issues."

In January 1986 a highly publicized survey revealed that 34 percent of the population believed that one could get AIDS by donating blood. I wonder about the significance of this finding because I suspect that a certain percentage of the population has always been unwilling to give blood because of some fear or other. For example, a study done 8 years ago in an area labeled as traditional by test marketing experts revealed that about 30 percent of those questioned were afraid that they could contract hepatitis by donating blood.

Since the discovery that AIDS can be transmitted by transfusion and since the implementation of HTLV-III antibody testing, periodic blood shortages have been attributed to the potential blood donor's fear of contracting AIDS or his wariness about the testing procedure. I find it difficult to accept this, for in the 30 years that I have been directly associated with blood banking, there have always been periodic blood shortages. The recent increases in requests for autologous transfusion and for directed donations reflect the public's fear of transfusion-transmitted AIDS. The flattening of the use curve may reflect the medical profession's awareness of a potential hazard. These factors do not necessarily show the effect of HTLV-III antibody testing on donor recruitment or on the voluntary blood donor.

The most significant effect HTLV-III antibody testing has on the voluntary donor may come when, as we slowly climb the learning curve of testing technology and interpretation, we falsely label the donor as HTLV-III-positive. The responsibility for the results cannot be taken casually. To continue to draw blood from donors who are repeatedly positive to EIA but negative to Western blot and then to destroy the blood is exploitive and, when revealed, may threaten the credibility of the collecting agency.

# Impact of HTLV-III Antibody Testing on Transfusion Practice: An Overview

Douglas MacN. Surgenor, Edward L. Wallace, and Suzanne G. Hale

About 1 out of every 100 persons in the United States will receive a transfusion this year. In deciding who will be transfused, given an adequate supply of blood, physicians will weigh the risk to the patient of not providing requisite transfusion support with blood or blood components against the risk of posttransfusion reactions and disease transmission, including the risk of transmission of the HTLV-III virus.

The question of whether transfusion practices are being affected by HTLV-III antibody testing is answerable provided the means exist to collect the required information on which reasonably informed estimates can be made. Within the Specialized Center of Research in Transfusion Medicine recently funded to the Center for Blood Research by NHLBI (HL-33774-01), and with the cooperation of the American Association of Blood Banks, the American Red Cross, and the Council of Community Blood Centers, we now have the capability of obtaining some answers to this question.

Given the magnitude of the AIDS epidemic and the widespread awareness of physicians and the public at large that AIDS can be transmitted by transfusion, it is reasonable to assume that the transfusion decision is receiving even greater scrutiny than it has before now; and that, as a result, transfusion practice may be changing.

In providing transfusion support for medical and surgical interventions, recent trends involve the use of separated components of blood--red cells, platelets, cryoprecipitate, and plasma--and in multiple amounts. In the most recent careful national survey of transfusion practice, for the year 1980 (Surgenor and Schnitzer, NIH Publication No. 85-2028), the mean number of units of red cells transfused per patient transfused was more than 3). It is thus not uncommon for patients to be transfused, in a given hospital stay, with 3 or more units of whole blood and red cells, 10 or more units of platelet concentrates, and several units of fresh frozen plasma. In the above case, where the patient might be exposed to components of the blood of, say, 13 or more blood donors, reduction by only one or two units would significantly lower the exposure of the patient to transfusion-transmitted disease. At the other end of the scale, a decision to reduce by one unit could of course mean that no transfusion is given at all. The impact of factoring the AIDS risk into the transfusion decision would thus most likely be seen either in alterations in the intensity of transfusion of blood components, or in numbers of patients transfused, or in both.

Alternatively, for patients requiring elective surgery, a considerable portion of the donor exposure to transfusion can be reduced if the physician and patient choose to take advantage of the autologous transfusion pathway. (This is discussed in Dr. Kruskall's paper.)

One of the surprising findings of the 1980 survey of the Nation's Blood Resource was the discovery of sizable regional differences in transfusion activities across the United States. Thus, for example, red cell transfusions varied from a national high of 50 units per thousand population in New England to 36 units per thousand in the Mountain region. Similar variations were observed in transfusions of platelets and fresh-frozen plasma, as well as in numbers of patients transfused. The explanation of these regional differences in transfusion rates is not known at this time, although there are some suggestions that they reflect regional variations in the practice of medicine and the utilization of various surgical procedures.

Nevertheless, in view of the regional differences in the prevalence of AIDS, the effect of HTLV-III testing should be looked for at the regional level of transfusion practice.

Underlying these issues is an even more fundamental problem: the impact of public health screening measures upon the source supply of blood and blood derivatives for transfusion. These measures, which now include screens for hepatitis B antigen and HTLV-III antibody, are about to be expanded by the imposition of ALT and anti-$HB_c$ testing as surrogate markers for non-A, non-B hepatitis. Since the application of each of these screens results in the exclusion of a unique cohort of blood donors from the donor base, a serious adverse effect on the national blood resource can be expected, at least in the short term, with corresponding effects on transfusion practice.

Some preliminary data bearing on these issues will be presented.

# New Trends in Transfusion Medicine: Autologous Transfusions and Directed Donations

Margot S. Kruskall

The recognition that HTLV-III infection could be spread by blood transfusions has resulted in the growth and utilization of two alternate approaches to standard homologous blood transfusions: autologous blood transfusions and directed donations.

## AUTOLOGOUS TRANSFUSION

The first autologous blood transfusions were reported in the late 1800's; Dr. James Blundell is credited as the first physician to directly reinfuse shed autologous blood back into women exsanguinating from post-partum hemorrhages. The recognition that shed blood could be salvaged from a bleeding patient for retransfusion, and the later appearance of protocols for drawing blood in advance of anticipated surgical blood loss, formed the basis for current autologous transfusion programs in this country. Autologous transfusion techniques include:

- Autologous blood donations:
  - Preoperative autologous blood donation: the removal of one or more units of blood from a donor anywhere between 3 days and many months in advance for later retransfusion during anticipated blood loss (usually during surgery or delivery).
  - Intraoperative hemodilution: the removal of one or two units of blood from a patient at the start of a surgical procedure. Blood volume is replaced by saline; the units are transfused at the end of surgery.
- Blood salvage:
  - Intraoperative salvage: the collection of shed surgical field blood for immediate retransfusion to the patient. This blood may be directly transfused through a filter, or alternatively the red cells may be washed with saline using an automated centrifuge device to remove excvess volume, products of hemolysis, and procoagulants.

- Postoperative salvage: the collection of postoperatively shed mediastinal blood, usually after open-heart surgery. This blood is usually directly retransfused through a filter without washing.

- Posttraumatic salvage: the collection of blood from a hemothorax, for direct retransfusion without washing.

Advantages of autologous blood include: the elimination of hemolytic transfusion reactions due to ABO and other blood group antibodies; the elimination of allergic and other reactions; the elimination of transfusion-transmitted diseases, including hepatitis and AIDS; the availability of blood for individuals with complex alloantibodies who would otherwise be difficult to transfuse; the sparing of the limited homologous blood supply for other patients unable to donate their own blood. Depending on the program size and choice of autologous transfusion protocols, there may also be fiscal advantages to autologous preoperative donation programs, the expenses of salvage programs have not been analyzed.

However, utilization of these procedures was limited until the last decade, when increasing concern about tansfusion complications, accelerated by the appearance of transfusion-transmitted AIDS, resulted in a marked increase in the number of transfusion facilities with autologous programs. For example, whereas in 1973 fewer than 100 institutions offered preoperative autologous blood programs, this number grew to 656 in 1984, according to statistics of the American Association of Blood Banks (AABB). Although it might have been anticipated that the introduction of HTLV-III antibody testing in 1985 might have reduced the fervor of patient participation in autologous programs, this appears not to have occurred. Beth Israel Hospital reported that 2.1 percent of all hospital red cell transfusions, and 7.2 percent of FFP transfusions, came from autologous donor products in 1983-84, the first year of its preoperative autologous program. It is likely that increased public awareness of this option will further encourage demand and participation.

Advances in red-cell preservative solutions, which increase the liquid storage period for red cells, would allow autologous blood donation programs to function without the need for more expensive red cell freezing procedures. Many other research opportunities exist, and the absence of critical information, particularly in the area of red cell salvage, may be hindering their adoption. For example, the efficacy of hemodilution in reducing homologous transfusion requirements has never been satisfactorily proven; and many questions exist about salvaged autologous blood, including the posttransfusion survival of such red cells, and what risks, if any, exist to the transfusion of unwashed salvaged blood.

DIRECTED DONATIONS

A directed blood donation is one given by a friend, family member, or other selected individual who has been specifically recruited by a potential recipient, or by a family member for a recipient, with the stipulation that the blood product subsequently be transfused to that recipient. This recipient-orchestrated procedure must be distinguished from other donor-specific transfusions, in which the donor's blood is chosen for a clear medical indication. Examples of the latter include the transfusion of whole blood from a kidney donor to the potential recipient prior to kidney transplantation, to enhance graft survival; the transfusion of maternal, antigen-negative platelets to a newborn with isoimmune thrombocytopenia; and the transfusion of red blood cells from blood relatives because they are the only compatible donors.

Patients and physicians who request directed donor (recipient-orchestrated) blood products argue that the purpose of the procedure is to avoid the use of blood from donors at high risk for carrying HTLV-III. The results of a recent AABB survey revealed the 81 percent of lay individuals thought that blood from friends or relatives could reduce the risk of TA-AIDS. However, in the same survey, only 5 percent of hospitals and transfusion services felt that there was a medical rationale for the procedure. In addition, major blood providers and medical advisory organizations, such as the AABB, the American Red Cross, the Council of Community Blood Centers, and the AMA, have strongly recommended that directed donor programs not be conducted.

Because the incidence of TA-AIDS is still quite low, it is difficult to prove that recipient-selected donors are less likely to transmit AIDS than volunteer blood donors. However, one large West Coast blood center which studied its 3500 directed donors found that the incidence of anti-HTLV-III positivity in this group was no lower than that in its volunteers; and an East Coast pediatric hospital transfusion service instead has observed the incidence to be higher in directed donors. Hepatitis B surface antigen positivity has also been seen as frequently among directed donors as volunteers. Thus, directed donors may not meet recipients' expectations regarding infectivity. This may be due, in some instances, to donors being unwilling to disclose some aspects of social history, to avoid exposure and placement in an HTLV-III high-risk group. Other donors may have withheld important medical history, such as hepatitis, in order to insure that they be able to fulfill the recipient's wish to use their blood to avoid AIDS.

Despite the lack of evidence of efficacy, some institutions continue to collect directed donations. The most frequently given explanation for this, in a recent AABB survey, was as a response to pressure by the patient, a relative, the patient's physician, or the community at large. Unfortunately, the collection of directed donor blood products sends the unintended message to the public that the medical community recognizes some scientific validity to this procedure.

Furthermore, directed donations create serious medical, logistical, and ethical problems. For example, donors' anonymity, and protection from legal liability in the event of a complication of transfusion, can no longer be guaranteed. In addition, directed donors are not strictly "volunteer," in that they have been coerced to donate, with pressures ranging from verbal requests to gifts or other financial incentives. The discovery in the 1960's that the incidence of hepatitis was increased up to sevenfold in nonvolunteer donors led to the gradual phasing out of such donor groups. The transfusion of directed donations is, paradoxically, tantamount to a return to this practice.

Directed donations set up medical double standards, pitting the "good" directed components against the "not-so-good" volunteer units. Where blood collection facilities have chosen to accede to requests for directed donations on an infrequent basis, two standards of medical care are implied: one for individuals whose persistence and influence allow them to overcome the hurdles set up by the collection facility, and the other for those stymied by the original refusal.

Directed donor programs are operationally complex and expensive for individual blood collection facilities and transfusion services. They may also have a devastating impact on the nation's blood supply, if widespread adoption were to result in the loss of regular donors who were saving themselves for potential requests for directed donations.

Finally, such programs have been used as marketing devices by some centers, who require recipients to bring two or three times as many donors as are needed to increase the center's blood supply. In addition, the availability of a directed donor program may be used to competitive advantage, attracting potential patients to one hospital over another. The promotion of a program with no medical benefits for financial gain is ethically troubling.

Thus, directed donor programs appear to offer no medical advantages, and many administrative, legal, and ethical problems. Their use should be actively discouraged.

REFERENCES

1. Bove JR. Transfusion-associated AIDS--a cause for concern. N Engl J Med 1984;310:115-6

2. Hauer JM, Thurer RL, Dawson RB, eds. Autotransfusion. New York: Elsevier/North Holland, 1981

3. Kruskall MS. Establishment of an autologous transfusion program in a transfusion service. In: Sandler GS, Silvergleid AJ, eds. Autologous Transfusion. Arlington, VA:AABB,1983, pp.57-70

4. Kruskall MS, Glazer EE, Leonard SS, Willson SL, Pcini DG, Donovan LM, Ransil BJ. Utilization and effectiveness of a hospital autologous preoperative blood donor program. Transfusion 1986 (in press)

5. Kruskall MS, Churchill WH, Brauer M, Kevy S, Ervin T, Kurtz S, Umlas J, Dzik W. Designated blood donations. N Engl J Med 1984;310:1194-5

6. Milles G, Langston HT, Dalessandro W. Autologous Transfusions. Springfield: Charles C. Thomas, 1971

7. Umlas J. Transfusion-related acquired immunodeficiency syndrome and directed donations: would the national blood supply be safer with directed donations? Human Pathology 1986;17:108-10

# Neonatal Transfusion Medicine: HTLV-III Implications

Naomi L. C. Luban

## INDICATIONS FOR TRANSFUSION OF THE NEWBORN

Statistics on the number of transfusions of blood and blood products and extent of donor exposures to neonates are difficult to obtain. One study demonstrated that three times as many red cell transfusions were required per day in newborns as in older children.[1] In another study, 25 percent of 4,906 newborn infants received transfusions, with more than two-thirds requiring multiple transfusions,[2] while in a large pediatric hospital, 33.5 percent of 3,056 transfusions were given to neonates.[3] The premature infant is most likely to require blood, frequently sporadically but over a long period, and usually obtained from multiple donors. If the infant requires component support, additional donor exposure is a certainty. The indication for RBC transfusion in these neonates may be exchange transfusion for hyperbilirubinemia or sepsis, where whole units of blood are used, but usually is anemia, where tiny amounts may be transfused. The etiology of the anemia, especially in the extremely premature infant, is frequently, but not exclusively iatrogenic--"bleeding into the lab." The necessity for precise monitoring of electrolytes, blood gases, and other elements despite the use of microtechniques has resulted in losses ranging from 3 ml/kg per infant per day in one study[4] to 35 ml/kg in 4 weeks of hospitalization in another study.[5] In yet another institution, a mean of 12.4 ml of blood is removed per infant per day.[6] The result of these losses is the repeated transfusion of small amounts of blood, variably called simple, booster, or topper transfusions.

Indications for simple transfusion in the neonate may be based on clinical indication (dyspnea, tachycardia, tachypnea, tiring at feeding), on a tabulated removal of blood equal to 5 to 10 ml per kg of the infant's estimated blood volume,[7] for apnea,[8] maintenance of a hematocrit greater than 40 percent, especially in those requiring ventilatory support, or, in the older premature, poor growth.[9] Each of these indications is arbitrary and not based on scientific evidence of improved oxygen delivery, although at least two studies have attempted to use a calculation that assesses available oxygen.[10,11] Because of the difficulty inherent in studying the physiology of cardiac output, metabolic rate, and oxygen extraction, transfusion of blood in this patient population remains empiric and variable. Only recently have there been attempts to justify simple RBC replacement transfusions.[12]

## SELECTION AND PROCESSING OF BLOOD FOR NEONATES

In 1972, McCormick et al detailed a system of transfusion for newborns that used small amounts of blood collected in heparinized syringes.[13] Others adopted this practice[14,15] and suggested many advantages of its use, including elimination of waste and limitation of donor exposure. Disadvantages of such a program were reviewed by other authors[16,17] including one proponent[14] and include inability to document donor source and lack of serological testing.

By the early 1980's, walking donor programs had all but disappeared and collection bags with sterile integrally attached transfer bags put collection and processing back into the hands of the blood bank. By using a quadripack (three transfer bags plus primary bag), and subsequently attaching single or multiple transfer packs, even smaller subdivisions can be made. Hence, many infants can be transfused from a single unit over the accepted shelf life of the transfer pack or unit of blood. Such systems increase blood utilization, decrease waste, and decrease cost. They also dramatically increase the chance that a number of infants will be exposed to an infectious agent from a single donor unit. Use of such systems has resulted in clusters of infants being infected with malaria,[18] hepatitis A,[19-21] and HTLV-III[22-24] from a single donor.

## HTLV III AND TRANSFUSION IN THE NEWBORN

As of March 31, a total of 273 infants and children have fit the stringent CDC classification of pediatric AIDS (PAIDS). Of these, 207 (76 percent) have acquired the disease from an at-risk parent, 12 (4 percent) from unknown sources, and 42 (15 percent) from transfusion. Of these latter 42 children, 12 cases (4 percent) are hemophiliacs and 30 acquired AIDS from contaminated, nonpooled blood or blood products.

The CDC definition for PAIDS has been modified to include histologically documented lymphoid interstitial pneumonia as an accepted criterion.[26] Patients manifesting disorders such as primary immunodeficiencies and secondary immunodeficiencies including immunosuppressive therapy, lymphoreticular malignancy, congenital infection, and malnutrition would be excluded from this definition.[27] There are no published estimates of the number of children who are HTLV-III-positive and asymptomatic, who have ARC, or who may have been excluded because of the stringent CDC criteria. At our institution alone, four recipients of blood from known high-risk donors are HTLV-III-positive and symptomatic, but would be excluded by CDC criteria for primary disease or concomitant immunosuppressive treatment, or both. In addition, the clinical manifestations of HTLV-III infection may be difficult to distinguish from the primary disease and its progression. While there are studies under way to evaluate children with maternal high risk, i.e., perinatal AIDS, there are very few studies addressing pediatric transfusion recipients.

Review of published data on pediatric transfusion-acquired immune deficiency syndrome (P-TAIDS), exclusive of hemophilic children, reveal the following characteristics:[28-36]

1. Males appear to be overrepresented in P-TAIDS.

2. History of prematurity or complex neonatal course requiring transfusion.

3. Presentation when patient fails to thrive, and exhibits oral and genital moniliasis, lymphadenopathy, hepatosplenomegaly, otitis media, and, frequently, respiratory distress.

4. In infants transfused as neonates, the age at presentation with clinical symptoms suggestive of HTLV-III disease is less than 1 year of age.

5. Incubation period of P-TAIDS is 21 months, although one case has presented as late as 5-1/2 years after transfusion.[33]

6. Hypogammaglobulinemia and IgG subclass deficiency may be found.[28,29,35]

7. Use of irradiated blood,[28] CMV negative blood,[35] or washed blood[25] does not protect against transmission of HTLV-III.

Some comparisons between adult and pediatric tranfusion-associated cases can be made from the work of Hardy and Peterman.[37,38] Based on population estimates and numbers of reported AIDS cases in 1983 and 1984, Hardy et al. attempted to calculate an incidence rate for pediatric recipients less than 1 year of age. The reported incidence of transfusion-associated AIDS in infants (2.43) was greater than in adults (0.40). When evaluated by number of transfusions received, infants who received 10 or more units had an incidence rate of 22.48 compared to 4.83 for adults receiving 10 or more units.[37] In a study by Peterman et al.,[38] infants accounted for 10 percent of all transfusion-associated AIDS, but were estimated to receive only 2 percent or less of whole blood or red cell transfusion according to 1980 statistics. Twenty-one of 194 cases were pediatric and 14 of the 21 were premature infants. Infants differed from adults in the mean incubation period (defined as time from exposure to diagnosis of AIDS) of 21 months compared to 31 months in adults. The interval from exposure to onset of symptoms is also different, being much shorter in children (15 months) compared to adults (27 months). To date, there are no published data detailing the pediatric transfusion-associated cases that might allow more thorough immunologic, clinical, and seroepidemiologic comparison either with adult cases or with pediatric cases acquired through vertical transmission. For example, the CNS manifestations of HTLV-III infection are not stressed by those reporting P-TAIDS cases, but appear to be a prominent feature of the parental risk-group cases. Retrospective assessment of P-TAIDS cases would be especially

valuable in assessing what factors might predispose to HTLV-III or other viral infections in this frequently transfused group of patients.

## UNANSWERED QUESTIONS ABOUT P-TAIDS

### Why Is the Neonate Particularly Susceptible to P-TAIDS?

The premature infant appears to be particularly susceptible to acquisition of HTLV-III disease. This group of patients has a propensity for acquisition of bacterial and viral disease based on immaturity of the phagocytic and reticuloendothelial as well as cellular and humoral immune systems. Studies of decreased neutrophil reserve, poor superoxide generation, low quantitative immunoglobulins, poor antibody response to polysaccharide antigens, and diminished T-cell response to antigens all support this concept. Repeated antigenic stimuli by infusion of blood and blood products, hyperalimentation solutions containing lipids and protein, intercurrent bacterial or viral disease, or both, and other unknown antigens may result in an immobilization of host phagocytic defense and easy acquisition of HTLV-III, a theory not yet confirmed.

Other factors may also contribute to the infants becoming infected. There may be a genetic predisposition to acquisition of viral disease. For example, prior to HTLV-III-antibody testing, HLA-DR-5 was suggested as a predisposing genetic factor in adult homosexuals with AIDS.[39] Transfusion of allogeneic lymphocytes of HLA specificities different from those of the recipient may result in immunosuppression which later results in an increased susceptibility to HTLV-III infection, irradiation of blood might decrease the potential for functional donor lymphocyte survival.[40] Immunologic abnormalities have been reported in adult, nonhemophilic patients receiving multiple blood transfusions and include variably increased T-helper and T-suppressor numbers in sickle cell and thalassemic patients, depressed natural killer (NK) function, and increased expression of HLADR antigen in both sickle cell and thalassemic patients.[41,42] Interestingly, these findings were most abnormal in those individuals who were most frequently transfused. No similar data are available for transfused infants. Depressed NK activity in animals increases susceptibility to viral infection and tumor engraftment.[43] Depressed NK activity has been reported in infants, as has decreased gamma interferon.[44,45]

Another speculation about susceptibility of infants and children is that the amount of virus administered relative to the infant's total blood volume may result in a single large transfusion from a single donor. Multiple aliquots of blood from a single infected donor during the course of the accepted shelf life of a transfer pack or unit of cells may be administered to a single infant and this may be the equivalent of a single exchange transfusion. Evaluation of cluster cases where infants have received small amounts from a single infected donor may assist in adequately answering this hypothesis, or provide new insights, although data to date would indicate that tiny amounts of transfused blood are capable of transmitting HTLV-III virus.[25]

Why Are Male Infants Particularly Susceptible?

Could there be an X-linked propensity for tropism of HTLV-III for T cells? In 1983, the last year for which statistics are available, there were 1,052 male births per 1,000 female births. Of all births, 6.8 percent were considered to be low birth weight defined as under 2,500 grams, but were not specified by sex.[46] Perinatal deaths reveal 119 male to 100 female deaths without regard to race in 1981, the last year for which statistics are available.[47] A structured analysis of pediatric transfusion recipients would allow confirmation of the suggestion that males are particularly susceptible to viral infection.

What Effect Does Concomitant Exposure to CMV Have on Acquisition of HTLV-III?

Transfusion-acquired CMV infection in newborn infants is thought to increase morbidity and mortality and has led to recommendations that exclusively seronegative or processed blood be used for certain select (less than 1,250 grams) or all transfused infants. The suspected cofactor effect of CMV and HTLV-III infection in male homosexual AIDS patients would suggest an even stronger rationale for use of blood negative or at least leukodepleted for CMV. We do not know the CMV antibody status of infected infants and donor units in cases reported to date, and that data might be helpful in sorting out this aspect of the complex cofactor issue. In adult studies of transfusion-transmitted HTLV-III, frozen, deglycerolized blood did not prevent HTLV-III antibody acquisition,[49] while use of frozen blood is thought to obviate CMV disease in infants.[50]

Mechanisms to Decrease Donor Exposure in Infants

Despite voluntary self-deferral, current HTLV-III antibody-testing and the prospects for improved sensitivity and specificity of assays for either HTLV-III antibody or antigen, there is still concern about the possibility of HTLV-III and other viral transmission in newborns. The current cost-effective and blood-conserving systems may have to be abandoned for what are presumed to be safer, but less efficient, systems of delivering small amounts of blood. The following list outlines some specific systems that possibly may be developed, some of which would require new product development, clinical efficacy trials, and appropriate approval by the Center for Drugs and Biologics and other agencies.

1. Placental blood collected into anticoagulant-preservative media that allows storage in bag system that permits removal of very small amounts.

2. Established pedigree donor lists for newborns where ALT, AST, CMV, and other analyses are assessed and updated with each donation.

    a. Draw into conventional multibag systems.

b. Develop bag systems with even greater aliquot potential.

c. Encourage donors to become repeat donors. Bank frozen aliquots of blood from multiple donations and then assign donor to a specific infant for duration of its hospitalization.

d. Employ plasmapheresis procedures on pedigree donors and separate plasma into amounts appropriate for transfusion, i.e., 20 to 30 ml aliquots. Need to study effect of storage device on plasma coagulation factors, sterility, etc. on product so stored.

e. Develop bag systems that allow for collection of whole blood to be made into small platelet packs with smaller amounts of platelet-poor plasma.

3. Use parents as donors in general, and especially for platelets and white cells, which are needed infrequently in most neonates.

   a. Develop smaller collection systems that allow for appropriate anticoagulant-to-blood ratio by collecting smaller amounts. This is especially important if the postpartum mother is to be used as a donor.

   b. Relax "directed donation" restrictions for parents.

4. Support clinical research in:

   a. Seroepidemiology of transfusion-transmitted disease in infants.

   b. Use and abuse of RBC transfusions in neonatal medicine--develop objective criteria and test hypotheses on the need for booster transfusions.

   c. Statistical analyses of transfusion of blood, blood components, and albumin in neonates--a nationwide survey. Gather data on use to establish a statistical basis upon which incidence for transfusion-transmitted disease can be calculated.

   d. In situ monitoring of the neonate. Establish methods to eliminate blood drawing.

   e. The ontogeny of cellular and humoral immunologic systems in premature and full-term infants with special attention to antigen recognition and processing--use of monoclonal and other techniques.

REFERENCES


1. Cohen A, Schwartz E. Transfusion in the newborn period. In: Sherwood WC, Cohen A, eds. Transfusion Therapy: The Fetus, Infant, and Child. Masson: New York, 1980:37-50

2. Forfar JO. Pediatrics and blood transfusion: practical aspects. In: Smit Sibling C, Das PC, Forfar JO, eds. Developments in Hematology and Immunology. Martinus Nijhoff: Boston, 1982:2:97-112

3. Kim HC. Red blood cell transfusions in the neonate. Semin Perinatol 1983;7:159-74

4. Kakaiya RM, Morrison FS, Rawson JE et al. Pedipack transfusion in a newborn intensive care unit. Transfusion 1979;19:19-24

5. Nexo E, Christensen NC, Olesen H. Volume of blood removed for analytic purposes during hospitalization of low birthweight infants. Clin Chem 1981;27:759-61

6. Wallas CW. Considerations and indications for the use of red cell products. In: Luban NLC, Keating L, eds. Hemotherapy of the Infant and Premature. AABB: Arlington, 1983:22

7. Schreiner RL. Care of the Sick Newborn. Raven Press: New York, 1980

8. Kattwinkle J. Neonatal aprea: pathogenesis and therapy. J Pediatr 1977;90:342-7

9. Stockman JA, Clark D, Levin E. Weight gain: a response to transfusion in preterm infants. Pediatr Res 1980;14:612

10. Anonymous. Available oxygen in preterm babies. Lancet 1979;1:419-20

11. Jones JG, Holland BM, Veale KEA, Wardrop CAJ. "Available oxygen" a realistic expression of the ability of the blood to supply blood to tissues. Scand J Haematol 1979;22:77-82

12. Blank JP, Sheargren TG, Vajaria J et al. The role of RBC transfusion in the premature infant. Am J Dis Child 1984;138:831-3

13. McCormick RA, Christman M, Boyles R. Mini-transfusions for neonatal patients. Wis Med J 1972;71:248-9

14. Pass MA, Johnson JD, Schulman IA et al. Evaluation of a walking donor blood transfusion program in an intensive care nursery. J Pediatr 1976;89:646-51

15. Blankenship WJ, Goetzman BW, Gross S, Hattersly PJ. A walking donor program for an intensive care nursery. J Pediatr 1975;86:583-5

16. Oberman HA. Transfusion of the neonatal patient. Transfusion 1974;14:183-4

17. Kakaiya RM, Morrison FS, Holbrook JC, Rawson JE, Lotz LL. Problem with a walking donor transfusion program. Transfusion 1979;19:577-80

18. Piccoli DA, Perlman S, Ephros M. Transfusion-acquired plasmodium material infection in two premature infants. Pediatrics 1983;72: 560-2

19. Seeberg S, Brandberg A, Hermodsson S, Larsson P, Landgren S. Hospitalization outbreak of hepatitis A secondary to blood exchange in a baby. Lancet 1981;i:1155-6

20. Noble RC, Kane MA, Reeves SA et al. Posttransfusion hepatitis A in a neonatal intensive care unit. JAMA 1984;252:2711-5

21. Sheretz RJ, Russell BA, Renman PD. Transfusion of hepatitis A by transfusion of blood products. Arch Intern Med 1984;144:1579-80

22. Azimi P, Roberto R, Guralnik J et al. Transfusion acquired hepatitis A in a premature infant with secondary nosocomial spread in an intensive care nursery. Am J Dis Child 1986;140:23-7

23. Wykoff RF, Pearl ER, Saulsbury FT. Immunologic dysfunction in infants infected through transfusion with HTLV-III. N Engl J Med 1985;312:294-6

24. Williams AE, Luban NLC, Fang CT, Dodd RW. Serial development of anti-HTLV-III and ARC in highly transfused children. Transfusion 1985;25:479

25. Luban NLC, Williams AE, Edwards M, Josephs S, Reaman G. Spectrum of illness in eight children receiving washed RBC's from two HTLV-III infected donors. Blood 1985;66:114a

26. Update: Acquired immunodeficiency syndrome (AIDS): MMWR 1984; 32:688-91

27. Current trends: Revision of the case definition of acquired immunodeficiency for national reporting. MMWR 1985;34:373-5

28. Amman AJ, Cowan MJ, Ware DW et al. Acquired immunodeficiency in an infant: possible transmission by means of blood products. Lancet 1983;30:956-8

29. Church JA, Lewis J, Spotkov JM. IgG subclass deficiencies in children with suspected AIDS. Lancet 1984;i:279

30. Church JA, Isaacs H. Transfusion associated immunodeficiency syndrome in infants. J Pediatr 1984;105:731-7

31. Tong TK, Andrew LR, Albert A, Mickell JJ. Childhood acquired immune deficiency syndrome manifesting as acrodermatitis enteropathica. J Pediatr 1986;108:426-8

32. Shannon K, Ball E, Wasserman RL, Murphy FK, Luby J, Buchanan GR. Transfusion associated cytomegalovirus infection and acquired immune deficiency syndrome in an infant. J Pediatr 1983;103:859-63

33. Maloney MJ, Cox F, Wray BB, Guill MG, Haglor J, Williams D. AIDS in a child 5-1/2 years after a transfusion. N Engl J Med 1985;9:312,1256

34. Berkowitz CD, Seidel JS. Spontaneous resolution of cryptosporidiosis in a child with acquired immunodeficiency syndrome. Am J Dis Child 1985;139:967

35. Wykoff RF, Pearl ER, Saulsburg FT. Immunologic dysfunction in infants infected through transfusion with HTLV-III. N Engl J Med 1985; 312:294-6

36. Cox F, Wray B, Chaudhary, Karlson K, Sherwood B, Greenberg M. Transfusion-associated acquired immunodeficiency syndrome in a twin infant. Ped Inf Dis 1985;4:106-8

37. Hardy AM, Allen Jr, Morgan WM et al. The incidence rate of acquired immunodeficiency syndrome in selected populations. JAMA 1985;253:215-20

38. Peterman TA, Jaffe HW, Feorina PM et al. Transfusion-associated acquired immunodeficiency syndrome in the United States. JAMA 1985; 254:2913-7

39. Marmor M, Friedman-Kien A, Bolla-Pazna S et al. Kaposi's sarcoma in homosexual men. Ann Int Med 1984;100:809-15

40. Shearer GM, Levy RB. Blood transfusion and susceptability to AIDS. N Engl J Med 1985;310:1601

41. Jason J, Hilgartner M, Homan MS et al. Immune status of blood product recipients. JAMA 1985;253:1140-5

42. Jascon P, Zoumbos NC, Young NS. Immunological abnormalities in patients receiving multiple blood transfusions. Ann Int Med 1984; 100:173-7

43. Heberman RB, Ortaldo JR. Natural killer cells: their role in defenses against disease. Science 1981;214:24-30

44. Uksila J, Lassila O, Hirvonen T et al. Development of natural killer cell ???? in the normal fetus. J I Manual 1983;130:153-6

45. Bryam YJ, Winter HS, Gard SE et al. Deficiency of immune interferon production by leukocytes of normal newborns. Cell Immunol 1980;55:191

46. Advance Report of Final Natality Statistics. National Center for Health Statistics. Monthly Statistics Report 1982;33:1-44

47. Powell-Grisner E. Perinatal Mortality in the United States 1950-1981. Monthly Statistics Report 1986;34:1-16

48. Williams AE, MacDonald M, Luban NLC et al. Low incidence of neonatal posttransfusion cytomegalovirus associated with the use of washed red blood cell products. Transfusion 1984;24:130

49. Jason J, McDougal S, Holman RC, et al. Human T-lymphotropic retrovirus type III/lymphadenopathy associated virus antibody. JAMA 1985; 253:3409-15

50. Adler SP. Neonatal cytomegalovirus due to blood CRC. Crit Rev Clin Lab Sci 1985;23:1-14