AIDS
MEMORANDUM
Acquired Immune Deficiency Syndrome

National Institute of Allergy and Infectious Diseases

Volume 1, Number 1 August 1983

IN THIS ISSUE

INTRODUCTION

This is the first issue of the AIDS Memorandum. This Memorandum is being published by the National Institute of Allergy and Infectious Diseases to provide a centralized forum for the rapid but informal dissemination of new clinical and experimental findings on AIDS. It is also intended that, in the Memorandum, novel ideas about the disease can be aired among members of the wide scientific audience concerned with this syndrome. To date, despite the diversity of approaches to research and treatment which have been taken by immunologists, epidemiologists, oncologists, virologists, parasitologists, internists, molecular biologists and others, AIDS remains a mysterious, devastating, lethal disease.

The AIDS Memorandum is modeled on other scientific memoranda, such as the Hepatitis, Leprosy, and Interferon Scientific Memoranda. The formats used for all memoranda include certain specific features which distinguish them from the standard journals with which every researcher is familiar. Because AIDS is a uniquely political disease, the format and the ground rules (see Page 2) devised specifically for the AIDS Memorandum consider, in addition, how proper use and accurate representation of information printed in the Memorandum can be guaranteed such that the professional interests of contributors will be protected.

The AIDS Memorandum will print preliminary data, negative findings, single case reports, and other types of material not ready or, in some cases, suitable for publication in formal journals. The expeditious sharing of these types of data may serve an important role in the eventual development of regimens for successful disease control. Material

submitted to the Memorandum will not be sent out for scientific review but will undergo review by the Memorandum's scientific and editorial staffs, so that the lag time between receipt of a manuscript and its distribution will be short (from 1 to 4 weeks). No information printed in the Memorandum can be cited except as prescribed in the ground rules. This caveat is intended to insure that publication of information in the Memorandum will in no way jeopardize or preclude future publication of refined, validated, or altered data in a formal journal. The Memorandum will be circulated only to researchers who contribute to it, so that a true information exchange can be effected.

This first issue of the Memorandum contains two articles describing experimental findings, related information about obtaining nonhuman primates for AIDS research and recommended safety precautions to be taken when experimental animals are used in AIDS studies, lists of available AIDS bibliographies and upcoming AIDS meetings, the latest case statistics reported by the Centers for Disease Control, and a questionnaire for users of the Memorandum. Future issues are expected to be more heavily weighted with original research findings. Researchers who have information to contribute can consult the Instructions for Authors found on the back page of the Memorandum.

This Memorandum is for its users. Its value and its success will depend on user participation.

GROUND RULES FOR USE OF THE AIDS MEMORANDUM

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Users must agree not to cite material from the Memorandum without first obtaining the consent of the author(s), and, with author permission, to cite information only as a personal communication. Author addresses are provided for this purpose.

Users must agree to contribute data or ideas to the Memorandum at least once a year. On an annual basis, the names of individuals who have not contributed to the Memorandum will be culled from the mailing list, so as to limit circulation of the Memorandum only to individuals actively working in the field.

Finally, users must agree to share material in the Memorandum only with other individuals willing to honor these ground rules.

SEARCH FOR ANTIBODY TO CANINE PARVOVIRUS (CPV) ANTIGEN IN SERA FROM AIDS PATIENTS

AIDS patients die of many different opportunistic infections. However, to date, no opportunistic organism has been shown to be the initiator of the disease syndrome. Because AIDS is a new disease,

totally unrecognized before June 1981, the possibility exists that it is caused by a new, mutant strain or recombinant agent which evolved and acquired new pathological potential and host specificity.

This report describes a study of one candidate etiologic agent, CPV. It is one of the small DNA parvoviruses, a group in which some members have shown marked evolutionary changes in both virulence and host specificity. The parvoviruses, unrecognized 15 to 18 years ago, are now found to be widespread throughout the animal kingdom.

One member of the group recently has been shown to be responsible for a number of disease syndromes in man. This virus, originally called B-19 (Cossart YE, Field AMM, Cant B, et al: Lancet, 1975, 1:72-73), has been shown to cause aplastic crises in patients with sickle cell anemia (Serjeant GR, Topley JM, Mason U, et al: Lancet, 1981, 2:595-597), hereditary spherocytosis (Kelleher JF, Luban NLC, Mortimer PP, et al: J Pediatr., 1983, 102:770-772), and pyruvate kinase deficiency (Duncan JR, Cappellini MD, Anderson MJ, et al: Lancet, 1983, 2:14-16). B-19 also has been shown to be responsible for erythema infectiosum (fifth disease) (Anderson MJ, Jones SE, Fisher-Hoch SP, et al: Lancet, 1983, 1:1378).

Another parvovirus was found to be responsible for an explosive, highly virulent, acute enteritis epidemic in dogs which occurred worldwide in 1978. The agent was new to dogs, since no antibody was found in samples collected prior to 1978. The responsible parvovirus is serologically related to feline panleukopenia virus (FPV) and to the virus which causes mink enteritis (Carmichael LE, Jourbert JC, Pollock RVH, et al: Am J Vet Res., 1980, 40:784-791). Although minor differences in these viruses allow them to be distinguished serologically, they are so closely related that they can be used reciprocally for vaccination purposes.

Another parvovirus, the minute virus of mice, has shown a marked change in both virulence and host cell preference. These changes resulted from a single mutation, a 40-50 base deletion (McMaster GK, Beard P, Engers HD, et al: J Virol., 1981, 38:317-326).

The possibility that a parvovirus could be the etiologic agent of AIDS fit with the timely appearance of CPV in the canine population and with the known ability of FPV to cross species barriers. Therefore, AIDS serum samples and various control serum samples were tested for the presence of antibody to CPV antigen.

A CPV tissue culture antigen, supplied by Dr. Leland Carmichael (State College of Veterinary Medicine, Cornell University, Ithaca, New York), was used in three in vitro assay systems: complement fixation (CF), hemagglutination inhibition (HI), and immune adherence hemagglutination (IAHA). The results of preliminary tests with dog serum samples known to be CPV positive and CPV negative are given in the table.

RECIPROCAL ANTIBODY TITER USING
4-8 ANTIGEN UNITS

Dog Serum	CF	HI	IAHA
CPV+	8	1024	1600
CPV-	<10	<10	<10

In addition to the control dog serum samples, a total of 124 human serum samples were tested. These included sera

from 42 homosexual men without AIDS, sera from 14 AIDS patients without Kaposi's sarcoma, sera from 28 AIDS patients with Kaposi's sarcoma, sera from 36 at-risk men with lymphadenopathy but not AIDS, and sera from 4 AIDS patients who used intravenous drugs. CPV antibody was not found in any of the 124 serum samples tested.

M. David Hoggan, Laboratory of Viral Diseases; Doris C. Wong and Robert H. Purcell, Laboratory of Infectious Diseases; National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20205.

DETERMINATION OF HELPER:SUPPRESSOR RATIOS IN CHIMPANZEE PERIPHERAL BLOOD LYMPHOCYTE SUBPOPULATIONS BY TWO-COLOR FLUORESCENT ANALYSIS

The characteristics of subpopulations of peripheral blood lymphocytes (PBLs) isolated from chimpanzees were defined and compared with the characteristics of similar cell preparations from human blood. Heparinized whole blood was layered onto gradients of Ficoll-Hypaque, and lymphocytes were collected. Surface characteristics of fresh or cryopreserved PBLs were analyzed using the fluorescence-activated cell sorter II (FACS II) and the Leu series of anti-T cell reagents: Leu 1-FITC, a pan-T cell marker; Leu 2-phycoerythrin, staining suppressor/cytotoxic cells; and Leu 3-FITC, staining helper/inducer cells. Following subpopulation enrichment, various functional assays were performed.

Chimpanzee and human PBLs were sorted, and four subpopulations were defined: I:Leu 1-, Leu 2-; II:Leu 1-, Leu 2+; III:Leu 1+, Leu 2+; IV:Leu 1+, Leu 2-. A representative sort is shown in Figure 1 for chimpanzee blood and in Figure 2 for human blood.

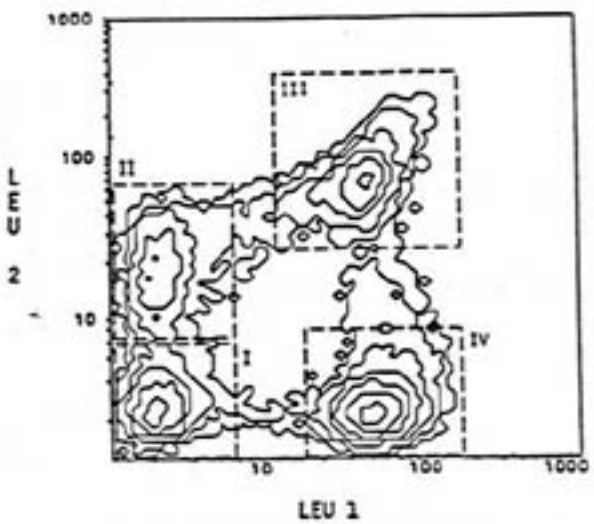


Fig. 1. Cryopreserved Unfractionated Chimpanzee Peripheral Blood

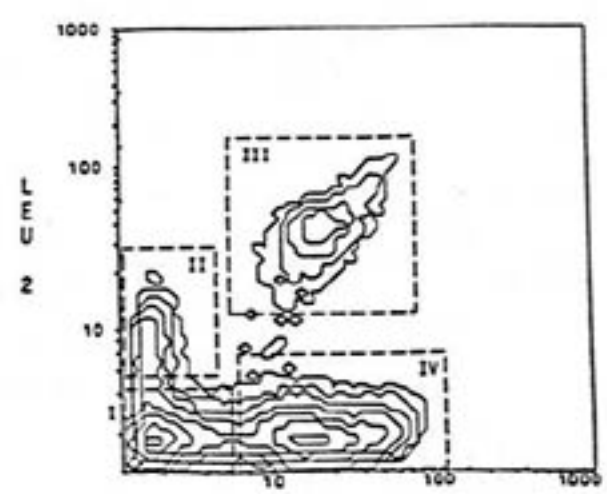


Fig. 2. Cryopreserved Unfractionated Human Peripheral Blood

A major difference in cell subpopulations was found when chimpanzee and human cells were compared. Leu 1-, Leu 2+ cells (subpopulation II) were increased in chimpanzee PBLs (Fig. 1 and Table 1) and, interestingly, were also found to be extremely high (12.5%) in human cord blood. This subpopulation accounted for only a small percentage of cells in adult human PBLs. The percentage of Leu 1-, Leu 2- cells (I) in the chimpanzee was low, and the drop compensated almost entirely for the Leu 1-, Leu 2+ cell enrichment.

TABLE 1

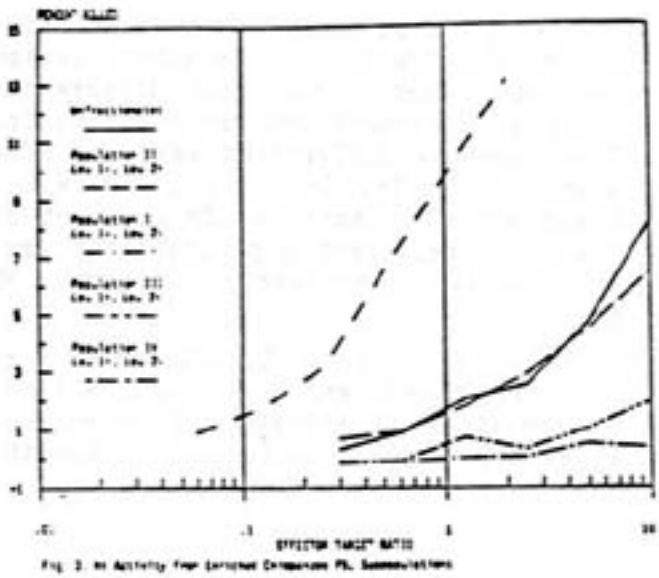
LEU 1 BY LEU 2 TWO-COLOR ANALYSIS OF PERIPHERAL BLOOD LYMPHOCYTES FROM CHIMPANZEES AND HUMANS

	Percent*		
	Adult Chimpanzee (>9 Kg)	Adolescent Chimpanzee	Adult Human
Leu 2+	31.4	24.4	22.7
Leu 1+	67.8	74.7	68.8
Leu 1+ + Leu 2+	81.7	82.9	74.6
Leu 1-, Leu 2-	18.3	17.1	25.3
Leu 1+, Leu 2-	50.3	59.5	51.9
Leu 1-, Leu 2+	13.9	8.2	5.8
Leu 1+, Leu 2+	17.5	15.2	16.9

* Average percentages from 10 humans and 8 chimpanzees.

In an experiment using all Leu 1- cells (population I plus population II) prepared from fresh cells, no proliferative activity was found when cells were incubated with three T cell mitogens, Con A, PHA, and PWM, each tested over a 100-fold range. However, all Leu 1- cells showed natural killer cell (NK) activity.

NK activity was further studied using re-sorted, enriched subpopulations. The Leu 1-, Leu 2+ subpopulation was enriched eight-fold, using a two-color quantitative sort of cryopreserved cells. NK activity was likewise enriched 8- to 10-fold (Fig. 3). Similar enrichment of Leu 1-, Leu 2- cells did not



result in comparable enrichment in NK activity. The residual NK activity found in the Leu 1-, Leu 2- population may derive from a less mature population of NK cells.

Of all the Leu 2+ cells in blood, the Leu 1-, Leu 2+ subpopulation comprised a significant fraction in adult chimpanzee samples (44%) and a smaller fraction in both adolescent chimpanzee samples (34%) and adult human samples (26%). These cells stained as suppressor/cytotoxic cells but not with a pan-T cell reagent. Their presence or absence in materials used in measuring helper:suppressor ratios markedly altered ratio values (Table 2). In addition, ratios measured

TABLE 2

HELPER:SUPPRESSOR RATIOS

	Adult Chimpanzee	Adolescent Chimpanzee	Adult Human
Leu 1+, Leu 2-: Leu 1+, Leu 2+	2.9:1	3.9:1	3.0:1
Leu 1+, Leu 2-: All Leu 2+	1.6:1	2.4:1	2.2:1

on Leu 1- cell populations which included the Leu 1-, Leu 2+ subpopulation indicated that there were differences between chimpanzee and human materials. These species differences were not seen when the Leu 1-, Leu 2+ cells were removed from the samples. This subset of cells may represent a phylogenetic (and ontogenetic?) precursor of the human NK cell.

T. Folks, D. Portnoy, L. Edison, R. Purcell, T. Chused, and K. W. Sell, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20205.

NONHUMAN PRIMATE RESOURCES FOR AIDS RESEARCH

Researchers who need help in finding nonhuman primates for AIDS studies should contact Dr. Thomas Wolfle, Executive Director, Interagency Research Animal Committee, Bldg. 12A, Room 4003, National Institutes of Health, Bethesda, MD 20205. Phone: (301) 496-5424.

The Interagency Research Animal Committee* (IRAC) can locate animals of all species of nonhuman primates. At this time, chimpanzees are the principal nonhuman primates of interest in AIDS studies: they have close evolutionary ties to humans, and they are unique among nonhuman primates in demonstrating a susceptibility to hepatitis B virus and other infectious agents. Because chimpanzees are an endangered species, only limited numbers of animals currently are available in domestic colonies.

IRAC plans to develop a registry of all nonhuman primates used in AIDS research projects. The registry will also serve as a central repository for information about ongoing AIDS studies in nonhuman primates, so that redundancy in experimental studies can be avoided.

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*IRAC, formerly IPSC, the Interagency Primate Steering Committee, was established in 1974. The committee includes representatives of the National Science Foundation, the Department of Defense, the Environmental Protection Agency, the Veterans Administration, the State Department, and the Department of Health and Human Services. The role of the committee is one of assuring that both short-term and long-term supplies of nonhuman primates will be available for biomedical research and other essential health activities.

SAFETY PRECAUTIONS FOR HANDLING EXPERIMENTAL ANIMALS USED FOR AIDS RESEARCH

The safety precautions advised for personnel involved with AIDS research were published in Morbidity and Mortality Weekly Reports in November 1982. The precautions specific to laboratory personnel handling experimental animals are reprinted here. Other portions of the recommendations will be reprinted in future issues of the AIDS Memorandum.

These precautions are advised for studies involving experimental animals inoculated with tissues or other potentially infectious materials from individuals with known or suspected AIDS.

- Laboratory coats, gowns or uniforms should be worn by personnel entering rooms in which inoculated animals are housed. Certain nonhuman primates, such as chimpanzees, may throw excreta and spit at attendants. Some animals may disturb excreta in their bedding when

they are handled. Therefore, personnel attending such animals should wear molded surgical masks and goggles or other equipment effective in preventing potentially infective droplets from reaching the mucosal surfaces of the mouth, nares and eyes.

- Personnel should wear gloves for all activities involving direct contact with experimental animals, their bedding and cages. Such manipulations should be performed carefully to minimize the creation of aerosols and droplets.
- Personnel should wear gowns and gloves for necropsy of experimental animals. If procedures are performed which generate aerosols, masks and goggles should be worn.
- Extraordinary care should be taken to avoid accidental sticks with needles or cuts with sharp instruments which may be contaminated with body fluids or tissues of experimental animals inoculated with material from AIDS patients.
- Animal cages should be decontaminated, preferably by autoclaving, before they are cleaned and washed.
- Only needle-locking syringes or one-piece needle-syringe units should be used to inject potentially infectious fluids into experimental animals.

The above precautions should be taken in both clinical and research laboratories. Biological safety cabinets and other safety equipment may not be generally available in clinical laboratories. If not, assistance should be sought from a microbiology laboratory to assure that containment is adequate to permit laboratory tests to be conducted safely.

AIDS BIBLIOGRAPHIES

Four bibliographies listing articles about AIDS are currently available.

AIDS Bibliography
(and monthly updates)
National Institute of Allergy
and Infectious Diseases
Building 5, Room 432
Bethesda, MD 20205

Free to individual scientists and clinicians and any organization.

AIDS Literature Search,
Updates and Supplements
National Library of Medicine
Reference Section
8600 Rockville Pike
Bethesda, MD 20209

Include name and address typed on a gummed label.

Gays and Acquired Immune
Deficiency Syndrome
Canadian Gay Archives
Box 639, Station A
Toronto, ON M5W 1G2
Canada

$4.00

AIDS: A Research and Clinical
Bibliography
The AIDS/KS National Foundation
54 Tenth Street
San Francisco, CA 94103

$5.00

AIDS CASES REPORTED TO THE CENTERS FOR DISEASE CONTROL AS OF AUGUST 8, 1983

UNITED STATES CASES

DISEASE	CASES	PERCENT OF TOTAL	DEATHS	PERCENT DEAD
KS without PCP	533	26.5	109	20.5
PCP without KS	1016	50.6	447	44.0
Both KS and PCP	148	7.4	80	54.1
OI without KS or PCP	311	15.5	138	44.4
TOTAL	2008	100.0	774	38.5

KS = Kaposi's sarcoma PCP = Pneumocystis carinii pneumonia
OI = Opportunistic infections

	MALES		FEMALES		TOTAL	
RISK GROUPS*	CASES	% OF TOTAL	CASES	% OF TOTAL	CASES	%
Homosexual or bisexual	1427	76.0	0	0.0	1427	71.1
IV drug user	273	14.5	66	50.8	339	16.9
Haitian	91	4.9	14	10.8	105	5.2
Hemophiliac	15	0.8	0	0.0	15	0.7
No apparent risk group or unknown	72	3.8	50	38.4	122	6.1
TOTAL	1878	100.0	130	100.0	2008	100.0

* The risk groups listed are hierarchically ordered; cases with multiple risk factors are tabulated only in the risk group listed first.

CASES REPORTED FROM OTHER COUNTRIES

NUMBER OF COUNTRIES	CASES
20	123

U.S. AND FOREIGN CASES REPORTED

TOTAL	2131

QUESTIONNAIRE FOR USERS OF THE AIDS MEMORANDUM

The questionnaire reprinted below was sent to potential users of the AIDS Memorandum. Anyone who did not receive the questionnaire at that time but would like to comment on the questions now is encouraged to send his/her comments to

AIDS Memorandum
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Building 5, Room 432
Bethesda, MD 20205

Are you familiar with the memorandum format?

If yes, have you contributed to a memorandum in the past?

Would you be willing to contribute to the AIDS Memorandum?

If no, why not?

If yes, what types of contributions would you be most likely to make?

Case reports
Positive experimental results
Negative experimental results
Positive clinical observations
Negative clinical observations
Commentaries Queries
New methodologies Theories
Others (Please describe)

Do you think this format fills a need which is not filled elsewhere?

If no, where is the need filled?

Letters to NEJM or Science
Rapid Publications in JCI
Elsewhere (Please describe)

What would make the AIDS Memorandum a valuable resource for you?

UPCOMING AIDS MEETINGS

Registration is still open for the following upcoming AIDS meetings.

NIH Workshop on the Epidemiology of AIDS
September 12-13, 1983
Holiday Inn, Crowne Plaza,
Rockville, MD

Program Information:
Robert Edelman, M.D.
(301) 496-5893
National Institute of Allergy
and Infectious Diseases
Building 31, Room 7A49
Bethesda, MD 20205
Registration Information:
Mr. Mark S. Brown
Social and Scientific Systems, Inc.
(301) 656-6346

ICAAC Symposium on AIDS
October 24-25, 1983
Las Vegas Hilton Hotel
Las Vegas, Nevada

Mr. Richard Bray
(202) 833-9680
American Society of Microbiology
1913 Eye Street, N.W.
Washington, D.C. 20006

International Conference on AIDS
November 14-17, 1983
Roosevelt Hotel, New York City

Conference Department, New York
Academy of Sciences
2 East 63rd Street
New York, NY 10021

Pre-registration by mail will begin at the end of September. Pre-registration is necessary because seating is limited.

INSTRUCTIONS FOR AUTHORS
CONTRIBUTING TO THE AIDS MEMORANDUM

Content: Articles published in the AIDS Memorandum must have obvious relevance to AIDS. They can describe clinical or experimental findings. Letters and other types of commentary are also welcome. In all cases, the text should be limited to 1000 words.

References: References should be integrated into the text in parentheses. Each citation should include journal title, year of publication, volume and issue numbers and inclusive page numbers. Citations from books should include book title, editor(s), publisher, year of publication and relevant page numbers.

Tables: Whenever possible, data should be organized into tables rather than figures.

Announcements of Meetings: Announcements of upcoming AIDS meetings should include meeting title, location and date and the name, address and telephone number of the organizer of the meeting.

Further Information: For further information call the AIDS Memorandum office at (301) 496-9537.

Mailing Instructions: Manuscripts for the AIDS Memorandum should be sent to this address:

AIDS Memorandum
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Building 5, Room 135
Bethesda, Maryland 20205

AIDS Memorandum
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AIDS
MEMORANDUM
Acquired Immune Deficiency Syndrome

National Institute of Allergy and Infectious Diseases

Volume 1, Number 2 October 1983

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RESPONSES TO THE AIDS MEMORANDUM QUESTIONNAIRE

In late summer, a questionnaire (reprinted in the first issue of the AIDS Memorandum) was mailed to everyone whose name was on the Memorandum mailing list. About 60% of the questionnaires were completed and returned, and a number of thoughtful comments and suggestions were made. In general, respondents expressed a willingness to share observations, ideas, and experimental findings. Over 90% said they would be willing to contribute to future issues of the Memorandum.

Several respondents pointed out that the Memorandum could serve the purposes generally served by meetings and the grapevine, providing clinicians and researchers with opportunities to communicate easily and frequently, pose questions for each other, and benefit from each others' insights. This is clearly the intention of the Memorandum.

Many people wrote that they would find the Memorandum of use as it was defined in the cover letter accompanying the questionnaire. Many suggested additional and/or more specific ways in which the Memorandum could be of special value to them. Most respondents were unfamiliar with the Memorandum format and unaccustomed to sharing, in writing, preliminary ideas and data. Therefore, to help spark in Memorandum participants ideas about the kinds of information which might be shared through the Memorandum, some of the specific requests for information are described here.

In the area of patient care, a number of specific requests were made. Respondents wanted information describing newly recognized clinical associations, autopsy findings, comparisons of AIDS with similar conditions found in transplant recipients, newly defined laboratory abnormalities which might be closely associated with the disease, and disease manifestations in specific patient groups. In addition, respondents expressed interest in exchanging ideas about methods for screening patients and advising and informing them about AIDS, about any therapeutic advances and/or promising treatment protocols which may arise, and about new strategies for improving patient care.

Other comments concerned laboratory data. The feeling was widely held that the exchange of negative data would provide an important opportunity for workers in the field to avoid dead ends and to benefit from the experiences and mistakes of others. Several respondents pointed out that the provision of a general overview of the status of ongoing experiments would be invaluable, especially if a willingness to submit recent work were coupled with presentation of data in sufficient detail to permit peer review of the merits of the work. Respondents wanted technical exchanges of various kinds, such as information on how and where to store biopsy materials and blood samples. They also wanted data describing the results of experiments using animal model systems.

Several respondents anticipated that the Memorandum could be of value in helping them establish worthwhile collaborations. This could happen in two steps, first, through heightened awareness of work carried out by other groups and, second, through periodic publication of a list of Memorandum participants.

Many respondents commented on the importance of a rapid turnover time for new information and leads. One suggested that, at a minimum, the AIDS Memorandum

should precede newspapers in delivering the "news." One economy-minded respondent was pleased that the Memorandum was free.

Some concern was expressed that the ground rule requiring all participants to contribute information or ideas to the Memorandum annually would have two negative effects: it would make the Memorandum unavailable to those who might benefit from the information in it but might not be able to contribute to it, and it would encourage participants to send in "junk" in order to remain on the mailing list. The example cited in support of the former concern was of an ophthalmologist who saw only one or two AIDS patients a year. Such a clinician can contribute a single case report each year or, perhaps more importantly, an insight into or thought about some clinical feature of the syndrome. With regard to the second concern, although the Memorandum is not a journal, articles are reviewed and edited, in some cases heavily, by the scientific editorial staff of the Memorandum. The mandatory participation policy has worked for all other memoranda in the past and was adopted to encourage and to promote active involvement in the Memorandum by all active AIDS workers.

Any additional thoughts on and answers to the question "What would make the AIDS Memorandum a valuable resource for you?" would be welcome at any time. The AIDS Memorandum is a forum for the exchange of ideas and data about the many problems associated with this syndrome which, to date, has eluded all efforts at solution.

EXPERIMENTAL TRANSMISSION OF SIMIAN AIDS AND KAPOSI'S-LIKE SKIN LESIONS

A spontaneous disease which is similar to human AIDS has been found to occur in monkeys. Simian AIDS (SAIDS) was transmitted experimentally from two California rhesus monkeys dying of the disease to four NIH rhesus monkeys which, at the time of inoculation, were negative for cytomegalovirus (CMV) antibody. The inocula consisted of the supernatant fluid from 10% homogenates of various tissues with or without buffy coat cells from blood.

Recipient animals developed lymphadenopathy, splenomegaly, neutropenia, polymyositis, and other signs of the disease within a few weeks after inoculation. Two animals developed Kaposi's-like "patch" and "plaque" skin lesions, and one animal died with sepsis and profound lymphoid depletion. All animals became infected with CMV; however, antibody levels were low in two animals, appeared and then disappeared in one animal, and never developed in the one monkey which died.

This abstract describes data presented in an article which has been accepted for publication in The Lancet.

W. T. London, J. L. Sever, D. L. Madden, R. V. Henrickson, M. Gravell, D. H. Maul, M. C. Dalakas, K. G. Osborn, S. A. Houff, and M. B. Gardner. Infectious Diseases Branch, Neurological and Communicative Disorders and Stroke, National Institutes of Health, Bethesda, Maryland 20205; and California Primate Research Center and Department of Medical Pathology, University of California, Davis, California 95616.

SERUM PROFILES OF PNEUMOCYSTIS CARINII (PC) ANTIGENS AND ANTIBODIES IN AIDS PATIENTS

Serum profiles were determined for patients meeting the Centers for Disease Control criteria for AIDS and having biopsy diagnosed and/or clinically diagnosed Pneumocystis carinii pneumonia (PCP). PC antigenemia was measured by counterimmunoelectrophoresis (CIE) (Pifer LL, Hughes WT, Stagno S, et al: Pediatrics, 1978, 61:35-41; Pifer LL: Pediatr Infect Dis., 1983, 2:177-183). Anti-PC IgG titers were measured by an enzyme-linked immunosorbent assay (ELISA) (Pifer L, Niell H, Neely C, et al: Proc 19th Am Soc Clin Oncol., 1983, 2:abstract C-191).

Ten AIDS patients with PCP were tested for PC antigenemia. Of these 10, five had AIDS and Kaposi's sarcoma, one was a heroin addict, one was an infant with hemophilia, two had homosexual life styles as the only known risk factors, and one had no known risk factors. During their clinical courses with PCP, 9/10 (90%) exhibited PC antigenemia. None of 44 controls exhibited antigenemia; of these, 23 were volunteer blood donors from Memphis, Tennessee, and 21 were local, asymptomatic homosexual males.

In many cases of PCP, antigenemia appears in the subclinical or prodromal period. The results presented here suggest that the PC antigen test may prove useful as an early, noninvasive diagnostic test for PCP in AIDS patients.

Seventy-five percent of the AIDS patients referred for PC serology had anti-PC antibody (IgG) titers ranging from 1:128 to 1:512 by ELISA analysis. Over 75% of the healthy volunteer blood donors had titers of 1:256 or greater. In contrast, 76% of asymptomatic homosexual males had titers of 1:64 or less (Table).

ELISA IgG TITERS TO PC

PC IgG Titer	Asymptomatic Homosexual Males		AIDS Patients*		Healthy Volunteer Blood Donors	
	No.	(%)	No.	(%)	No.	(%)
1:16	17	(26)	2	(8)	0	(0)
1:32	17	(26)	1	(4)	0	(0)
1:64	16	(24)	1	(4)	2	(9)
1:128	14	(21)	6	(25)	1	(4)
1:256	1	(1.5)	7	(29)	3	(13)
1:512	1	(1.5)	5	(21)	14	(61)
1:1024	0	(0)	2	(8)	3	(13)
	—		—		—	
	66		24		23	

* All of these sera were referred to our laboratory from other states for PC serologic profiles.

It has been well documented that total IgG and IgA levels in AIDS patients are either within normal limits or elevated (Rogers MF, Morens DM, Stewart JA, et al: Ann Intern Med., 1983, 99:151-158). The preliminary data presented here show a difference in the specific humoral responses to PC in patients with AIDS and in asymptomatic homosexual males when compared with the responses in normal controls. AIDS patients have lower antibody titers than do normal controls, but their titers are not as low as those of the asymptomatic homosexuals. This suggests the possibility that some factor in the homosexual lifestyle is altering immune responsiveness. A reversal in the T helper/suppressor cell ratio has, for example, been established (Kornfield H, Van Stouwe RA, Lange M, et al: N Engl J Med., 1982, 307:729-731). Such a change may adversely affect the processing of PC antigens or may impair the natural process by which a normal antibody titer to PC is achieved and maintained. The finding of higher titers of anti-PC antibodies in AIDS patients as compared with asymptomatic homosexual controls is consistent

with the diagnosis of PCP in AIDS and with the clinical course of PCP which involves host humoral immune responses for resolving infection. Further investigations will be required to clarify the full significance of these preliminary findings.

Our laboratory will test specimens from AIDS patients for PC antigen and for antibody to PC. The tests will be performed without charge, although the sender must assume air freight charges. Please phone (901) 528-5942 or (901) 528-5932 for details.

L. L. Pifer, H. B. Niell, C. L. Neely, C. C. Edwards, and D. R. Woods. Immunology Laboratory, The University of Tennessee, Center for the Health Sciences, Memphis, Tennessee 38163.

AN ANALYSIS OF *PNEUMOCYSTIS CARINII* PRE-MORTEM AND POST-MORTEM IN AIDS

Pneumocystis carinii pneumonia (PCP) is the most common clinical feature of AIDS, having been identified in 58% of patients to date (CDC Surveillance data). However, little has been written on the prevalence of *Pneumocystis carinii* (PC) in autopsy specimens of patients who die of AIDS (Masur H, Michelis MA, Greene JB: *N Engl J Med.*, 1981, 308:1431-1438).

Forty-one AIDS patients were examined for evidence of PC organisms at autopsy, and many of these were also evaluated pre-mortem. The population consisted of 23 Haitians, 13 homosexual men, four intravenous drug abusers, and one hemophiliac. For all patients, at least one section of lung was stained with a Gomori-methenamine silver stain for PC, regardless of whether eosinophilic alveolar exudates were present or not.

PCP was diagnosed either pre-mortem, post-mortem, or both in 21 of the cases (51%). A pre-mortem diagnosis of PCP was made by identifying PC in lung tissues in 14 of the 41 cases (34%). Of these 14, PC could also be detected at autopsy in nine patients, and the cause of death was considered to be PCP in seven patients. The mean duration of clinical PCP from the time of tissue diagnosis to autopsy in the nine patients showing PC both pre-mortem and post-mortem was 20 days (range: 6 to 38 days). The therapy for PCP consisted of either trimethoprim and sulfamethoxazole or pentamidine; both of these may have toxic effects, especially in AIDS patients (Mitsuyasu R, Groopman J, Volberding P: *N Engl J Med.*, 1983, 308: 1535). The therapy appeared to be effective in controlling PC in only those five patients in whom organisms were not seen at autopsy.

A post-mortem diagnosis of PCP was made by identifying PC in the autopsy specimens from 16 of the 41 cases (39%). Eleven of these patients had previously been shown to have PC pre-mortem. The cause of death in 11 patients was attributed to PCP; in seven of these, PC was detected during life while in four PC was detected only post-mortem. Death in two of the cases was considered to be caused by PCP, although disseminated cytomegalovirus infection could not be excluded with certainty. There were two additional cases for which PCP was not considered to be the primary cause of death, although PCP certainly was a significant secondary contributory cause of death. In another three cases positive at autopsy for PC but for which the cause of death was not PCP, only rare foci were present in the lungs and should not have been significant clinically.

The diagnosis of PCP in 51% of AIDS cases reported in this paper is similar to the national figure of 58%.

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CYCLOSPORIN IMMUNOSUPPRESSION AS THE POSSIBLE CAUSE OF AIDS

Many investigators have suggested that AIDS is caused by a transmissible infectious agent, most probably a virus (Curran J: N Engl J Med., 1983, 309:609-610). We propose that a non-viral infectious agent may act either as the primary causative agent of AIDS or as a secondary agent responsible for maintaining the disease state. Our hypothesis suggests that the severe impairment of the immune system and the subsequent fatal opportunistic infections in AIDS result from the systemic release of a potent cyclosporin-like immunosuppressive molecule from a fungal infectious agent.

Three different strains of the same fungal species have been isolated from long-term monocyte cultures of three AIDS patients. Simultaneous culture and examination of six normal human control monocyte cultures in the same culture plate showed no fungal growth or contamination. The fungal strains have been identified as atypical isolates of Thermoascus crustaceus (Dactylomyces crustaceus). Unlike the majority of soil or plant fungi, their optimum growth temperature is 37°C. Such fungi, including other species of Thermoascus, have never previously been isolated at the National Institutes of Health from either patients or normal individuals. They are unique isolates from clinical material from patients with AIDS.

The mycelia of these isolates contain a cyclosporin-like compound (CyAIDS) as detected by high-pressure liquid chromatography (HPLC) analyses. CyAIDS was found in high concentration near the reference peaks for cyclosporin A (CyA) and cyclosporin D standards (provided by Sandoz, Ltd). Mass spectrographic analyses of these samples are underway.

CyAIDS was also found in plasma samples studied by HPLC. Four out of four samples from patients with AIDS had CyAIDS peaks. The level of CyAIDS in the plasma of one patient was estimated to exceed 1,000 ng/ml. Two control blood samples failed to show significant levels of cyclosporin-like peaks. In contrast to these findings, no significant plasma cyclosporin levels could be measured in a radioimmunoassay for cyclosporin using a polyclonal sheep anticyclosporin antibody (provided by Sandoz, Ltd) (A. Palestine, personal communication). It is possible that CyAIDS produced by the fungi isolated from AIDS patients is sufficiently distinct immunologically that it cannot be detected by the sheep antibody. (Several different types of cyclosporins have been identified so far.) It is also possible that the AIDS patients produce antibodies against CyAIDS, and these could interfere with the radioimmunoassay.

The cyclosporins are hydrophobic, cyclical, neutral peptides containing 11 amino acids and having molecular weights of approximately 1,200 daltons (Wenger R: in White DJG (Ed): Cyclosporin A: Proc Int Conf CyA, Elsevier Biomed Press, 1982, 19-34). The CyA currently licensed by Sandoz for use in

transplantation (see below) is produced from a soil fungus strain originally classified as Trichoderma polysporum Rifai and now identified as Tolipocladium inflatum Gams (Borel J: in White DJG (Ed): Cyclosporin A: Proc Int Conf CyA, Elsevier Biomed Press, 1982, 5-17).

CyA is well known as a potent immunosuppressive substance. The mycelial extracts from Sabouraud broth cultures were observed to have an immunosuppressive effect in the mixed leukocyte culture assay. CyA has been shown to cause immunosuppression by inhibiting the production of interleukin-2 (IL-2) (Wagner H: Transplant Proc., 1983, 15:523-526) and by inhibiting the expression of IL-2 receptors on T helper cells (Palacios R, Moller G: Nature, 1981, 290:792-794). CyA also inhibits synthesis of gamma interferon (Reem G, Cook L, Vilcek J: Science, 1983, 221:63-65). When T cells are co-cultured with antigen or mitogen in the presence of CyA, they will not be transformed into activated cells. However, once a T cell expresses cytotoxic activity, it becomes resistant to the action of CyA. T suppressor functions are apparently not affected by CyA (Borel J: Transplant Proc., 1983, 15: 1881-1885).

Cyclosporin is used to induce immunosuppression following transplantation. Two to 13% of patients immunosuppressed in this way develop opportunistic infections and malignancies. In some cases, these effects may represent reactivation of Epstein-Barr virus (Sheil AGR: Transplant Proc., 1977, 9:1133-1138; Bird AG: in White DJG (Ed): Cyclosporin A: Proc Int Conf CyA, Elsevier Biomed Press, 1982, 307-315). One known effect of CyA therapy in man is the reversal of the T helper to T suppressor ratio through depletion of the number of T helper cells (Kerman RH, Van Buren CT, Flechner S, et al: Transplant Proc., 1983, 15:1971-1973). CyA therapy in dogs causes lassitude, fatigue, weight loss, diarrhea, and elevated globulin levels (Ryffel B: in White DJG (Ed): Cyclosporin A: Proc Int Conf CyA, Elsevier Biomed Press, 1982, 45-75).

Plasma from AIDS patients exerts an inhibitory effect on normal lymphocytes. It prevents such cells from responding to mitogens or to allogeneic lymphocytes (Cunningham-Rundles S, Michelis M, Masur H: J Clin Immunol., 1983, 3:156-165). An inhibitory factor in plasma from AIDS patients has been purified and has been shown to be a low molecular weight compound. This compound impairs the production of IL-2 (G. Quinnan, personal communication). Typically, the T cells from AIDS patients fail to develop IL-2 receptors (J. Fahey, personal communication). In vitro, IL-2 can restore the cytotoxic response of lymphocytes from AIDS patients (Rook A, Masur H, Lane C, et al: J Clin Invest., 1983, 72:1-6).

The isolates of T. crustaceus were obtained from monocyte cultures. It seems unlikely that monocytes are the primary targets of infection in AIDS patients. However, if the fungi can grow in monocytes, their transmission would be possible from one individual to another through a needle stick or through blood components.

These results are extremely preliminary. The fungi may simply be contaminants of the monocyte cultures or opportunistic infectious agents in the AIDS patients. More isolations are needed. Further studies of the CyAIDS compounds isolated from both blood from patients with AIDS and mycelia of the fungus will be needed to determine whether the immunosuppressive activity will have any consequence in vivo. The fungus and the CyAIDS may simply be cofactors which,

along with other infectious agents, are necessary for inducing the full impairment of the immune system characteristic of AIDS. However, the types of immunologic impairments typical of AIDS and many of the immunosuppressive activities produced by the cyclosporins are comparable and would be consistent with an active role for a cyclosporin-like molecule in the immune suppression characteristic of AIDS.

This fungus may not prove on further evaluation to be the etiologic agent of AIDS. It is important, however, to consider a wide range of infections and infectious agents which might be responsible for the immunodeficiencies seen in the AIDS patients. It is also important to consider etiologic factors other than infectious agents as possible cofactors or initiators of AIDS.

This article includes information contained also in a letter which has been accepted for publication in the New England Journal of Medicine.

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HISTOLOGIC OBSERVATIONS IN AIDS AND KAPOSI'S SARCOMA (KS)

An etiologic role for bacteria has not been systematically explored in AIDS and KS. This report describes histologic observations made on biopsy materials from a 29-year-old white homosexual man with AIDS and KS. Permission for autopsy could not be obtained in this case.

A lymph node showing reactive hyperplasia was excised and examined with a Fite stain 2 months before the patient's death. Intracellular, purple coccoid forms and large Russell bodies were seen within a stained, acid-fast section of the node. The Russell bodies appeared to develop from the coccoid forms. Staphylococcus epidermidis was cultured from the node. Similar structures were seen in the surrounding connective tissue. Intracellular coccoid forms were seen within liver cells in liver biopsy sections characterized as showing nonspecific inflammation.

The patient developed multiple KS skin lesions on his face 2 weeks before death. Both intracellular and extracellular purple coccoid forms (Fite stain) and very rare pink coccoid forms (Gram stain) were observed throughout the dermis. These coccoid forms resembled some of the coccal forms of beta-Streptococcus, group G, which were isolated from a blood culture obtained 1 day before death. Some aberrant "large forms" of streptococci were similar in size to some of the Russell bodies observed in vivo within the lymph nodes.

The histopathological finding of coccoid forms in vivo in AIDS and KS is not a syndrome-specific finding. Similar structures have been observed in forms of cancer, collagen diseases, lymphoproliferative diseases, and in "normal" tissue (Cantwell AR, Jr: in Domingue GJ (Ed): Cell Wall Deficient Bacteria: Basic Principles and Clinical Significance. Addison-Wesley Publishing Company, Reading, Massachusetts, 1982, 321-360). However, other studies from this and other laboratories have also shown intracellular and extracellular coccoid forms associated with AIDS and KS. They have

been seen within enlarged lymph nodes of one suspected AIDS patient and within the skin lesions in two homosexual men with AIDS (Cantwell AR, Jr: Growth, 1982, 46:331-336; Cantwell AR, Jr: Cutis, 1983, 32:58-64, 68). Cell wall deficient bacteria (CWDB) have been detected in necroscopic analyses of sections of the heart, lungs, intestines, and in KS skin lesions of a 74-year-old Jewish man who died without clinical evidence of ante-mortem infection. Various bacteria--Corynebacterium sp. and Propionibacterium acnes from one case and Staphylococcus epidermidis and Streptococcus viridans from another--were cultured from the skin lesions of two of three elderly, heterosexual Jewish men with KS (Cantwell AR, Jr: Growth, 1981, 45:79-89). In eight of nine patients with AIDS and KS, acid-fast Mycobacterium avium-intracellulare have been detected at autopsy (Zakowski P, Fligiel S, Berlin GW, et al: J Am Med Assoc., 1982, 248:2980-2982). The Russell bodies and other bacterial forms seen in in vivo sections might be related to cell wall deficient and acid-fast forms of staphylococci, streptococci, and corynebacteria-like organisms which have been observed and cultured from samples of blood of both healthy and diseased individuals (Wuerthele-Caspe Livingston V, Livingston AM: Trans NY Acad Sci., 1972, 34:433-453).

Further studies are necessary to establish a link between histologic observations and clinical isolates. "Occult" bacteria were finally determined to cause "legionnaires' disease"; they may, likewise, prove to have more than an opportunistic role in AIDS.

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AIDS FROM CENTRAL AFRICA IN A HETEROSEXUAL DANISH MALE

The second Danish patient with AIDS of probable African origin recently died in Copenhagen at age 31. He was a previously healthy businessman who moved to central Africa in 1974. From 1974 to 1976 he lived mostly in Rwanda and from 1976 to 1980 in neighboring Burundi. During this time he paid short visits to Kenya; he also spent 2 days in Zaire. Between 1979 and 1981 he visited the Ivory Coast for 1 month and Canada for 1 week (crossing briefly into the United States). In December 1981 he left Burundi. From then until his death, he lived in France, the Ivory Coast, and Denmark.

The patient had never received a blood transfusion, and he denied homosexuality and intravenous drug abuse.

While in Rwanda in 1974, he contracted infectious mononucleosis. The diagnosis was confirmed in Denmark. In 1976 he developed bilateral orchitis of unknown origin. He was treated for gonorrhoea on several occasions in Burundi and for syphilis once in France after his last visit to Burundi. The venereal diseases were probably acquired from native (Watutsi) bar girls in Bujumbura, the capital of Burundi.

The patient was slightly obese but otherwise in good health until his return to Europe from Burundi in January 1982. He developed fatigue and fever and possibly lymphadenopathy. He was treated for toxoplasmosis in France, but a firm diagnosis was never established; and serological tests performed in 1983 for toxoplasmosis were negative. He had episodes of fever, and his general level of health gradually deteriorated. In November 1982, while taking antimalarials for fever, a long-lasting skin

eruption appeared. He was hospitalized in December of that year with a bleeding nose.

The patient suffered from functional dyspnoea and weight loss during 1983. He was examined for malaria because of recurrent fever. Malaria was not confirmed. By August of that year, he had lost 25 kg and was dyspnoeic even when at rest.

On August 12 he was rehospitalized. He required artificial respiration, as the initial discrete bilateral pulmonary infiltrates rapidly progressed despite high-dose erythromycin, sulfamethoxazol-trimethoprim, and prednisone therapies. An open lung biopsy revealed Pneumocystis carinii (PC) and cytomegalovirus (CMV) infections. Pentamidine and acyclovir therapies were started, but pneumothorax, progressive respiratory insufficiency, and later hypotension with anuria supervened. He died on August 31. An autopsy was not performed.

Lymphocyte counts of cells in peripheral blood showed severe lymphopenia ($0.14 \times 10^9/l$). No proliferative responses could be measured to mitogens and antigens in vitro. The T helper/T suppressor ratio was low (0.09), and NK cell activity was moderately decreased. (Lymphocyte studies were performed by the Tissue Type Laboratory, Rigshospitalet.) The S-IgA level was above normal; IgG and IgM levels were normal. Antinuclear antibodies and lymphocytotoxic antibodies were not found. The anti-CMV antibody titer was positive (1:128) as was the Epstein-Barr IgG antibody titer.

The patient fulfills the AIDS criteria but does not fit into any of the risk groups defined to date. We suggest that "Africans" be included in the list of risk groups. In addition, since this patient is suspected of having acquired his immune deficiency syndrome from heterosexual contact with Africans, we suggest that such contact would constitute another risk factor for AIDS.

In certain central African countries Kaposi's sarcoma (KS) is common. The highest prevalence of KS--about 12% of all cancers--is found in Zaire (Hutt MSR: Antibiot Chemother., 1981, 29:3-8).

The first case of an AIDS-like disease of probable African origin occurred in 1976 in a 46-year-old Danish woman surgeon who had been working in Zaire. She died of PC pneumonia in 1977 (Bygbjerg IC: Lancet, 1983, 1:925). Reports from Belgium (Clumeck N, Mascart-Lemone F, de Maubeuge J, et al: Lancet, 1983, 1:642) and France (Brunet JB, Bouvet E, Chaperon J, et al: Lancet, 1983, 1:700-701) point to Zaire and Chad as risk areas for AIDS. Next to Zaire, Burundi has the highest prevalence of African KS (Hutt, 1981). Other cases of AIDS are expected to develop in African immigrants to Europe and among Europeans who visit or live in Africa. Cases probably have occurred but may simply have been overlooked in the past. The case of AIDS described in this report reinforces the connection between KS and AIDS in the central African area.

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A PERSPECTIVE ON AIDS CASES AMONG HEALTH CARE WORKERS

It has been common knowledge at least since early 1982 that the epidemiology of AIDS is similar in many ways to that of hepatitis B. As a result, the

possibility that the disease might be transmitted to health care workers or laboratory staff handling materials from AIDS patients has been a constant concern. Formal recommendations for the protection of clinical and laboratory workers were drawn up by consensus among USPHS agencies and published in November, 1982 (Morb Mort Weekly Rep., 1983, 31:577-580). In mid-July, 1983, the Centers for Disease Control (CDC) published abstracts of four cases of AIDS among health workers who did not appear to belong to any of the recognized high-risk groups (Morb Mort Weekly Rep., 1983, 32:358-360). Although the editor concluded that "these four cases provide no new information regarding occupational risk related to health care personnel," the anecdotal reports have heightened the level of anxiety among persons whose responsibilities include caring for AIDS patients or analyzing biological specimens derived from them.

Before one attempts to consider the significance of the observation of four AIDS cases among medical personnel, it is necessary to estimate how many cases might have been expected merely on the basis of chance. In mid-July, 1983, the total number of AIDS cases that had been reported to CDC was 1902, of whom 110 could not be assigned to any of the designated high-risk groups. The four health workers were among this group of 110. According to the 1980 census, the United States population in the age brackets 18-64 totaled 137.2 million (US Bureau of the Census, Statistical Abstract of the United States, 1982-1983, 103rd ed, Washington, DC, 1982, xviii). This age span encompasses almost all employed persons and virtually all AIDS cases. The National Center for Health Statistics (NCHS) reports that in 1980 there were approximately 7.23 million persons employed in the health industry (NCHS: Health, United States, 1982, DHHS Publication No. (PHS) 83-1232, Table 51, 112). If, then, employment in the health industry bears no relationship to risk of AIDS, the number of health workers that would be expected among the 110 "unexplained" cases = $110 \times 7.23/137.2 = 5.8$, which exceeds the four observed. No elaborate statistical analysis is required to realize that this comparison does not support a hypothesis that health workers are at increased risk for the acquisition of AIDS. On the other hand, neither does it argue for cavalier disregard of common-sense precautions.

R. S. Gordon, Jr., National Institutes of Health, Bethesda, Maryland 20205.

SAFETY PRECAUTIONS FOR PERFORMING LABORATORY TESTS ON SPECIMENS FROM KNOWN OR SUSPECTED AIDS PATIENTS

The safety precautions advised for personnel involved with AIDS research were published in Morbidity and Mortality Weekly Reports in November 1982. The precautions specific to personnel performing laboratory tests or studies on clinical specimens or other potentially infectious materials from known or suspected AIDS cases are reprinted here. The precautions recommended for personnel handling experimental animals were reprinted in the first issue of the AIDS Memorandum, and other precautions will be reprinted in future issues.

- Mechanical pipetting devices should be used for the manipulation of all liquids handled in the laboratory. No mouth pipetting should be allowed.
- Needles should not be bent after use. They should be placed in a puncture-resistant container used only for

their disposal. They should not be reinserted into their original sheaths, since this process frequently is the cause of needle-associated injuries.

• Disposable syringes and needles should be used. Only needle-locking syringes or one-piece needle-syringe units should be used to aspirate fluids from patients, so that subsequent discharge of the fluid can be performed safely. If reusable syringes must be used, they should be decontaminated before reprocessing.

• Laboratory coats, gowns, or uniforms should be worn while work with potentially infectious materials is being done, and they should be discarded appropriately before leaving the laboratory.

• Gloves should be worn to avoid skin contact with the following: blood, specimens containing blood, blood-soiled items, body fluids, excretions, secretions, and surfaces, materials, and objects exposed to these specimens.

• All procedures and manipulations of potentially infectious materials should be performed carefully to minimize the creation of droplets and aerosols.

• Biological safety cabinets and other primary containment devices (e.g., centrifuge safety cups) should be used whenever procedures are conducted that are likely to create aerosols or infectious droplets. Such procedures include centrifuging, blending, sonicating, vigorous mixing, and harvesting infected tissues from animals or embryonated eggs. Fluorescence activated cell sorters also generate droplets that might form infectious aerosols. Translucent plastic shielding between the droplet-collecting area and the equipment operator should be used. Primary containment devices should be used for handling materials that might contain infectious agents or organisms in higher concentrations than expected in clinical specimens.

• Laboratory work surfaces should be decontaminated following any spill of potentially infectious material and at the completion of work activities. A disinfectant, such as sodium hypochlorite solution (a 1:10 dilution of 5.25% sodium hypochlorite [household bleach] with water), should be used.

• All potentially contaminated materials used in laboratory tests should be decontaminated, preferably by autoclaving, before disposal or reprocessing.

• All personnel should wash their hands following completion of laboratory activities, removal of protective clothing, and before leaving the laboratory.

NATIONAL AIDS/PRE-AIDS EPIDEMIOLOGICAL NETWORK (NAPEN)

In August 1983, NAPEN was officially formed. The idea for the network arose out of a suggestion to the CDC's AIDS Task Force that active surveillance of AIDS and sexually transmitted diseases common in homosexual populations should be initiated. A time course for disease progression was envisioned. Communities showing different incidence rates for AIDS were considered to be at unlike points along the time line; some communities would be at the point of introduction of the etiologic agent(s) into the community, others would be at the point of saturation with the agent(s), and others would be at the point of maximum occurrence of disease. Through a prospective study carried out simultaneously in several homosexual male communities with differing AIDS incidence rates, useful information could be

gained which might clarify the natural history and the etiology of AIDS.

The objectives of NAPEN have been formulated to include the following. The organization will serve as a forum for the exchange of ideas, methodologies, and information among epidemiological investigators. It is anticipated that such exchanges will result in adoption of standardized core epidemiological data bases and methodologies. A uniform data base will be developed for studying national trends and major risk and protective factors. Uniform reporting and data collecting instruments and procedures will be developed in conjunction with and distributed to investigators throughout the U.S. and Canada.

Anyone interested in joining NAPEN or in receiving further information should contact Laura Coats, Howard Brown Memorial Clinic, 2676 N. Halsted Street, Chicago, Illinois 60614, (312) 871-5777.

The requirements established for voting members are active involvement in AIDS epidemiologic research (including adherence to the confidentiality provisions of the Federation of AIDS Organizations), willingness to contribute data to NAPEN, and an initial membership fee of $10. Non-voting observers (administrators, funding agencies, and the like interested in furthering AIDS epidemiological investigations) and consultants (those performing a particular task and/or lending expertise) are also welcome. To date, there are 24 voting members in 19 cities, 30 observers, and three consultants.

D. G. Ostrow, Director of Research, Howard Brown Memorial Clinic, Associate Professor of Psychiatry and Community Health/Preventive Medicine, Northwestern University Medical School, Chicago, Illinois 60614.

UPCOMING AIDS MEETINGS

Registration is still open for the following upcoming AIDS meetings.

NAPEN Meeting (held in conjunction with the Annual Meeting of the American Assoc. of Public Health)
November 13, 1983
Dallas Hyatt Regency
Dallas, Texas

Contact:
Laura Coats
Howard Brown Memorial Clinic
2676 N. Halsted Street
Chicago, IL 60614
(312) 871-5777

UCLA Symposium: AIDS
February 5-10, 1984
Park City, Utah

Program Information:
Dr. Michael S. Gottlieb
103 Molecular Biology Institute
University of California
Los Angeles, CA 90024
(213) 206-6292
Registration Information:
Deadline for applications is November 1, 1983.

NAPEN Meeting (held in conjunction with the joint annual meeting of AAPHR and the National Coalition of Gay STD Services)
April 25-29, 1984
New Orleans, Louisiana

Contact:
Laura Coats
Howard Brown Memorial Clinic
2676 N. Halsted Street
Chicago, IL 60614
(312) 871-5777

AIDS CASES REPORTED TO THE CENTERS FOR DISEASE CONTROL AS OF OCTOBER 19, 1983

UNITED STATES CASES

DISEASE	CASES	PERCENT OF TOTAL	DEATHS	PERCENT DEAD
KS without PCP	665	26.5	146	21.9
PCP without KS	1282	51.0	599	46.7
Both KS and PCP	180	7.2	107	59.4
OI without KS or PCP	386	15.3	196	50.8
TOTAL	2513	100.0	1048	41.7

KS = Kaposi's sarcoma PCP = Pneumocystis carinii pneumonia
OI = Opportunistic infections

	MALES		FEMALES		TOTAL	
RISK GROUPS*	CASES	% OF TOTAL	CASES	% OF TOTAL	CASES	%
Homosexual or bisexual	1805	76.9	0	0.0	1805	71.8
IV drug user	337	14.4	87	52.7	424	16.9
Haitian	102	4.3	15	9.1	117	4.7
Hemophiliac	16	0.7	0	0.0	16	0.6
No apparent risk group or unknown	87	3.7	63	38.2	151	6.0
TOTAL	2347	100.0	165	100.0	2513	100.0

* The risk groups listed are hierarchically ordered; cases with multiple risk factors are tabulated only in the risk group listed first.

CASES REPORTED FROM OTHER COUNTRIES

NUMBER OF COUNTRIES	CASES
21	156

U.S. AND FOREIGN CASES REPORTED

TOTAL	2669

AIDS
MEMORANDUM
Acquired Immune Deficiency Syndrome

National Institute of Allergy and Infectious Diseases

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IN THIS ISSUE

GROUND RULES FOR USE OF THE AIDS MEMORANDUM

The AIDS Memorandum serves as a forum for the rapid exchange of new information and ideas among clinicians and scientists involved in AIDS research and management. Material contained in the Memorandum can be of several kinds: positive and/or negative results, clinical and/or experimental findings, preliminary and/or validated data, observations, questions, theories, commentaries, and others. This material is not subjected to peer review. Therefore, users of the Memorandum must agree to treat all material as privileged information and to consider it as tentative and subject to change prior to formal publication in a refereed journal.

Users must agree not to cite material from the Memorandum without first obtaining the consent of the author(s), and, with author permission, to cite information only as a personal communication. Author addresses are provided for this purpose.

Users must agree to contribute data or ideas to the Memorandum at least once a year. On an annual basis, the names of individuals who have not contributed to the Memorandum will be culled from the mailing list, so as to limit circulation of the Memorandum only to individuals actively working in the field.

Finally, users must agree to share material in the Memorandum only with other individuals willing to honor these ground rules.

AIDS IN EUROPE: EPIDEMIOLOGIC FEATURES

The World Health Organization of Europe (WHO-Europe) and the Danish Cancer Society sponsored a meeting in Aarhus, Denmark, October 19-21, 1983, for European and US AIDS researchers. The meeting was convened in order to summarize the epidemiologic and clinical features of cases of AIDS which have occurred in Europe and to formulate recommendations for public health policies pertinent to AIDS. The meeting was attended by representatives of the national governments and academic institutions from almost every country in Europe. Along with the invitation to attend the meeting, participants had been sent a questionnaire concerning the epidemiology of AIDS. Data from the questionnaires which had been returned were summarized in a manuscript which was distributed, discussed, and amended at the meeting and eventually adopted as the consensus of the participants. Additional data updating case numbers and correcting misunderstandings regarding the diagnosis of AIDS were presented at the meeting.

The total number of cases in Europe which have been diagnosed as AIDS according to the most recent update is 268. An important area of agreement which emerged from the meeting was that the CDC case definition would be used by everyone, at least for the purpose of epidemiologic surveillance. France reported the greatest number of cases (94), followed by the Federal Republic of Germany (42), Belgium (38), the United Kingdom (24), Switzerland (17), Denmark (13), and the Netherlands (12). Eight other countries reported fewer than 10 cases each. Cases of AIDS were reported from all areas of Europe. Two cases were known in Eastern Europe, one of whom was an African student living there.

As in the United States, AIDS has been diagnosed in Europe with increasing frequency since 1979. According to information contained in the questionnaires, eight cases occurred prior to 1979. (These were reported retrospectively.) During 1982, 67 cases were reported. By the time the conference was held, 104 cases had been reported in 1983.

Of the 200 cases for which detailed information was provided, 74% were individuals of European origin, 21% were individuals of African origin, and 10 were individuals originating from North and Central America (Haiti 8, US 1, and Nicaragua 1). One major difference between the cases evaluated in Europe and those seen in the US was the large number of cases from Africa. To date, 42 African cases have been diagnosed in Belgium, France, Switzerland, and Czechoslovakia. These cases have been in individuals originating mainly from Zaire and other adjacent African countries in the Congo Basin. No African cases have been seen in the United Kingdom, where the large African population originates mostly from West, East, and South African countries. Although the African cases have been diagnosed more frequently in the most recent period, it is unclear from these data whether this represents a referral and recognition bias or a real increase in the occurrence of AIDS in Africa.

Of the cases of AIDS in individuals of European origin, 128/148 (86.4%) could be assigned to a risk group. The distribution of individuals into the various risk groups was similar to the distribution seen in the United States: 80% were homosexual men, 4.8% were hemophiliacs, and 1.4% were heterosexual

drug addicts. In most of the remaining cases, the information provided was inadequate for making a classification.

One hundred eighty-nine of the cases cited in the questionnaires were described by the following clinical diagnoses—opportunistic infections, opportunistic infections and Kaposi's sarcoma, and Kaposi's sarcoma. The distribution of these cases according to the area of origin of the individuals is given in the table.

	All Cases					
Diagnosis	No./Total No.	(%)	European	African	Haitian	American
OI only	123/189	(65.1)	86/143	29/36	6/8	2/2
OI and KS	37/189	(19.2)	23/143	3/36	2/8	
KS only	39/189	(20.6)	34/143	3/36	0/8	
Total cases	189		143	36	8	2

Abbreviations: OI, opportunistic infection; KS, Kaposi's sarcoma.

The 34 European cases of Kaposi's sarcoma only were almost exclusively seen in homosexual men.

Further details about the epidemiology, clinical features, and policy recommendations will be published in the European Journal of Cancer. The information was collected by WHO and should be considered preliminary until confirmed and published.

Submitted on behalf of the AIDS in Europe—Status Quo 1983 Meeting by R. J. Biggar, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20205.

IS AFRICAN KAPOSI'S SARCOMA ENDEMIC AIDS?

It has been assumed that AIDS is a new disease, appearing de novo in the US in 1979. However, there are marked epidemiological similarities between AIDS and the endemic form of Kaposi's sarcoma (KS) occurring in central Africa. If an infectious agent causing endemic KS in Africa were recently introduced into the US, this could explain how epidemic AIDS emerged in the US.

KS has been a rare tumor in Europe and in the US. In these areas, its prevalence is 0.01-0.06/100,000, and it occurs primarily in older people (Safai B, Good RA: CA, 1981, 31:2-12). In a recent update of data regarding the current AIDS epidemic, it was reported that 26% of all US cases have presented with KS alone (Morb Mort Weekly Rep., 1983, 32(35):465-467). This represents well over 500 cases.

In contrast, in central Africa, KS has been a common tumor. KS accounts for 12.8% of all malignant tumors in adults in Zaire, where the highest world wide prevalence of KS is known (Hutt MSR: Antibiot Chemother., 1982, 29:3-8). The epidemiology of KS in Africa, as reviewed by Hutt, showed that this tumor occurred in all the countries bordering Lake Victoria. Within this area, the tumor is most common in males, with a male:female ratio of at least 13:1 in all series. Fifty percent of all cases occur in individuals aged 25-40. There is a small peak for those aged 1-2, and, in this group, the male:female ratio is 1 (Kyalwazi SK: Antibiot Chemother., 1982, 29:59-67). KS is highly area-specific, with marked variations in incidences over short distances; numerous case clusters have been reported. This epidemiology strongly suggests an infectious etiology (Giraldo G, Beth E, Kyalwazi SK: Antibiot Chemother., 1982, 29:12-29). No thorough study of the immunology of African KS has been undertaken. However, it has been observed that immunoglobulin titers were normal while delayed-type hypersensitivity testing was negative in cases of aggres-

sive KS (Master SP, Taylor JF, Kyalwazi, SK, et al: Br Med J., 1970, 1:600-602).

The table lists features of African KS and AIDS KS and demonstrates similarities in the epidemiologies of the two diseases. Although no record was made of opportunistic infections in African KS patients, this population in general has a high incidence of life-threatening infections. A series of post-mortem examinations of Africans dying of KS did demonstrate an unexpectedly high incidence of infection as a cause of death, including pulmonary infection and dysentery (Templeton A: Cancer, 1972, 30:854-867).

COMPARISONS OF AFRICAN KS AND AIDS

Feature	African KS	AIDS
Sex ratio (M:F)	13:1	14:1
Age	Small peak 2-3 yr; increase after 20 yr; median 25-40 yr	Small peak 1-2 yr; increase after 20 yr; median 30-39 yr
Geographical distribution	Equatorial Africa; highly area-specific	USA, Europe; highly area-specific
Social distribution	All tribal groups; upper/lower classes	All ethnic groups; all classes
Infectivity	Clustering	Clustering; sexually transmitted; blood borne
Associated infections	CMV; HSV; EBV; HBV; Eh	CMV; HSV; EBV; HBV; Eh; syphilis
Opportunistic infections	Not recorded; ? Missed	50% PCP; 25% Other
Humoral immunity	Normal	? Normal
Cellular immunity	DTH absent	DTH absent; lymphopenia; T helper deficit

Abbreviations: CMV, cytomegalovirus; HSV, herpes simplex virus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; Eh, Entamoeba histolytica; PCP, Pneumocystis carinii pneumonia; DTH, delayed type hypersensitivity.

If African KS is an infectious disease, what accounts for the high male:female ratio in the adult cases? Such a pattern can be seen in infectious diseases where males and females have differential occupational exposures, as is the case for cutaneous Leishmaniasis in Mexico. However, Hutt was unable to demonstrate such a difference in the life styles between the sexes in Uganda.

How prevalent homosexuality is in central Africa is unknown. However, this area has the highest incidence of polygamy in the world, and delayed marriage for males is common (Dr. P. Spencer, personal communication). Because a large number of post-adolescent males are denied access to young females, homosexual contact is thought to occur before later heterosexual marriage. If African KS is caused by a sexually transmitted factor, then homosexuality in the young adult group could explain the pattern of the tumor in this population. The smaller number of childhood cases could be explained by vertical transmission.

A putative agent causing KS in Africa could have been introduced into a susceptible population in the US, possibly carried by homosexual visitors to East Africa. The recent reports of AIDS in Zaire and of 59 cases of AIDS in Europe whose only risk factor was exposure to central Africa strengthen the links between AIDS and African KS. If AIDS is an epidemic form of endemic KS, then closer examination of the disease in Africa will answer many questions on the course and cause of this mysterious disease.

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THE INCIDENCE OF KAPOSI'S SARCOMA IN THE US AND PUERTO RICO, 1973-1981

The epidemiology of Kaposi's sarcoma (KS) has attracted considerable interest

because of the many cases associated with AIDS. The AIDS outbreak, which includes both opportunistic infections and KS, was first recognized in 1981, although, in retrospect, cases began to appear somewhat earlier. While several high-risk groups have been identified, most of the AIDS cases have occurred among young homosexual men.

Using data from the Surveillance Epidemiology End Results (SEER) program of the National Cancer Institute, we examined the incidence of KS in the US and Puerto Rico. The incidence of KS in 1973-79 was found to be higher than is usually cited for the pre-epidemic KS incidence rate: 0.29 male and 0.07 female cases per 100,000 per year. Collectively, the nine SEER registries in the US showed only a slight increase in the incidence of KS between 1973-79 and 1980-81. However, the SEER registry covering San Francisco, where a large number of AIDS cases have occurred, showed a marked increase in KS in 1981.

The incidence rates of KS in the SEER registry of Puerto Rico were generally higher than those in the US registries, despite data which suggested that KS may be underreported. The demographic characteristics of KS in Puerto Rico suggested the classical rather than the AIDS-related form of KS. Puerto Rico and perhaps other Caribbean islands may be endemic areas of KS.

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FACTOR VIII, KAPOSI'S SARCOMA AND AIDS

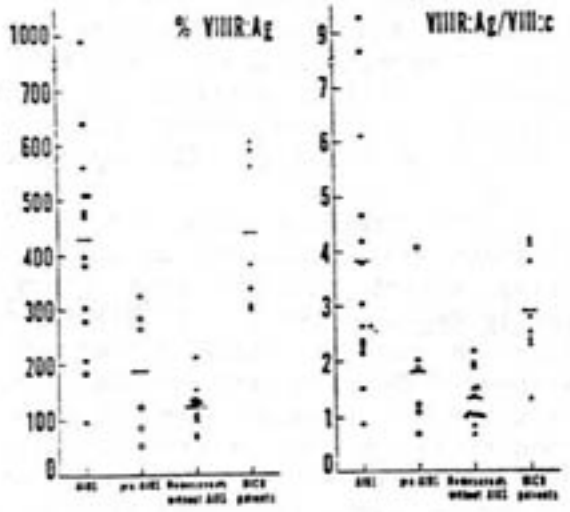
Our autopsy observations on 26 victims of AIDS indicate that, in virtually every case, generalized (lymphadenopathic) Kaposi's sarcoma (KS), a tumor thought to be of endothelial origin, is present (data to be published). We have also observed KS lesions in biopsy specimens of lymph nodes in a high proportion of AIDS patients. Since coagulation factor VIII has been shown to be associated with the neoplastic cells of KS (Nadji M, Morales AR, Ziegles-Weissman J, et al: Arch Pathol Lab Med., 1981, 105:274-275), we hypothesize that factor VIII may be elevated in the peripheral blood of AIDS patients.

The molecular complex of factor VIII consists of at least two subunits, the von Willebrand-related antigen (VIIIR:Ag) which is produced chiefly by endothelial cells and a procoagulant (VIII:c) which is synthesized by the liver. If the common denominator of AIDS is KS and if KS cells contribute to an elevation of factor VIII in the blood, we would further speculate that levels of VIIIR:Ag in the blood of AIDS patients would rise disproportionately compared to levels of VIII:c. Accordingly, we have measured levels of these factor VIII subunits in blood of AIDS patients and controls.

Thirty-three patients were studied. Fourteen were diagnosed as having AIDS using strict CDC criteria (Morb Mort Weekly Rep., 1982, 31(37):507-514). Thirteen patients were homosexual men without AIDS (some of whom had generalized lymphadenopathy). Six patients were homosexual men with a pre-AIDS syndrome defined by having at least four of the following symptoms or characteristics: fever of unknown origin, weight loss and/or diarrhea, lymphadenopathy, skin test anergy, lymphopenia (less than 1,500 lymphocytes per cubic mm), oral thrush, greater than 1,000 different sexual partners, multiple infections,

inverted T-helper to T-suppressor lymphocyte ratio. In addition, assays were performed on the blood of seven patients who were hospitalized in our medical intensive care unit (MICU) for serious acute illnesses unrelated to AIDS. This group provided data, previously unavailable, on the ratio of VIIIR:Ag to VIII:c in acute disease (factor VIII is an acute phase reactant).

Measurements of levels of peripheral blood factor VIII:c and VIIIR:Ag were made using standard methods (Miale JB: in Mosby CV (Ed): Laboratory Medicine Hematology, 6th ed, St. Louis, 1982, 929-932). Data are presented in the figure in two ways. The concentration of VIIIR:Ag is expressed as % of normal expected values (normal values are in the range of 50-150%). The ratio of VIIIR:Ag/VIII:c is given directly (with ratios for normals approximately = 1).



There were marked elevations in both the % VIIIR:Ag and the VIIIR:Ag/VIII:c ratios in patients with AIDS, although, for both parameters, the ranges of values were large. There were more modest elevations in the % values and ratios obtained for pre-AIDS subjects. Homosexuals without AIDS had % values and ratios within normal limits. The % values and ratios also were elevated in the acutely ill patient subset. The differences in the values and ratios for AIDS patients and MICU patients were not significant and do not support a conclusion that the rises measured can be related directly to KS. In order to further assess the value of these assays for determining the presence and/or ubiquity of KS in AIDS, we are currently studying serially the blood of various patient groups, including persons with KS but without opportunistic infections.

Note added in proof: The pre-AIDS patient with the highest ratio shown in the figure (= 4) has recently developed overt AIDS. Another patient who had originally been in the pre-AIDS group developed AIDS during the study and was transferred to the AIDS category at that time. Because these two patients had the two highest values in their original subset, high ratio values may prove to be predictive of AIDS development.

S. D. Weiss, F. Civantos, N. S. Penneys, L. B. Moskowitz, J. W. Kent, and G. T. Hensley, School of Medicine, Jackson Memorial Hospital, Miami, Florida 33101.

CYCLOSPORINE-LIKE SUBSTANCES NOT DETECTED IN AIDS PATIENTS

It has been suggested recently that AIDS may be caused by the "systemic release of a potent cyclosporin-like immunosuppressive molecule from a chronic fungal infection in AIDS patients" (Sell KW, Folks F, Kwon-Chung KJ, et al: N Engl J Med., 1983, 309:1065). This suggestion was based on analogies between

immunosuppressive effects produced by cyclosporine and changes in immune status which are characteristic of AIDS and by high-performance liquid chromatography (HPLC) analyses of AIDS plasma.

Cyclosporine has a unique cyclic undecapeptide structure (Ruegger A, Kuhn M, Lichti H, et al: Helv Chim Acta, 1976, 59:1075-1092). Analytical techniques for detecting cyclosporine include radioimmunoassay (RIA) (Donatsch P, Abisch E, Homburger M, et al: J Immunoassay, 1981, 2:19-32) and several HPLC methods (Neiderberger W, Schaub P, Beveridge T: J Chromatogr., 1980, 182:454-458; Carruthers SG, Freman DJ, Koegler JC, et al: Clin Chem., 1983, 29:180-183; Yee GC, Gmur TJ, Kennedy MS: Clin Chem., 1982, 28:2269-2271; Sawchuk RJ, Cartier LL: Clin Chem., 1981, 27:1368-1371). The RIA is sensitive to the cyclic undecapeptide structure only. However, there is a sufficiently broad spectrum of cross-reactivity in this assay that cyclosporine-like compounds possessing an intact cyclic structure but having different substituents on the ring are measured together with cyclosporine. The HPLC techniques are specific for cyclosporine, but are plagued by the presence of co-eluting peaks due to endogenous plasma components. Even column switching techniques do not completely eliminate this problem (Smith HT, Robinson WT: J Chromatogr., 1984, 305:in press).

We have analyzed samples of blood, plasma, and serum for cyclosporine using RIA and HPLC techniques. Samples were tested from six patients who fulfilled the Centers for Disease Control criteria for diagnosis of AIDS, two patients who were classified as having the AIDS prodrome and, for control purposes, 15 AIDS-free patients, 10 of whom belonged to several AIDS "risk groups."

The sensitivities of the analytical methods were verified by analyses of cyclosporine-positive blood specimens from a normal, healthy volunteer who had been entered into a study assessing the dose-proportionality of cyclosporine (Abolin CR, et al: Study No. 40, Volumes 3.80-3.84, Section 12(h) of Cyclosporine (Sandimmune™) New Drug Application). His blood samples had been stored for 1 year at -20°C.

All samples were analyzed blind. Sample aliquots for RIA were fortified with normal human blood to eliminate matrix differences between the blood, plasma, and serum specimens; all samples were then diluted and analyzed according to instructions provided with the cyclosporine RIA kit (Ciclosporin RIA-Kit Instructions, 1st ed, 14 Feb 1983, Sandoz Ltd., Switzerland). For the HPLC analyses, aliquots of blood or plasma samples were extracted with diethyl ether, and the extracts were chromatographed according to the conditions of Carruthers et al. (ref. above). Their method was chosen as the one most likely to coextract and chromatograph "cyclosporine-like" materials. The HPLC eluate was collected starting at several minutes before the retention time for dihydrocyclosporine C and ending with the retention time for cyclosporine D. Both compounds are used as internal HPLC standards, and their retention times bracket those of cyclosporine A. Therefore, any cyclosporine-like compounds in the samples should be eluted in this window. The HPLC eluates were evaporated, the residues reconstituted with small volumes of RIA buffer containing surfactants to enhance redissolution, and the concentrates analyzed by RIA.

All samples from the positive control volunteer showed a positive RIA response. The concentration data obtained in this analysis showed less than 10%

difference from data obtained 1 year ago, validating the RIA and also demonstrating the stability of cyclosporine in frozen blood. In contrast, we detected no cyclosporine or cyclosporine-like substances in either patient or control samples above the limit of quantitation of the RIA (conservatively set at 30 ng/ml). Analysis of variance of RIA responses between AIDS and control samples showed that there were no statistically significant differences. These analyses suggest that cyclosporine or cyclosporine-like substances are absent at concentrations less than 30 ng/ml as well.

In the UV tracings of the HPLC analyses for both control and AIDS samples, we noticed various and variable peaks that are known to arise from endogenous extractable materials. We did not find any peaks in the AIDS samples that were unique to and limited to this subgroup. All samples known to contain cyclosporine showed cyclosporine peaks in the chromatograms consistent with the expected concentration of cyclosporine (corrected for extraction and recovery methods). RIA analyses of all HPLC fraction concentrates were negative for the control and AIDS samples but positive for the samples known to contain cyclosporine.

We take no issue with the hypothesis that systemic release of an immunosuppressive agent by an invading fungus may be a possible cause of AIDS. Our data indicate, however, that the putative immunosuppressive agent in the blood of AIDS patients is neither cyclosporine nor cyclosporine-like.

This note includes information contained also in a letter which has been accepted for publication in The New England Journal of Medicine.

H. F. Schran, A. E. Hassel, D. L. Winter, W. A. Krivoy, J. Raskova, and K. Raska, Jr. Pharmaceutical Research and Development, Sandoz, Inc., East Hanover, New Jersey 07936 and Department of Pathology, University of Medicine and Dentistry of New Jersey-Rutgers Medical School, Piscataway, New Jersey 08854.

NON-TRANSMISSION OF AIDS BETWEEN SEXUAL PARTNERS

This study describes clinical and laboratory analyses of a bisexual man with AIDS and of his wife. Despite continued sexual activity, the transmission of AIDS or of any measurable immunodeficiency has not occurred to date between these two sexual partners.

A 42-year-old man presented with Pneumocystis carinii pneumonia after a 2 month prodrome of malaise, fever, anorexia, and a 10 lb weight loss. The patient's lymphocyte count was 850 per mm^3, of which 585 (69%) were T cells. There were 99 OKT4+ cells and 474 OKT8+ cells per mm^3 (OKT4:OKT8 = 0.21). He was anergic to four cutaneous recall antigens (candida, trichophyton, mumps, and diphtheria-tetanus toxoid). He was seropositive for cytomegalovirus (CMV) antibody by ELISA analysis, and CMV was isolated from his urine. However, there was no blastogenic response to CMV. Blastogenesis to phytohemagglutinin (PHA) was normal. The patient received sulfamethoxazole-trimethoprim therapy and transient respirator support. Eight weeks later, his immunologic status was unchanged, but he appeared outwardly well.

The patient had been married for 18 years. Sexual activity with his wife was limited to kissing, manual genital contact, and penile-vaginal intercourse. Intercourse occurred once or twice a

week in the 5 years preceding the patient's illness. The wife corroborated this history.

The patient had had several experimental homosexual encounters from the time he was 14 until he was 18 years old. He resumed homosexual activity at age 32, usually meeting anonymous partners in parks or public rest rooms. He had a total of about 50 such contacts, averaging 3-5 per year in the 3 years preceding his illness. Most of these involved mutual orogenital contact, although active or receptive anal intercourse occasionally occurred. Several of the homosexual encounters had occurred in or near San Francisco. The patient had had hepatitis B 10 years before the onset of his current illness, and an assay for anti-HBs antibody was positive. The fluorescent treponemal antibody absorption test was also positive; the VDRL was nonreactive. The patient denied having had other sexually transmitted diseases (STD) and had never received a transfusion or blood products.

The wife, age 40, gave a history of lifelong monogamy and had no history of STD or transfusion. She was examined 8 weeks after her husband's illness (4 months after the onset of his prodromal symptoms). She was asymptomatic and had a normal physical examination. She was seropositive for anti-CMV antibody, but cultures of her urine, cervix, rectum, and pharynx were negative for CMV. The lymphocyte count was 1,598 per mm^3, of which 1,374 (86%) were T cells. There were 605 OKT4+ lymphocytes and 179 OKT8+ lymphocytes per mm^3 (OKT4:OKT8 = 3.38). Her lymphocytes showed normal blastogenic responses to CMV and PHA. Positive skin reactions were measured to the mumps recall antigen (54 mm induration) and to candida (4 mm). There was no response to trichophyton or diphtheria-tetanus toxoid. The wife remains well 8 months later but has declined to undergo further immunologic and virologic testing.

Sexual transmission of AIDS is suspected on several epidemiologic grounds, including observations that the sexual partners of AIDS patients commonly have subclinical cellular immunodeficiencies or, occasionally, overt AIDS. These observations have been made primarily in homosexual men. However, many homosexual men without AIDS have subclinical immunologic abnormalities. Therefore, the relationship of immunodeficiency to specific sexual contacts or activities is not yet clear.

In this study, AIDS and immunodeficiency were not transmitted from a bisexual man to his wife. There are several possible explanations for the normal clinical and immunologic status of the wife; they are not mutually exclusive. AIDS may not be caused by a specific transmissible agent, the putative etiologic agent of AIDS may not yet have been transmitted from the patient to his wife, the evaluation of the wife may have been carried out during an incubation period, or the wife may have had a subclinical infection with the putative AIDS agent, perhaps with the development of a protective immune response. Further attempts to reexamine the wife are underway.

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T-LYMPHOCYTE SUBSET ABNORMALITIES IN HEMODIALYZED ADULTS WHO HAVE RECEIVED BLOOD TRANSFUSIONS

Adults on chronic maintenance hemodialysis who have received blood transfusions show prolonged renal allograft survival which appears to be correlated with defective cell-mediated immunity (Watson MA, Briggs JD, Diamandopoulos AA, et al: Lancet, 1979, 2:1323-1326). To study this phenomenon, we examined the peripheral blood lymphocytes (PBL) of 29 hemodialyzed adults, 19 of whom had received blood transfusions (BT) and 10 of whom had not (NT). Data were also obtained on more than 40 age-matched normal volunteers.

		Controls	BT	NT
PBL	% /mm³	29.7 ± 1.6 1989 ± 108	28.9 ± 3.3 1441 ± 172	33.5 ± 1.8 2331 ± 401
OKT3+	% /mm³	69.1 ± 1.4 1323 ± 86	64.2 ± 2.4, 918 ± 118†	60.5 ± 3.7* 1433 ± 255
OKT4+	% /mm³	48.1 ± 1.1 924 ± 64	35.5 ± 3.1‡ 486 ± 60§	44.7 ± 3.3 1062 ± 225
OKT8+	% /mm³	26.4 ± 1.0 506 ± 36	30.9 ± 2.7 483 ± 96	27.5 ± 3.1 619 ± 88
OKT4+/OKT8+		1.98 ± 0.10	1.35 ± 0.20*	1.87 ± 0.27

*p <0.05, †p <0.01, ‡p < 0.001, §p <0.0001 as compared to control subjects.

When compared with controls, recipients of BT showed statistically significant decreases in the absolute numbers of OKT3+ cells, the percent representation and absolute numbers of OKT4+ cells, and the OKT4+/OKT8+ ratio. These findings are similar to those seen in other individuals who have received BT (Kessler CM, Schulof RS, Goldstein AL, et al: Lancet, 1983, 1:991-992). The NT subjects showed decreases only in the percent representations of OKT3+ cells.

We wish to emphasize that none of the subjects of this study, including those with depressed numbers of OKT4+ cells, have signs or symptoms associated with AIDS, such as unexplained fevers, weight loss, or lymphadenopathy. These data, however, may explain both the decrease in cell-mediated immunity in transfused hemodialyzed subjects and their decreased renal allograft resistance. These changes may also have relevance to cases of AIDS developing in those individuals who have been exposed to blood or blood products.

Whether these changes were induced by the transfusions or are present as a result of the generalized hypofunction of the bone marrow is not known. A prospective study is currently underway to help determined the pathogenic effects of BT and will be reported in a future issue of the Memorandum.

B. S. Bender, J. E. Nagel, and W. H. Adler, Clinical Immunology Section, National Institute on Aging, National Institutes of Health, Baltimore City Hospitals, Baltimore, Maryland 21224.

AIDS AND FLOW CYTOMETRY: CALL FOR PAPERS

A workshop on AIDS and Flow Cytometry, sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), will be held April 3, 1984, at the Bethesda Marriott Hotel. This meeting will precede a meeting on Flow Cytometry which is being held by the Becton Dickinson Company on April 4-5 at the same place. Anyone with data to present at a session on AIDS and FACS should contact Dr. Thomas Folks, NIAID, Building 10, Room 11C216, Bethesda, Maryland 20205, (301) 496-4553 or Dr. Thomas Chused, NIAID, Building 5, Room 228, Bethesda, Maryland 20205, (301) 496-2789.

SPECIFICITY OF LYMPHOCYTOTOXIC ANTIBODIES IN AIDS AND PRE-AIDS PATIENTS

Antilymphocyte antibodies have been detected in AIDS patients, but, to our knowledge, no reports have been published on the specificities of such antibodies for subpopulations of T lymphocytes. This report describes the reactivity of lymphocytotoxic antibodies (LCA) with T helper, T suppressor, and non-T mononuclear cells in patients with AIDS and patients with pre-AIDS symptoms.

Thirteen patients (3 with AIDS, 10 with pre-AIDS symptoms), 6 healthy homosexual controls, and 17 healthy heterosexual controls were the subjects of this study. Of the 13 patients, five were drug addicts (3 males, 2 females) and 8 were male homosexuals. Blood was collected from all individuals. One portion was heparinized for cellular studies, and another portion was allowed to coagulate for studies of sera. Mononuclear cells from patients and controls, fractionated using Ficoll-Hypaque, were typed by an indirect immunofluorescence technique using various monoclonal antibodies: OKT3 (a pan T cell marker), OKT4 (a T helper/inducer cell marker), and OKT8 (a T suppressor/cytotoxic cell marker). Sera from patients and controls were examined for LCA using a microcytotoxic test which was a modification of the Terasaki technique (Mottironi VZ, Terasaki PI: in Terasaki, PI (Ed): Histocompatibility Testing, Munksgaard, Copenhagen, 1970, 301-308). Target cells for these studies were preparations of either purified T cells, T helper cells, T suppressor cells, or a mixture of B cells plus macrophages from healthy donors. The results of cytotoxic assays were expressed as the cytotoxic index (CI) (100 × % dead cells in test sample/% dead cells in control). Values for control, positive samples were usually in the range of 90-95% dead cells. A CI ≥20% was considered positive for LCA, while a CI ≤20% was considered negative.

Lymphocytotoxic antibodies were detected in all of the symptomatic individuals (AIDS and pre-AIDS groups) but in only one (6%) of the healthy heterosexual controls and in none of the healthy homosexual controls. Titers of lymphocytotoxic antibodies in the patients ranged from 125-625. The antibodies were detected at 15°, 20°, and 37°C, but the reactivity at 37°C was 20-40% lower than at 15°C. Antibodies from all of the patients reacted with both T helper and T suppressor cells, but in nine of the 13 serum samples the reaction was higher with the T helper cells ($p < 0.05$). No correlation could be found between the levels of T helper lymphocytes or the T helper/T suppressor cell ratio and the levels of lymphocytotoxic antibodies in patients ($p > 0.1$). Sera of seven patients and three of nine healthy heterosexual controls tested reacted with non-T mononuclear cells (B cells plus monocytes). The degree of cytotoxicity with these cells did not correlate with the levels of lymphocytotoxic antibodies to T cells.

Two new findings have emerged from these studies: LCA react with both purified T helper and T suppressor cell preparations and both homosexual men with AIDS and drug addicts with AIDS have LCA which demonstrate these specificities.

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AIDS CASES REPORTED TO THE CENTERS FOR DISEASE CONTROL AS OF JANUARY 23, 1984

UNITED STATES CASES

DISEASE	CASES	PERCENT OF TOTAL	DEATHS	PERCENT DEAD
KS without PCP	858	26.0	198	23.1
PCP without KS	1695	51.2	809	47.7
Both KS and PCP	225	6.8	145	64.4
OI without KS or PCP	530	16.0	280	52.8
TOTAL	3308	100.0	1432	43.3

KS = Kaposi's sarcoma PCP = Pneumocystis carinii pneumonia
OI = Opportunistic infections

	MALES		FEMALES		TOTAL	
RISK GROUPS*	CASES	% OF TOTAL	CASES	% OF TOTAL	CASES	%
Homosexual or bisexual	2355	76.3	0	0.0	2355	71.2
IV drug user	462	14.9	120	54.3	582	17.6
Haitian	126	4.1	21	9.5	147	4.5
Hemophiliac	21	0.7	0	0.0	21	0.6
No apparent risk group or unknown	123	4.0	80	36.2	203	6.1
TOTAL	3087	100.0	221	100.0	3308	100.0

* The risk groups listed are hierarchically ordered; cases with multiple risk factors are tabulated only in the risk group listed first.

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The AIDS Memorandum is an informal forum for the exchange of information and ideas among clinicians and scientists actively involved in AIDS research, clinical investigations, and management.

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INSTRUCTIONS FOR AUTHORS CONTRIBUTING TO THE AIDS MEMORANDUM

Content: Articles published in the AIDS Memorandum must have obvious relevance to AIDS. They can describe clinical or experimental findings. Letters and other types of commentary are also welcome. In all cases, the text should be limited to 1000 words and typed double spaced.

References: References should be integrated into the text in parentheses. Each citation should include journal title, year of publication, volume and issue numbers and inclusive page numbers. Citations from books should include book title, editor(s), publisher, year of publication and relevant page numbers.

Tables: Whenever possible, data should be organized into tables rather than figures.

Announcements of Meetings: Announcements of upcoming AIDS meetings should include meeting title, location and date and the name, address and telephone number of the organizer of the meeting.

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AIDS
MEMORANDUM
Acquired Immune Deficiency Syndrome

National Institute of Allergy and Infectious Diseases

Volume 1, Number 4 April 1984

IN THIS ISSUE

GROUND RULES FOR USE OF THE AIDS MEMORANDUM

The AIDS Memorandum serves as a forum for the rapid exchange of new information and ideas among clinicians and scientists involved in AIDS research and management. Material contained in the Memorandum can be of several kinds: positive and/or negative results, clinical and/or experimental findings, preliminary and/or validated data, observations, questions, theories, commentaries, and others. This material is not subjected to peer review. Therefore, users of the Memorandum must agree to treat all material as privileged information and to consider it as tentative and subject to change prior to formal publication in a refereed journal.

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ETHICAL AND LEGAL ISSUES IN THE PREVENTION AND TREATMENT OF AIDS

This article is an excerpt of a paper presented at a conference on AIDS in October 1983.

I. Responsibilities to AIDS Patients

These remarks presuppose that there is no clear evidence for the transmission of AIDS through casual contact.

The first moral obligation of health professionals to AIDS patients may seem self-evident, but it is not, either in practice or in some major codes of professional ethics. It is the obligation to treat AIDS patients.

There have been anecdotal reports of instances in which health professionals have refused to become involved with AIDS victims. The primary motive for such actions is no doubt fear, but there may be included in the refusals the sentiment that "After all, they have brought the problem on themselves." I will address first the sentiment, then the fear.

The sentiment clearly does not apply to all AIDS patients. In their AIDS report of October 17, 1983, the CDC noted that 16 hemophiliacs not known to be members of other high-risk groups have contracted AIDS. In addition, there are 157 US cases of AIDS in which the risk factors causing the disease are either anomalous or unknown. Thus, for approximately 7% of AIDS patients in the US, the assertion that "They have brought the problem on themselves" is likely to be both untrue and unfair.

But what about the 72% of AIDS patients who are male homosexuals or bisexuals and the 17% who are intravenous drug users? They fall within the much larger category of persons in our society whose lifestyles are or may be significant factors in their health status. (It should be noted, however, that the earliest victims of AIDS could not have known that their style of life placed them at greater risk for such a devastating disease.) But if we are going to consider voluntary risks to health as criteria for health-care eligibility, then the discussion should be broadened to include not just AIDS, and not just the sexually transmitted diseases, but rather a wide variety of lifestyle factors. For example, in a standard public health textbook, the following behavioral factors are listed as risks to health: smoking, alcohol and drug abuse, nutritional abuse, lack of adequate physical activity, motor vehicle accidents, violence, lack of adequate family supports, sexual promiscuity and contraceptive carelessness, and excessive television viewing (Somers AR: in Last JM (Ed): Maxcy-Rosenau Public Health and Preventive Medicine, 11th ed., Appleton Century Crofts, New York, 1980, 1046-1065). Thus, the watchwords should probably be "We have brought many problems on ourselves," rather than "They have brought the problem on themselves." Health professionals who prefer not to treat self-induced morbidity should probably begin by refusing to help heavy smokers who develop lung cancer or teenage drivers whose speeding results in their being critically injured.

It is the obligation of health professionals to treat all patients who seek their aid without regard to the causes of the patients' illnesses or injuries. But what can be said about the other concern--perhaps the major concern--that AIDS patients constitute a threat to the health of their caretakers? There is no clear evidence that AIDS has ever been transmitted from a patient to a member of a health care

team (Morb Mort Weekly Rep., 1983, 32 (27):358-360).

In contrast, there is clear positive evidence that several other diseases are regularly spread from patients to their caretakers (for example, Berman J, Levin ML, Orr ST, et al: Am J Public Health, 1981, 71(11):217-222; Ahlfors K, Ivarsson SA, Johnsson T, et al: Acta Paediatr Scand., 1981, 70(6):819-823; Platonov SA, Orgel MI, Matoshko GV, et al: Vrach Delo., 1981, 11:107-110). In 1981 Yale-New Haven Hospital reported that, between 1972 and 1979, 34 of its employees contracted hepatitis B while fulfilling their health-related duties. The incidence of occupational disease was highest among persons administering venipunctures, followed by emergency room personnel, members of the dialysis unit, housestaff, laboratory personnel, nurses, and support service personnel (Pantelick EL, Steere AC, Lewis HD, et al: Am J Med., 1981, 70(4):924-927). In short, health care professionals knowingly accept a small risk of contracting several diseases from patients; but, as far as is known, AIDS is not one of those diseases.

Since the epidemiology of AIDS seems to be similar to that of hepatitis B, it is conceivable that at some point in the future a health care professional will contract AIDS through an accidental needlestick or through contact with tissues or fluids from an AIDS patient. Should health professionals accept such a hypothetical risk for the sake of their patients?

From a legal standpoint, a physician has no obligation to help any particular patient (Holder AR: Medical Malpractice Law, 2nd ed., John Wiley and Sons, New York, 1978, 7-19). Further, legally speaking, a private hospital is generally obliged to provide only emergency care; it need not accept a seriously ill patient for long-term care (Warren DG: Problems in Hospital Law, 3rd ed., Aspen Systems Corp., Germantown, Maryland, 1978, 81-91).

Even in the major codes of professional ethics, there is apparent hesitation to acknowledge a general duty to care for the ill. The American Medical Association's Principles of Medical Ethics (1980) asserts that, except in emergencies, "A physician shall, in the provision of appropriate patient care, ... be free to choose whom to serve ..." (reprinted in Beauchamp TL, Walters L: Contemporary Issues in Bioethics, 2nd ed., Wadsworth Publishing Co., Belmont, California, 1982, 122). Similarly, the 1976 Code for Nurses of the American Nurses' Association (ANA) also qualifies the duty to treat: "If personally opposed to the delivery of care in a particular case because of the nature of the health problem or the procedures to be used, the nurse is justified in refusing to participate" (Ibid: 123). The nurses' right of conscientious refusal applies in all nonemergency situations.

However, other parts of the nurses' code and the great tradition of professional practice point toward a general moral duty to provide care to anyone who needs it, despite potential risks to one's own health. Thus, the ANA Code begins with the declaration that "The nurse provides services with respect for human dignity and the uniqueness of the client unrestricted by considerations of social and economic status, personal attributes, or the nature of the health problem." In her Notes on Nursing, published in 1860, Florence Nightingale was even more explicit about the moral duty to care. She wrote: "True nursing ignores infection, except to prevent it.

Cleanliness and fresh air from open windows, with unremitting attention to the patient, are the only defence a true nurse either asks or needs" (Nightingale F: Notes on Nursing: What It Is, and What It Is Not, Dover Publications, New York, 1969, 33-34). The medical profession also has its examples of physicians exemplifying profiles in courage (Eisenberg L: Science, 1977, 198(4322): 1105-1110; Barrett-Connor E: JAMA, 1979, 241 (1):37).

Thus, despite the hesitation evident in two recent codes of professional ethics, the history of health care theory and practice lends strong support to what might be called the altruistic thesis--namely, that health professionals have a moral duty to care for all who need their help. This responsibility holds even if many AIDS patients, like many patients with other serious diseases, have contributed to the compromise of their good health. This moral duty to provide care will remain a duty even if the transmission of AIDS from a patient to a physician, nurse, or clinical laboratory worker is one day documented.

In addition to the general duty to provide care for AIDS patients, health professionals have specific moral duties which are of great importance to AIDS patients. I will briefly mention two: the duty to respect privacy and the duty to provide appropriate care for the dying.

All of the major codes of health-care ethics stress the obligation of health professionals to preserve the confidentiality of information that passes from patients to their caregivers. The duty of confidentiality is especially important when sensitive information about sexual practices or drug use is elicited from patients for diagnostic or therapeutic purposes.

One legal step that has been taken by some government agencies involves the provision of a protective "shield" for sensitive medical information. In New York City, for example, medical records concerning drug abuse, sexually transmitted diseases, and AIDS are immune to subpoena (D. Lorimer, personal communication). Similar legislation has been enacted at the federal level to protect the confidentiality of health information gathered by the National Center for Health Statistics (U. S. Code, Title 42, Paragraph 242m(d)).

A second specific duty of health professionals is to provide appropriate care for patients who are in the terminal stages of their disease. Many AIDS patients die a lingering death in the hospital, sometimes after having lost contact with their social support systems. As ethicist Paul Ramsey has so eloquently reminded us, health professionals have an ongoing responsibility to care for the dying, even when all possibility of cure is gone (Ramsey P: in The Patient as Person, Yale University Press, New Haven, 1970, 113-164). Similarly, the great English clinician, Thomas Percival, made the point in his Medical Ethics, published in 1803, that "the offices of a physician may continue to be highly useful to the patient and comforting to the relatives around him, even in the last period of a fatal malady; by obviating despair, by alleviating pain, and by soothing mental anguish" (Percival T: in Leake CD (Ed): Percival's Medical Ethics, Williams & Wilkins, Baltimore, 1927, 98).

II. Responsibilities to Other Members of the Society

Contrary to popular mythology, AIDS is not likely to be spread through casual contact with AIDS patients. Since AIDS seems to be transmitted sexually or

through blood or blood products, there are three major groups at risk of contracting AIDS from AIDS patients: (1) their sexual partners, if any; (2) persons who share needles with AIDS patients, if the patients use intravenous drugs; and (3) persons receiving blood or blood products donated by AIDS patients. The public health dimension of AIDS is complicated by uncertainty about the absolute levels of risk for these three groups and by uncertainty about whether persons who have latent AIDS without major clinical symptoms can transmit the disease to others.

It can be argued that the close personal associates of a patient who has clinically demonstrated AIDS (groups 1 and 2 above) have a moral right to know about the patient's condition. This right would be based on the life-threatening character of AIDS, the possibility of transmitting the disease from patient to associate through sexual contact or shared needles, and the possibility of reducing the relative risk of such transmission. Even if this moral right to know is granted to the patient's associates, there remains a critical question: Who has the corresponding moral duty to inform those associates?

Here one despairs of formulating a general rule to cover all cases. However, in a society that is as committed to individual civil liberties as we profess to be, the preference should go to voluntaristic approaches that rely on (a) the concern of AIDS patients for their associates and (b) the information that members of high-risk groups have received and will receive from carefully targeted public education programs. This voluntaristic approach can be combined with the mandatory reporting of AIDS cases for surveillance purposes, provided that personal identifiers are removed from case reports to protect the anonymity of individual patients.

The third group at possible risk of contracting AIDS from AIDS patients is comprised of distant neighbors, the recipients of blood or blood products donated by AIDS patients, or perhaps even by future AIDS patients who have not yet developed frank disease. As noted earlier, there are 16 hemophiliacs who are not known to be members of high-risk groups but who have nonetheless contracted AIDS, most probably from the blood products used for their therapy. Several cases of suspected transmission of AIDS through transfusions have also been reported (JAMA, 1983, 249(12):1544-1545). Understandably, the reports of these cases have aroused both fear and resentment within the community of hemophiliacs and among many persons contemplating their own possible future need for blood transfusions. Even though the probability of harm to any given recipient of whole blood or antihemophilic factor is very slight, the magnitude of the harm when it occurs is great indeed.

In the long run, hemophiliacs and transfusion recipients will be best protected by either an effective screening test for the etiologic agent in AIDS or a method for inactivating that agent. In the interim, recipients of blood and blood products have little recourse but to rely on the good will of members of groups at high risk for contracting and transmitting AIDS. Newsletters oriented to the gay community and blood and plasma collection centers have urged members of high risk groups to refrain voluntarily from donating blood or selling plasma. Some centers have developed creative techniques for screening donors while maintaining donor anonymity.

Health professionals have moral obligations both to AIDS patients and to the other members of society. There are clearly tensions between these two sets of responsibilities. In fact, these tensions are reminiscent of venerable conflicts between the duties of primary caregivers and public health officials. If the irrational fears surrounding AIDS can somehow be allayed, I am convinced that health professionals will succeed in providing respectful and increasingly effective care for AIDS patients, while at the same time discovering new and creative ways to protect other members of society from the devastating impact of this disease.

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ASSOCIATION OF AIDS WITH A HISTORY OF BLOOD TRANSFUSION

Investigators at the CDC (Curran JW, Lawrence DN, Jaffe H, et al, N Engl J Med., 1984, 310:69-75) incriminate transfusion of blood and blood fractions as a risk factor for the acquisition of AIDS. Their evidence, while compelling, depends on an analysis that many may find difficult to follow. Their finding is that, although no blood donor with manifest AIDS was encountered, high-risk donors are uniformly found among those who have contributed blood to persons who subsequently developed AIDS. This finding is highly improbable under the null hypothesis which posits that the number of patients with transfusion-associated AIDS exposed to a high-risk donor would not be greater than the number expected by chance on the basis of the total number of donors to which each patient was exposed and the estimated prevalence of high-risk donors in the overall donor population. Although a simpler approach would be to compare the actual frequency of a history of blood transfusion among these AIDS patients with the frequency of transfusions in the general population, survey data that directly address the frequency of transfusion histories in the US population do not exist (J. Feldman, personal communication).

An indirect approach to estimating the expected frequency of transfusion histories can be made by combining available data from several sources. Friedman and colleagues (Friedman BA, Burns TL, Schork MA, et al: in Homburger HA and Batsakis JG (Eds): Clinical Laboratory Annual, Appleton Century Crofts, New York, 1982, 1:147-169) published a study showing the frequency of transfusions in the US using over one million hospital discharge records collected by the Commission on Professional and Hospital Activities. In another report, prepared by the National Center for Health Statistics (NCHS Series 10, No. 141, DHHS Publication (PHS) 82-1569, Table 15), estimates of the frequency of hospitalization, by age and sex, in the US population have been published. The product of values derived from these two studies can provide an estimate of the frequency with which any person or group of persons receives a transfusion. This value overlooks the rare transfusion administered to an ambulatory patient. The result will tend to overestimate the probability of a past transfusion history, because of the implicit assumption that no mortality difference exists between those who do and those who do not receive a transfusion. However, this approach should provide an upper limit to the number of AIDS patients who would be expected to give a history of blood

transfusions under the null hypothesis which assumes that there is no association between transfusions and AIDS.

The figures in Table 1 were very kindly provided by Dr. Friedman and his colleagues from unpublished tabulations in their investigation. Fitting a straight line by least squares analysis to the transfusion frequency as a function of the mid-point of each age interval made it possible to obtain by interpolation the first four transfusion frequencies for each sex (column 4 of Table 2). The fifth is taken directly from Table 1. The age and sex distribution

TABLE 1
PATIENTS DISCHARGED FROM HOSPITALS: AGE, SEX, AND TRANSFUSION HISTORY

	Percent Transfused	
Age	Male	Female
0-19	1.25	1.51
20-34	2.75	2.53
35-49	4.11	4.56
50-64	6.86	6.29
65 and over	9.55	9.72

TABLE 2
OBSERVED AND EXPECTED TRANSFUSION HISTORIES AMONG AIDS PATIENTS NOT BELONGING TO MAJOR RISK GROUPS

Age	No. AIDS Patients Reported to CDC	US Population Hospitalization Rate (%)	Hospital Transfusion Rate (%)	No. Cases Giving a Transfusion History	
				Expected	Observed
Males					
Under 25	4	7.0	2.175	0.03	1
25-34	19	7.4	3.278	0.23	1
35-44	19	9.5	4.439	0.40	2
45-64	29	18.2	6.181	1.59	12
65 and over	3	31.4	9.55	0.42	2
Totals	74			2.67	18
Females					
Under 25	8	21.0	2.313	0.19	0
25-34	23	21.9	3.305	0.82	3
35-44	7	13.8	4.349	0.21	0
45-64	15	16.9	5.916	0.74	7
65 and over	4	26.3	9.72	0.49	1
Totals	57			2.45	11
Grand Totals	131			5.12	29
				($p < 0.0001$)	

of the 131 adult cases of AIDS not belonging to any of the four major risk groups and having Pneumocystis carinii pneumonia are given in columns 1 and 2. These data, which were reported to CDC up to January 10, 1984, and the numbers of AIDS patients giving a history of transfusion within the past 5 years (column 6) were kindly provided by Dr. Curran. The expected number of AIDS patients giving a history of transfusion within 5 years (column 5) was computed according to the formula $E = N\ [1-(1-HT)^5]$ where E = expected number giving transfusion history, N = number of AIDS cases in the category (column 2), H = annual hospitalization rate (column 3), T = in-hospital transfusion rate (column 4).

The number of cases observed in each age-sex group exceeds expectation (columns 5 and 6), except where no cases were observed. Altogether, 29 cases were observed compared with an expectation of just over five. The strength and the consistency of the association speak for themselves. However, it is also of interest to note the value of Z for the standard statistical comparison of two rates or proportions. The result is 4.38, corresponding to a p value of less than 0.0001.

This analysis, using an entirely independent argument, appears to offer strong confirmation for the conclusions of Curran and colleagues.

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ARE SWINGERS AT RISK FOR AIDS?

Demographic studies traditionally have been of use in unraveling the mysteries of infectious disease processes. Such studies permit the construction of Venn diagrams which show the complex relationships of various factors in and to a disease. The peculiar demography of AIDS is evidenced in Venn diagrams showing relationships among homosexual preference, exposure to blood and blood products, geographical area, and so on. The diagrams can provide useful guides to laboratory research.

Most models designed to explain AIDS include both a mechanism by which immune responsiveness is diminished in affected individuals and an etiologic role for a new or altered strain of virus. The latter is invoked in part because AIDS is a new disease affecting mostly homosexual men, yet homosexual behaviors are not new (although they may now possibly involve greater degrees of promiscuity).

A number of the hypotheses concerning the etiology and spread of AIDS envision disease transmission through anal intercourse. However, no difference in the prevalence of anal intercourse has been reported between AIDS patients and matched healthy homosexual male controls (Darrow WW, Jaffe HW, Curran JW, Lancet, 1983, 2:160). In addition, anal intercourse is common as a heterosexual variant.

I suggest that a critical population to study in an effort to resolve some of the etiologic issues might be the group of so-called swingers who exist in precisely the geographic areas (New York, San Francisco, Los Angeles) where AIDS has its highest reported prevalence. Swingers have numerous heterosexual partners and may be as promiscuous as the most promiscuous male homosexuals

affected with AIDS. The "ground rules" for swingers usually exclude direct male-to-male contacts within the group but include heterosexual anal intercourse as a sexual variant. Most swingers are "tri"-sexuals (who will try anything). Drugs are usually frowned upon.

The swinger population is not epidemiologically closed: some of the male members engage in bisexual or homosexual activities outside the group in geographic areas where AIDS is prevalent. Clearly, if AIDS involves a specific venereal infection, the incidence of altered immunity should be demonstrable in swingers, particularly in those belonging to groups in which "exploration of the homosexual option" is encouraged. (In a study conducted in 1973-74, the only transmissible infections which members of this subculture reported as troublesome were trichomoniasis and angular conjunctivitis. More recently anxiety about the transmission of genital herpes has been reported. No major venereal disease(s) nor unusual ill health appear to have been reported.)

This group is small but is accessible for study by virture of its being organized. It does not appear to have been studied to date. A systematic study would provide data of use in constructing Venn diagrams for certain important elements which have been postulated as being contributory to both the spread and causation of AIDS. Among these would be exposure to numerous partners, practice of male-female anal intercourse, exposure to whole blood, exposure to seminal antigens from successive acts of coitus by more than one male with a single female, and transmission of an infectious agent through heterosexual contact. In addition, a study of immune competence in relation to these factors among multi-partnered individuals might throw light on a critical and underexplored side issue, that gender dysphoria itself assorts with some type of immune deficiency. Gender dysphoria is not a characteristic of the swinger subgroup.

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SEXUAL CONTACTS OF HOMOSEXUAL MEN WITH AIDS OR AIDS PRODROME

Epidemiologic evidence suggests that a transmissible agent in body secretions or blood is responsible for the spread of AIDS. We evaluated 18 sexual contacts of seven homosexual AIDS patients and seven homosexual men with the AIDS-related complex (ARC). All ARC patients had generalized lymphadenopathy, unexplained fever, weight loss, or malaise. Eleven of the 18 contacts had contact with AIDS patients and seven with the ARC patients. Of the 18, six had symptoms or signs and 12 were asymptomatic. The four groups of men were compared with 57 asymptomatic homosexual men with no known contact with AIDS patients. Lymphocyte counts, total T cells, T-cell subsets, skin test reactivity to five recall antigens, and immunoglobulin concentrations were recorded (Table).

AIDS and ARC patients showed T-cell lymphopenia, depletion of helper lymphocytes (OKT4), and markedly abnormal helper:suppressor (OKT4:OKT8) ratios. In symptomatic contacts (SXC), values for these parameters resembled those of AIDS and ARC patients. In contrast, asymptomatic contacts (ASC) showed values for lymphocytes, T cells, T-cell subsets, and OKT4:OKT8 ratios which were similiar to those of controls. Anergy to five

skin test antigens was present in a high proportion of men with AIDS, ARC, and SXC compared to 18% of ASC and control patients. Hypergammaglobulinemia was most marked in the AIDS patients; it was more frequent in those with ARC, SXC, and ASC than in controls.

Only one of the 11 contacts of AIDS patients was himself symptomatic, while five of seven ARC contacts were symptomatic. Five of the sexual contacts have been re-examined 4-12 months after the initial evaluation. Three of these had contact with AIDS patients. Two of the three were initially asymptomatic and have remained free of symptoms. One contact initially had lymphadenopathy and weight loss. Four months later he had gained weight and showed a decrease in lymph node size. At follow-up, there were no changes in the lymphocyte counts, total T cells, or numbers of T-cell subsets in these men. Two of the three men had reversed OKT4:OKT8 ratios due to increases in the percentages and absolute numbers of OKT8 cells.

Two contacts of ARC patients initially had lymphadenopathy, fatigue, and weight loss. At follow-up, the lymphadenopathy persisted but other symptoms had improved. Both men initially and at follow-up showed a reversal of OKT4:OKT8 ratios and one developed lymphopenia.

The wife and 13-year-old son of a bisexual man with Pneumocystis carinii pneumonia have also been studied. Both were asymptomatic at the time of evaluation and had normal numbers of T cells and T-cell subsets.

In this study symptoms at the time of evaluation rather than contact history correlated with alterations in immune status.

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IMMUNOLOGIC MEASUREMENTS IN PATIENTS, CONTACTS, AND CONTROLS

	AIDS (7)*	ARC (8)	SXC (6)	ASC (12)	Controls (57)
Total Lymphocytes†	1420±442	2013±654	1635±533	2235±678	2430±828
OKT3	1167±410	1569±511	1220±137	1710±494	1951±691
OKT4	351±278	687±337	419±214	876±226	1142±542
OKT8	752±257	922±272	758±192	915±429	1051±402
(OKT4:OKT8)	0.47±0.31	0.72±0.26	0.57±0.35	1.15±0.60	1.13±0.52
Anergy‡	83	43	33	18	18
IgG§	2954±847	1454±502	1514±308	1384±472	1194±245
IgA	485±345	188±77	350±117	199±49	231±94
IgM	217±132	173±73	225±120	232±97	191±83

* (Number of patients). † Cells/mm³. ‡ % of patients. § µg/ml.

BONE MARROW CHANGES IN AIDS

Bone marrow aspirates from 14 patients with AIDS seen at the East Orange Veterans Administration Hospital between May 1982 and December 1983 were studied by light microscopy using routine Giemsa staining procedures. Three specimens were inadequate. Of the remaining 11, ten shared an unusual feature. These ten marrow preparations contained occasional mononuclear cells which had a thin rim of pale blue cytoplasm without granules. The nuclei were irregular in shape with cerebriform convolutions. The chromatin was clumped and a large nucleolus was easily identified. These cells were comparable in size to myelocytes.

The unusual cells accounted for about 0.5% of the nucleated marrow cells. Such cells were rarely seen, if at all, in marrow from non-AIDS patients.

These mononuclear cells are clearly not of either the myeloid or the erythroid series. Their cytoplasmic features are not typical of mature monocytes; nor are the nuclear features typical of lymphocytes. However, they could represent activated monocytes or lymphocytes.

This finding is probably not pathognomonic for AIDS. However it constitutes an additional finding to consider when evaluating patients suspected of having AIDS.

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AFRICAN EOSINOPHILIC BODIES IN VIVO IN TWO MEN WITH KAPOSI'S SARCOMA AND AIDS

Histologic analyses were performed on biopsy specimens from cutaneous Kaposi's sarcoma (KS) tumors of two men with AIDS. One patient was a 51-year-old, promiscuous, bisexual, black American man with extensive lesions of KS on the trunk, bilateral parotid swelling, and Whipple's-like intestinal disease. The other patient was a 42-year-old, promiscuous, homosexual, Mexican-American man with multiple cutaneous lesions of KS and Pneumocystis carinii pneumonia.

With routine hematoxylin-eosin staining procedures, pink-stained, variably sized, coccoid-shaped, intracellular and extracellular eosinophilic bodies were seen. Such forms are commonly observed in histologic analyses of specimens taken from African cases of KS (Murray JF, Lothe F: Acta Unio Int Cancer, 1962, 18:413-428). The eosinophilic bodies can be identified in sections of KS specimens stained with Gram's stain or the Giemsa stain, as previously noted by pathologists in Africa (Lee FD: J Clin Pathol., 1968, 21:119-128). In this study, these forms were best identified in Fite (acid-fast) stained sections using the oil-immersion lens (×1000).

The exact nature of the eosinophilic bodies is unknown. Such structures have been reported in other types of tumors (Ibid: 119-128) and are thought to be related to Russell bodies. They are very similar to and may be identical to the acid-fast coccoid forms and Russell bodies detected previously in various forms of cancer and in KS and AIDS (Cantwell AR Jr: Growth, 1982, 46:331-336; Growth, 1983, 47:129-134; Cutis, 1983, 32:58-68). These eosinophilic bodies may be directly related to the cell wall deficient forms of bacteria

which can be demonstrated in vivo. They may also be related to the elusive and mysterious "agent" of KS and AIDS.

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CHEMOIMMUNOTHERAPY PROTOCOL FOR EPIDEMIC KAPOSI'S SARCOMA

A protocol has been initiated at the Rita and Stanley H. Kaplan Cancer Center at New York University to evaluate the effects of concurrent therapies with recombinant alpha-2 interferon (IFN) (Schering Corp., Kenilworth, NJ) and etoposide (VP-16) in the treatment of patients with the epidemic form of Kaposi's sarcoma (EKS).

The extent of disease in patients will be determined according to the classification of Krigel et al. (Krigel RL, Laubenstein LJ, Muggia FM: Cancer Treat Rep., 1983, 67:531-534) and only those in stages III and IV subsets A and B will be eligible. All patients must not have received prior systemic therapy and must not have current opportunistic infections.

Escalating doses of both IFN (15-50 × 10^6 U, days 1-5) and VP-16 (100-150 mg/m^2, days 1-3) will be administered intravenously in 21 day cycles for a total of 4-6 cycles.

After completion of this induction phase, patients in whom a complete response (CR) is achieved will receive either maintenance therapy or no further therapy. The effect of IFN on the duration of CR will be evaluated. Other effects of the therapeutic protocol which will be evaluated include effects on immune functioning, on the subsequent development of opportunistic infections and classification of these infections, and on overall survival. Patients showing partial responses (PR will be measured as reduction in the size of lesions by more than 50% in cross-sectional area) following initial therapy will receive further IFN therapy; observations will then be made on the ability of IFN to convert PR into CR.

It is hoped that the combination therapy, aimed at both immune modulation and anti-neoplastic effects, will yield better results than can be obtained using each agent alone. Both IFN (Krown SE, Real FX, Cunningham-Rundles S, et al: N Engl J Med., 1983, 308:1071-1076; Krown SE, Real FX, Cunningham-Rundles S, et al: N Engl J Med., 1983, 309:923-924; Volberding P, Gottlieb M, Rothman J, et al: Proc Am Soc Clin Oncol., 1983, 2:53) and VP-16 (Laubenstein LJ, Krigel RL, Hymes KB, et al: Proc Am Soc Clin Oncol., 1983, 2:228) have known activities in EKS when given as single therapeutic agents.

The study was begun on January 1, 1984. Further information concerning entry into and conduct of the study can be obtained from Drs. R. L. Krigel or C. Odajnyk at (212) 340-7226 or (212) 340-6485.

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A PILOT STUDY OF IN VIVO IMMUNOMODULATION BY ISOPRINOSINE IN AIDS AND AIDS-RELATED COMPLEX

The immunomodulatory effects of isoprinosine were studied in vivo in nine patients with AIDS and AIDS-related complex. All patients had been stable clinically for at least 4 weeks before

the initiation of therapy. Isoprinosine (Newport Pharmaceuticals International, Inc., Newport Beach, CA) was administered in doses of 4 gm/day for 4 weeks to patients who had given written informed consent. Blood samples were drawn just before treatment was started, on the 14th and 28th days of therapy, and 14 days after discontinuation of the drug. T cells were analyzed phenotypically for OKT4 and OKT8 markers. Lymphocyte proliferative responses to mitogens were quantitated before therapy, on the 28th day of therapy, and 14 days after the discontinuation.

There was no significant association of isoprinosine treatment and alteration of OKT4:OKT8 ratio in any subject. There were no significant enhancements of lymphocyte proliferative responses to phytohemagglutinin (PHA), concanavalin A (Con A), and pokeweed mitogen (PWM) in five patients with AIDS.

The mean lymphocyte proliferative responses to PHA in four patients with AIDS-related complex increased from 39,109(±35,442) cpm to 64,546(±35,307) cpm after 28 days of treatment and then decreased to 15,481(±10,096) cpm 14 days after discontinuation. Similarly, the mean lymphocyte proliferative responses to Con A in the patients with AIDS-related complex increased from 10,681 (±8,245) cpm to 60,478(±33,119) cpm after 28 days of therapy ($p < 0.05$) and decreased to 12,418(±10,395) cpm 14 days after discontinuation of the drug. The proliferative response to PHA in one of four patients with AIDS-related complex increased markedly after 28 days of treatment with isoprinosine, while the Con A response was enhanced in all four.

Further trials appear warranted with isoprinosine in a larger group of patients with AIDS-related complex to establish immunologic effectiveness, appropriate dosages, and mechanism(s) of immune enhancement.

M. H. Grieco, M. M. Reddy, M. L. Moriarty, D. Manvar, and K. K. Ahuja. R. A. Cooke Institute of Allergy, St. Luke's/Roosevelt Hospital Center, New York, New York 10019.

UPCOMING AIDS MEETING

Conference on AIDS: Diagnosis and Management. A Conference Designed for the Physician in Primary Care.

June 8-10, 1984
Warwick Post Oak Hotel
Houston, Texas

Information will be presented on the etiology and epidemiology of AIDS. Clinical presentations, diagnostic procedures (especially immunologic methods), treatments, and complications associated with AIDS and KS will be reviewed. The infectious complications and treatment protocols using chemotherapy, immunotherapy, and immune restoration will be emphasized.

Speakers: J. Knox, D. Schottenfeld, D. McMurrey, C. Ericsson, V. Fainstein, J. L. Melnick, C. Noonan, I. Shivitiz, P. Volberding, F. Hagemeister, C. Lane, A. Rios, C. Plager, M. Grieco, Y. Patt, P. W. Mansell, G. Newell, and E. Hersh.

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AIDS CASES REPORTED TO THE CENTERS FOR DISEASE CONTROL AS OF April 2, 1984

UNITED STATES CASES

DISEASE	CASES	PERCENT OF TOTAL	DEATHS	PERCENT DEAD
KS without PCP	989	25.0	243	24.6
PCP without KS	2042	51.6	975	47.7
Both KS and PCP	266	6.7	167	62.8
OI without KS or PCP	657	16.6	338	51.4
TOTAL	3954	100.0	1723	43.6

KS = Kaposi's sarcoma
OI = Opportunistic infections
PCP = Pneumocystis carinii pneumonia

	MALES		FEMALES		TOTAL	
RISK GROUPS*	CASES	% OF TOTAL	CASES	% OF TOTAL	CASES	%
Homosexual or bisexual	2819	76.6	0	0.0	2819	71.3
IV drug user	547	14.9	150	55.1	697	17.6
Haitian	141	3.8	24	8.8	165	4.2
Hemophiliac	28	0.8	0	0.0	28	0.7
No apparent risk group or unknown	147	4.0	98	36.0	245	6.2
TOTAL	3682	100.0	272	100.0	3954	100.0

* The risk groups listed are hierarchically ordered; cases with multiple risk factors are tabulated only in the risk group listed first.

INSTRUCTIONS FOR AUTHORS CONTRIBUTING TO THE AIDS MEMORANDUM

Content: Articles published in the AIDS Memorandum must have obvious relevance to AIDS. They can describe clinical or experimental findings. Letters and other types of commentary are also welcome. All manuscripts should be typed double spaced.

References: References should be integrated into the text in parentheses. Each citation should include the names of up to three authors, the journal title, the year of publication, volume and issue numbers, and inclusive page numbers. Citations from books should include the names of up to three authors, book title, editor(s), publisher, publisher's location, year of publication, and relevant page numbers.

Tables and Figures: Whenever possible, data should be organized into tables. Figures should be clear and no wider than 3½ inches.

Announcements of Meetings: Announcements of upcoming AIDS meetings should include meeting title, location, and date and the name, address, and telephone number of the organizer of the meeting.

Further Information: For further information call the AIDS Memorandum office at (301) 496-9537.

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AIDS
MEMORANDUM
Acquired Immune Deficiency Syndrome

National Institute of Allergy and Infectious Diseases

Volume 1, Number 5 May 1984

IN THIS ISSUE

GROUND RULES FOR USE OF THE AIDS MEMORANDUM

The AIDS Memorandum serves as a forum for the rapid exchange of new information and ideas among clinicians and scientists involved in AIDS research and management. Material contained in the Memorandum can be of several kinds: positive and/or negative results, clinical and/or experimental findings, preliminary and/or validated data, observations, questions, theories, commentaries, and others. This material is not subjected to peer review. Therefore, users of the Memorandum must agree to treat all material as privileged information and to consider it as tentative and subject to change prior to formal publication in a refereed journal.

Users must agree not to cite material from the Memorandum without first obtaining the consent of the author(s), and, with author permission, to cite information only as a personal communication. Author addresses are provided for this purpose.

Users must agree to contribute data or ideas to the Memorandum at least once a year. On an annual basis, the names of individuals who have not contributed to the Memorandum will be culled from the mailing list, so as to limit circulation of the Memorandum only to individuals actively working in the field.

Finally, users must agree to share material in the Memorandum only with other individuals willing to honor these ground rules.

A NEW HUMAN T-LYMPHOTROPIC RETROVIRUS: CHARACTERIZATION AND POSSIBLE ROLE IN LYMPHADENOPATHY SYNDROME AND AIDS

The T-lymphotropic retrovirus (LAV1) isolated from a patient with lymphadenopathy syndrome (LAS) (Barré-Sinoussi F, Chermann JC, Rey F, et al: Science, 1983, 220:868-871) has been further characterized. Cultured T lymphocytes from either umbilical cord or peripheral blood of healthy, virus-negative, adult donors were suitable for virus propagation (Ibid; Vilmer E, Barré-Sinoussi F, Rouzioux C, et al: Lancet, 1984, 1:753-757). Virus production usually started 9-15 days after infection and lasted for 10-15 days. In no case was the emergence of a continuous permanent line observed.

Electron microscopy of ultrathin sections of virus-producing cells showed two types of virus particles. These were presumed to correspond to the immature and mature forms of the virus. The immature particles were seen to bud at the cell surface, with a dense crescent in close contact with the plasma membrane. Ribosome-like structures could sometimes be observed in these particles. Mature particles had small, dense, eccentric cores of mean diameter = 41 nm. Most of the virions were round (mean diameter = 139 nm) or ovoid. In some pictures, a tailed morphology could also be observed. This form was seen in particles in cytoplasmic vesicles released into the medium; it was first observed in particles in the original culture from which the virus was isolated.

The morphology of mature LAV particles is clearly distinct from the morphology of human T-cell leukemia virus (HTLV) particles. Both mature and immature forms of LAV were morphologically similar to particles of equine infectious anemia virus (EIAV) (Tables 1 and 2).

TABLE 1
COMPARISON OF LAV1 AND HTLV1

Similarities	Differences
1. Human retroviruses	1. Major core proteins, LAV p25, HTLV p24, not antigenically related
2. Mg^{++}-dependent reverse transcriptase	2. Morphology (EM): Eccentric core in LAV half the size of HTLV core
	3. Co-cultivation not required for infection of lymphocytes with LAV1
	4. No immortalized T-cell line obtained after LAV infection to date

The main protein isolated from LAV had a molecular weight of 25,000 daltons (p25). It was the only protein recognized by serum from the patient from whom it was isolated. Immunoelectron microscopy experiments showed that the protein is located in the viral core: viral cores could be agglutinated by the patient's serum (S. Rousset, personal communication). Major proteins of other retroviruses have also been shown to be core-associated.

No homology was found between p25 of LAV1 and p24 of HTLV (types 1 and 2) (Barré-Sinoussi F, Chermann JC, Rey F, et al: Science, 1983, 220:868-871). Antisera against p24 and p25 did not

TABLE 2
COMPARISON OF LAV1 AND EIAV

Similarities	Differences
1. Retroviruses	1. Target cells are not the same in vitro and in vivo
2. Mg++-dependent reverse transcriptase	2. LAV1 does not grow in fibroblastic human lines nor in equine dermis cell line
3. Morphology (EM): eccentric asymmetric core	
4. p25 proteins antigenically related	
5. Active production (with cytopathic effect) in a small proportion of infected cells	
6. Same pattern of major polypeptides: core protein = p25 envelope protein = gp40? p15?	

cross precipitate the two proteins. No cross-reactivity was found between LAV1 and bovine leukemia virus, feline leukemia virus, or simian sarcoma-associated virus. A weak cross-reactivity with EIAV was detected through immunoprecipitation of polyacrylamide gel electrophoresis bands using an antiserum against p25. However, immunodiffusion tests using sera from patients positive against LAV1 did not show a precipitin line to EIAV antigens (B. Toma, personal communcication). Preliminary experiments showed no homology between DNA from LAV1-infected cells and an HTLV DNA probe, even under low stringency of hybridization conditions (F. Wong-Staal, personal communication).

The majority of cultured T cells isolated from the patient's lymph node reacted with homologous serum in immunofluorescence studies of fixed cells. (The main antigen recognized in this test is presumed to be p25 viral protein.) Therefore, even though production of mature virions as detected by reverse transcriptase (RT) activity was rather low, most of the cells in culture were infected with the virus and expressed viral proteins. When the virus was propagated in lymphocytes from normal donors, only between 2 and 10% of cells contained virus, as indicated by immunofluorescence studies of fixed cells, at the peak time of virus production. Increasing the amount of virus used to infect the cells did not result in an increase of virus production. From normals, therefore, only a minority of T cells were in a state conducive to virus production.

When lymphocytes were fractionated into subsets and infected with LAV1 (D. Klatzmann et al, in preparation), the virus showed an obvious tropism for the OKT4+ subset. Immunofluorescence staining indicated that approximately 10% of the OKT4+ cells expressed viral antigens. The OKT4+ phenotype remained unchanged during virus production. No gross changes, such as cell lysis or impairment of cell growth, could be seen in virus-producing cultures. However, since only a minor fraction of T-helper cells seems to produce virus, a specific cytopathic effect on this subset cannot be excluded.

OKT8+-enriched cell cultures infected under the same conditions did not produce any detectable RT activity, even 6 weeks after virus infection. Adherent cells (macrophages) and B cells after

mitogenic stimulation also did not produce virus. Preliminary experiments with bone marrow cells suggested that immature (OKT3-depleted) cells could be infected and produce virus.

The tropism for helper T cells may also exist in vivo. A healthy black Caribbean woman carried a virus similar or identical to LAV1 in blood lymphocytes. When these cells were fractionated into subsets, put in culture, and stimulated, only the OKT4+ subset produced virus as detected by RT activity.

Activated lymphocytes from a healthy donor which were spontaneously releasing a virus similar to LAV1 in culture were infected in vitro with LAV1. A few giant polycaryons appeared in these cultures after a lag of 6-7 days. Electron microscopic examination showed numerous particles of the LAV type budding at the cell surface. Examples of progressive cell fusions were also seen. The giant cells rapidly degenerated in the cultures. HTLV-producing cell lines (Popovic M, Sarngadharan MG, Read E, et al: Science, 1984, 224:497-500) also include giant cells which probably arise from virus-induced cell fusions.

It is possible that cell-fusion activity, after repeated infections with LAV1 or similar retroviruses, could lead to the degeneration of a fraction of the T-cell population. Viral proteins at the plasma membrane (and perhaps in other membranes) of host cells could greatly affect specialized functions of the cells. The degeneration of giant cells may represent the extreme situation of viral cytopathic effects.

Cells of lymph nodes from five other LAS patients were put in culture. No virus production could be detected (as measured by RT activity). However, antiserum from the original patient detected a p25 protein in cytoplasmic extracts of T cells in three cases. All of the six LAS patients had antibodies against LAV p25, indicating that all had been infected at some time with a similar or identical virus. From lymphocytes of one of the patients, a p24-p25 band showed weak but definite immunoprecipitation with goat antiserum raised against HTLV1. The patient's serum had antibodies against both HTLV and LAV1, suggesting a double infection.

LAV1 or LAV-like viruses were also isolated from lymphocytes taken from lymph nodes or blood of individuals with authentic cases of AIDS (see accompanying paper). The retroviruses (referred to as immune deficiency-associated viruses [IDAV1 and IDAV2]) of two of the AIDS cases have been propagated on normal lymphocytes and partially characterized. So far, they are similar if not identical to LAV1. The virus yield from lymphocytes from one blood donor was three to four times higher when cells were infected with IDAV1 or IDAV2 than when they were infected with LAV1.

The viruses have the main characteristics of retroviruses. LAV1 shows measurable Mg^{++}-dependent RT activity in culture supernatants, a density of 1.16 in sucrose gradient, and morphogenesis by budding at the plasma membrane. Preliminary data show a fast-sedimenting RNA component. It is tropic for OKT4+ T-helper lymphocytes and has a slight cytopathic effect in cells actively producing virus.

While LAV1 is clearly distinct from HTLV (1 and 2) isolates, it shows some analogy to EIAV. The similarities between these two retroviruses include identical morphologies and common antigenic determinants of the major core proteins. EIAV infection causes lifelong severe infection in horses, characterized by bursts of fever with anemia. Each burst seems to coincide with the appearance of a new antigenic variant of

the viral glycoprotein (Issel CJ, Coggins L: J Am Vet Med Assoc., 1979, 174: 727-733). In LAS patients, antibodies against viral envelope proteins were not found in sera. If this is an indication that similar antigenic variations occur in LAV1, such variations may be relevant to how pathogenicity is accomplished by the virus. Both EIAV and LAV1 appear to be relatively stable: the LAV-related viruses isolated from a hemophiliac patient and from his brother were probably transmitted in blood-derived preparations in which they survived several steps of purification (Vilmer E, Barré-Sinoussi F, Rouzioux C: Lancet, 1984, 1: 753-757).

The evidence for the role of LAV and LAV-related viruses in LAS and AIDS, although indirect and circumstantial, is as follows: (1) The virus is present and expressed in cultured lymphocytes from LAS and AIDS patients in the majority of the cases investigated. (2) The virus replicates exclusively in OKT4 lymphocytes. These are the very cells depleted in AIDS. Although adsorption of the virus can take place in unstimulated blood lymphocytes, virus production by these lymphocytes requires stimulation and the continuous presence of T-cell growth factor. (3) Serologic data indicate that most of the LAS patients have been infected with LAV-related viruses, and only a minority with HTLV1 (see accompanying paper). (4) Based on the finding of LAV in the hemophiliac siblings, the virus seems to be transmissible through blood and blood products.

Final proof that LAV or a LAV-like virus plays an etiologic role in AIDS (and perhaps other diseases) will require confirmation of the initial results, additional data, and production of the disease in an animal system. The available data do allow us to draw a general outline for the virus etiology of AIDS.

We postulate that T-lymphotropic retroviruses--including LAV and HTLV-related viruses--are the primary agents of the disease. The primary infection in most cases would not be apparent, because only a small population of T lymphocytes (from blood, lymph nodes, bone marrow) would be infected and would integrate the viral genome. For the secondary phase, many antigenic stimuli (including repeated viral and bacterial infections) might stimulate the T-cell system, including the already infected lymphocytes. Stimulated, infected cells would actively produce virus; the virus could then infect other stimulated lymphocytes and diffuse throughout the T-helper system. This phase of the disease could sometimes be limited to lymph nodes and induce a lymph node hyperplasia (LAS). In the final phase, the whole T-cell population, including stem cells, would be infected, and the patient would be in danger of developing severe and irreversible immune deficiencies.

The exact mechanisms by which the retroviruses induce AIDS in this scheme remain to be determined. The simplest explanation would involve a direct cytopathic effect, and some of our data can support this explanation. It is also conceivable that insertion of viral proteins into the plasma membrane may disturb helper cell functions. Finally, an autoimmune disease may occur: infected cells could generate a host defense mechanism (interferon, cytotoxic cells) which in turn would affect T-cell multiplication and functions.

Clearly, AIDS is a complex disease in which many genetic and environmental factors are involved. The availability of molecular probes for human lymphotropic retroviruses will help greatly in

defining the exact role of such viruses in the disease.

This article includes information from a paper (Human T-Cell Leukemia/ Lymphoma Virus. The Family of Human T-Lymphotropic Retroviruses. Their Role in Malignancies and Association with AIDS, 1984) which will be published by Cold Spring Harbor Laboratory and is reprinted here with permission from the publisher.

L. Montagnier, J. C. Chermann, F. Barré-Sinoussi, S. Chamaret, J. Gruest, M. T. Nugeyre, F. Rey, C. Dauguet, C. Axler-Blin, F. Vézinet-Brun, C. Rouzioux, G-A. Saimot, W. Rozenbaum, J. C. Gluckman, D. Klatzmann, E. Vilmer, C. Griscelli, C. Foyer-Gazengel, and J. B. Brunet. Institut Pasteur; Hôpital Claude Bernard; Hôpital La Pitie-Salpétriére; Hôpital Necker-Enfants Malades; Direction Generale de la Santé; Paris, France.

DETECTION OF IgG ANTIBODIES TO LYMPHADENOPATHY-ASSOCIATED VIRUS IN PATIENTS WITH AIDS AND WITH LYMPHADENOPATHY SYNDROME

An enzyme-linked immunosorbent assay (ELISA) was developed to determine whether specific IgG antibodies capable of reacting with the first isolate of lymphadenopathy-associated virus (LAV)--a new human retrovirus isolated from lymph node-cultured T lymphocytes of a homosexual man with lymphadenopathy syndrome (LAS) (Barré-Sinoussi F, Chermann JC, Rey F, et al: Science, 1983, 220: 868-871)--were present in sera from various other patients with LAS and in patients with AIDS. ELISA results have been compared with results obtained by a radioimmune precipitation assay (RIPA) detecting antibodies to the LAV p25 protein. In addition, anti-human T-cell leukemia virus (HTLV1) antibodies and anti-cytomegalovirus (CMV) IgG antibodies have been measured in order to evaluate the possibility of correlations among these three immunologic markers.

Serum samples were obtained from five groups: 51 patients with LAS (as defined in Morb Mort Weekly Rep., 1982, 19:249-251), 48 patients with AIDS, 44 healthy homosexual men who visited a venereal disease clinic in Paris, 100 unselected blood donors, and 30 healthy laboratory workers.

The LAV ELISA was set up in Nunc™ ELISA microtiter plates. Details of the technique are in press (Lancet). The LAV RIPA method has been described elsewhere in detail (Barré-Sinoussi F, Chermann JC, Rey F, et al: Science, 1983, 220:868-871). HTLV1 p24 antibodies were measured with a commercial ELISA (Bionetics) or by radioimmunoassay (RIA). The IgG antibodies to CMV were titrated by ELISA (Schmitz H, Doerr HW, Kampa D, et al: J Clin Microbiol., 1977, 5:629-634).

The results of the various antibody assays are shown in the table. Antibodies to LAV were detected in 74.5% of LAS patients. In 11 of 12 of these patients for whom blood samples had been collected more than once during the disease, sera remained either positive or negative for LAV antibodies throughout the study. The 12th patient first developed antibodies to LAV 2 years after the onset of LAS. In 18 cases, antibodies to LAV p25 were also determined by RIPA. In 13 of these, ELISA and RIPA results were perfectly correlated. In the other five cases, antibodies could be detected by RIPA but not by ELISA.

Viruses similar to LAV were isolated from cultured T lymphocytes derived from lymph nodes of two additional LAS patients. Sera from both contained LAV antibodies. One of these two went on to

POSITIVE SERUM SAMPLES

	LAV IgG ELISA	p24 HTLV ELISA*	CMV IgG ELISA
LAS	38/51 (74.5%)	5/51 (9%)†	46/50 (92%)
Homosexual men	29/40	4/40	37/40
Drug addicts	6/8	0/8	6/7
Haitians	3/3	1/3	3/3
AIDS	18/48 (37.5%)	6/48 (12.5%)‡	45/46 (98%)
OI	12/30	5/30	
KS	3/12	0/12	
OI + KS	2/5	1/5	
Brain lymphoma	1/1	0/1	
B hemophiliac	1/1	0/1	
Homosexual men	10/35	4/35	
Haitians	3/4	1/4	
Africans	4/8	1/8	
Controls			
Homosexual men	8/44 (18%)	0/44 (<1%)	41/44 (93%)
Blood donors	1/100 (1%)	0/100	45/100 (45%)
Lab workers	0/30	0/30	ND

Abbreviations: CMV, cytomegalovirus; ELISA, enzyme-linked immunosorbent assay; HTLV, human T-cell leukemia virus; KS, Kaposi's sarcoma; OI, opportunistic infection; LAS, lymphadenopathy syndrome; LAV, lymphadenopathy-associated virus; ND, not determined.

* When all sera were tested by p24 HTLV radioimmunoassay, only one from a homosexual man with LAS remained positive (L. Schaffar, personal communication).

† 3/6 were also LAV positive.

‡ 4/5 were also LAV positive.

develop AIDS. He is a French homosexual man who had lived for 2 years in Haiti (1980-81), developed a persistent fever in January 1982, LAS in March 1983, and mucosal and cutaneous KS in June 1983. Antibodies to LAV were first detected in January 1982, suggesting that viral infection had preceded other signs of disease.

There was no correlation between seropositivity to LAV and to CMV, since 92% of all LAS patients were positive for CMV IgG. There was also no correlation between decreases in T4:T8 ratios--in most cases resulting from increases in the number of cells in the OKT8 subset--and positivity for LAV antibodies.

Fewer patients with frank AIDS (37.5%) were positive for LAV. When tested by ELISA, 12.4% had HTLV1 antibodies, but none of the sera were positive for p24 HTLV1 antibodies when tested by RIA. In two of the AIDS patients, serologic studies began before the onset of AIDS. Both had LAV antibodies in the first serum samples tested. In one, the antibody titer decreased at the onset of AIDS; in the other, the antibody titer did not change. In two other AIDS cases, sera were analyzed during the development of AIDS. In one, the LAV titer remained positive throughout the test period; in the other, the titer shifted from positive to negative. In the latter, HTLV1 antibodies were also negative in the last sample tested, while the CMV IgG titer remained positive.

Sera of 25 AIDS patients were also tested for LAV by RIPA. In 18, RIPA and ELISA results coincided. In five, antibodies were detected by RIPA and not by ELISA. In two, antibodies were detected by ELISA but not RIPA.

Eighteen percent of healthy homosexual controls were seropositive for LAV antibodies. All but one seropositive individual had more then 50 sexual partners per year. None had HTLV1 antibodies, while most had CMV IgG. Only one blood donor and no healthy laboratory workers had LAV antibodies. The CMV IgG prevalence in controls was appropriate to a 30- to 40-year-old Northern European population (Boue A, Cabaun N: Nouv Presse Med., 1978, 7:3135-3139).

Retroviruses similar to LAV were isolated from several patients with frank AIDS. The viruses have been named immune deficiency-associated viruses (IDAV). IDAV1 was isolated from an AIDS patient with Kaposi's sarcoma. Serum samples from this patient were negative for LAV antibodies by ELISA but positive for IDAV1 antibodies in an ELISA in which IDAV1 was used as antigen. IDAV2 was isolated from peripheral lymphocytes of a B hemophilia patient. A virus similar to IDAV2 was isolated from the patient's healthy brother who was also a hemophiliac (Vilmer E, Barré-Sinoussi F, Rouzioux C, et al: Lancet, 1984, 1:753-757). IDAV3 was isolated from peripheral blood lymphocytes of a Zairian woman who emigrated to France.

LAV and the IDAV isolates appear to belong to a new group of viruses which have the usual characteristics of retroviruses (see preceding paper). Despite imperfections and some differences in results depending on the assay used, the picture emerging from these studies is that a high proportion of patients with LAS have IgG antibodies to LAV, indicating prior or current infection with this or a related virus.

In the group of frank AIDS patients, the number of patients who were seropositive was significantly different from control groups but lower than the % positive in LAS patients. Two hypotheses have been suggested to explain this lower association.

First, LAV may be more closely related to LAS than to AIDS. LAV may be but one of the opportunistic viral agents found in AIDS, and other viruses may have a role in the onset of the disease. HTLV is one candidate. In our studies, none of the AIDS sera had antibodies to the HTLV1 major core protein by RIA. In other reports (Essex M, McLane MF, Lee TH, et al: Science, 1983, 220:859-862), antibodies to antigens expressed on the cell surface of HTLV1-transformed lymphocytes were detected in the sera of 25-36% of AIDS patients, 25-30% of patients with LAS, and 1% of matched homosexual controls or blood donors. More recent studies implicate HTLV3 isolates (Gallo RC, Salahuddin SZ,

Popovic M, et al: Science, 1984, 224: 500-502).

Alternatively, the severe immune impairment at the late stage of the disease may affect B lymphocytes (Lane HC, Masur H, Edgar LC, et al: N Engl J Med., 1983, 309:453-458) such that a humoral response against viral proteins may become undetectable. A large proportion of the sera which were tested were in fact collected at late stages of AIDS. One AIDS patient who was LAV positive at presentation did become negative at a later stage. Similarly, the hemophiliac had a decreased titer of LAV IgG antibodies at the time of onset of AIDS, even though the IDAV2 retrovirus could continuously be isolated from his peripheral T lymphocytes.

There are indications that LAV infection is present in AIDS patients living in the US and in Equatorial Africa. Prospective seroepidemiological studies are required to confirm the involvement of LAV in AIDS. Comparative studies are currently underway on groups considered to be at risk for AIDS and on control populations in various countries.

Note added: LAV antibodies assayed by ELISA and RIPA were present in 94% of AIDS patients in Zaire and in only 19% of controls. In the positive controls (5/26), four controls had reversed OKT4: OKT8 ratios due to decreased circulating T-helper lymphocytes. In addition, two sexual contacts of AIDS patients in Zaire were also found to be positive for LAV antibody (T. Quinn, personal communication).

This article includes information from a paper which has been accepted for publication in the Lancet.

F. Vézinet-Brun, C. Rouzioux, F. Barré-Sinoussi, D. Klatzmann, A. G. Saimot, W. Rozenbaum, L. Montagnier, and J. C. Chermann. Hôpital Claude Bernard; Institut Pasteur; Hôpital Pitie-Salpétriére; Paris, France.

PREVALENCE AND INCIDENCE OF CYTOMEGALOVIRUS INFECTIONS AMONG HOMOSEXUAL MEN

There is evidence that cytomegalovirus (CMV) infections can be transmitted by sexual contact, especially among homosexual men. In one study of male homosexuals in San Francisco, a very high prevalence of antibodies to CMV was found (94%); and 14% of the men under 30 years of age had CMV viruria (Drew WL, Mintz L, Miner RC, et al: J Infect Dis., 1981, 143:188-192). In a Danish study, the antibody prevalence among homosexual men was related to the duration of homosexual activity (Melbye M, Biggar RJ, Ebbesen P, et al: Acta Pathol Microbiol Immunol Scand [B], 1983, 91:357-364).

During a recent hepatitis B vaccine efficacy study, we followed a large group of homosexual men over a period of nearly 2 years (Coutinho RA, Lelie PN, Albrecht-van Lent P, et al: Br Med J., 1983, 286:1305-1308). This gave us the opportunity to study the prevalence and incidence of CMV infections among this group of men and the relationships of CMV infections to a number of risk factors.

A total of 710 homosexual men participated in this study. The mean age was 30.1 ± 7.0 years. The participants lived in and around Amsterdam. Blood samples were collected from the participants at monthly intervals for 5 months and every 3 months thereafter. The first and the last blood samples were tested for the presence of antibodies to CMV (anti-CMV). If either a seroconversion or a significant rise in titer was found, all samples taken in-between were tested. A primary CMV infection was defined as a seroconversion for anti-CMV for which anti-CMV IgM antibodies could be detected in at least two sequential blood samples. A recurrent CMV infection was

defined as a >4-fold rise in titer in a person already positive for anti-CMV; confirmation of the rise was required in at least one following blood sample.

Of the 710 men, 501 (70.6%) were found to have complement fixing antibodies to CMV at entry into the study; 209 (29.4%) were seronegative. During the follow-up, 69 CMV infections were detected. Fifty of these were primary infections among the seronegative participants; 19 were recurrent infections among the seropositive men. At the end of the study (23 months), the attack rate for primary infections was 27.3% and for recurrent CMV infections was 6.2%.

Using stepwise logistic regression analyses (Coutinho RA, Albrecht-van Lent P, Lelie PN, et al: Br Med J., 1983, 287:1743-1745), four characteristics of the participants were found to be correlated with seropositivity for CMV. The duration of homosexual activity had the highest correlation ($p < 0.002$). The probability of seropositivity increased 1-2% for each year of homosexual activity. This effect was independent of age. The next important risk factor was the number of different sexual partners in the preceding 6 months ($p < 0.03$), with the risk increasing with increasing numbers of partners. A history of syphilis and a history of anal sexual contact were also significantly correlated with seropositivity.

For seronegative men, the primary CMV attack rate was correlated with a history of syphilis (relative risk = 2.21) and anal sexual contact (relative risk = 2.49) as analyzed by life-table methods (Ibid).

The relatively low (70.6%) anti-CMV prevalence among the homosexual men in this study as compared with the prevalence (94%) in the San Francisco study is probably a reflection of the selection method for participants, all of whom were negative for hepatitis B markers. Among the 209 seronegative men, a very high primary CMV attack rate was found. Among the 501 seropositive men, the recurrent CMV infection rate was much lower. It is, however, difficult to draw a conclusion about the recurrent infections, as only serological data and not viral culture data were collected.

We conclude from this study that CMV infections are very prevalent among homosexual men and that anal sexual contact plays an important role in the transmission of the virus.

This article includes information accepted for publication in the British Journal of Venereal Diseases.

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REINFECTION WITH CYTOMEGALOVIRUS IN AIDS PATIENTS

Hirsch and his colleagues have shown that primary cytomegalovirus (CMV) infections induce transient immunosuppression (Rinaldo CR Jr, Carney WP, Richter BS, et al: J Infect Dis., 1980, 141:488-495). We have suggested that CMV may contribute to the etiology of AIDS: repeated episodes of primary CMV infections with different strains of CMV could perpetuate a state of immunosuppression (Drew WL, Miner RC, Ziegler JL, et al: Lancet, 1982, 2:125-127).

To determine whether multiple and different CMV infections actually occur, we have studied autopsy tissues from

four AIDS patients. CMV isolates recovered from these tissues were studied for genetic relatedness by Southern blot analysis of CMV DNA using ^{32}P-labeled probes made from plasmid-cloned CMV DNA fragments.

As shown in the table, tissue samples from each of the four patients had at least two different strains of CMV. These results indicate that exogenous reinfection with CMV does occur in AIDS patients. In a study reported by Plotkin et al., two renal transplant recipients were found to excrete different strains of CMV from different sites. These results suggest that exogenous reinfection may occur in these highly immunocompromised patients as well (Plotkin SA, Smiley ML, Friedman HM, et al: in Plotkin SA (ed): CMV, Pathogenesis and Prevention of Human Infection. Alan R. Liss, New York, 1984).

CMV ISOLATES FROM HOMOSEXUAL MEN WITH AIDS

Patient	Diagnosis	Tissue	Isolate Type*
1. LC	KS	KS tumor	A
		Lung	B
		Prostate	B
2. JT	KS	Lung	C
	PCP	Prostate	D
3. GR	KS	Lung	E
		Prostate	F
4. RG	KS	Prostate	G
		Kidney	H

Abbreviations: CMV, cytomegalovirus; KS, Kaposi's sarcoma; PCP, Pneumocystis carinii pneumonia.

* Different strains by restriction digest analysis.

To determine whether CMV contributes to the pathogenesis of AIDS, it will be important to determine if exogenous reinfection with CMV occurs in healthy homosexual men. We are currently pursuing this objective in a prospective study.

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ULTRASTRUCTURAL MARKERS IN AIDS

Considerable interest has been engendered by the intracytoplasmic inclusions --tubuloreticular structures (TRS), test tube and ring-shaped forms (TRF), vesicular rosettes (VR), and virus-like particles (VLP)--observed in tissue specimens taken from AIDS patients (Sidhu GS, Stahl RE, El-Sadr W, et al: Lancet, 1983, 1:990-991; Orenstein JM: Lancet, 1983, 2:284-285; Kostianovsky M, Kang YH, Grimley PM: Ultrastruct Pathol., 1983, 4:331-336; Ewing EP Jr, Spira TJ, Chandler FW, et al: N Engl J Med., 1983, 308:819-822; Feremans W, Menu R, Dustin P, et al: Lancet, 1983, 2:52-53; Gardiner T, Kirk J, Dermott HE: Lancet, 1983, 2:963-964). This report describes such inclusions in over 125 specimens from AIDS patients, homosexual men with lymphadenopathy and/or systemic symptoms and reversed T4:T8 ratios, asymptomatic homosexual men, hemophiliacs, and controls. The specimens were studied by transmission electron microscopy.

TRS were observed in all 27 specimens from 18 AIDS patients. These included specimens of lymph node, buffy coat, lung, thymus, and small cell carcinoma of the rectum. TRS were readily found in endothelial cells in all of the tissue

samples and in up to 30% of the lymphocytes in the lymph nodes and buffy coats. TRS were also observed in at least one specimen from 12 homosexual men, one bisexual man, and five proclaimed heterosexual men with lymphadenopathy and/or systemic symptoms but without AIDS, and in one healthy hemophiliac. Ten of these patients had reversed T4:T8 ratios of 1.2 or less.

TRF were observed in 17 specimens from 13 AIDS patients from whom either lymph node (5), buffy coat (2), thymus (1), or lung with bronchial mucosa (9) specimens were available for study. To our knowledge, this is the first report of TRF in the bronchial epithelium (Jackson D, Tabor E, Gerety FJ: Lancet, 1979, 1:1249-1250; Shimizu YK, Feinstone SM, Purcell RH, et al: Science, 1979, 205:197-200; Shamoto M, Murakami S, Zenke T: Cancer, 1981, 47:1804-1811; Prineas JW, Wright RG: Lab Invest., 1978, 38:409-421).

There appears to be an association between TRS and TRF in specimens from AIDS patients: TRF are not observed in the absence of TRS, the two types of inclusions are often in the same cell, and they are occasionally in close proximity. In many studies, TRS have been most readily found in endothelial cells. However, in this laboratory, TRF have never been observed in endothelial cells, even in samples rich in TRF-positive mononuclear cells. TRF were reported as rarely observed in endothelial cells in one published study, although this was not illustrated (Ewing EP Jr, Spira TJ, Chandler FW, et al: Lancet, 1983, 2: 285). There also has been no mention of TRF in the in vitro systems in which TRS have been induced readily by alpha-interferon (α-IFN) (Grimley PM, Yang Y-H, Silverman RH, et al: Lab Invest., 1983, 48:30A; Rich SA, Science, 1981, 213:772-775).

Although TRF were common in bronchial epithelia, we have observed only a single TRS in one bronchial cell. In transbronchial biopsies from two AIDS patients, the epithelial cells contained TRF as well as small numbers of structures identical to "attaching curved membranes" (type II) (Pfeifer U, Thomssen R, Legler K, et al: Virchows Arch., 1980, 33:233-243). These structures are considered by Pfeifer et al. to be the precursors of TRF in the chimpanzee non-A, non-B (NANB) hepatitis system. The two AIDS patients were not known to have NANB hepatitis. To our knowledge, this is the first description of these structures in clinical materials (Chandra S: Lab Invest., 1968, 18:422-428; Smith RD, Deinhardt F: J Cell Biol., 1969, 41:269-279).

VR were not observed in any specimens. VLP, which are morphologically identical to multivesicular bodies, were observed in a wide variety of cell types in every specimen. Their prevalence appeared to reflect the "activated" state of the cells, particularly lymphocytes and macrophages.

An additional "tubular" structure, apparently not previously described, was observed in a small percentage of mononuclear cells in five of five lymph nodes from AIDS patients and in the thymus of another. They were also seen in nine of 14 TRS-positive lymph nodes from seven of 12 non-AIDS TRS-positive patients, and in the lymph nodes of two of three asymptomatic homosexual men without AIDS or other disease markers. These aperiodic structures were either straight or undulating. They were approximately 20 nm thick and appeared to be free in the cytoplasm. On cross-section, clusters of these structures often had a regular arrangement. They were only occasionally seen in cells containing TRS and/or TRF. They were

never observed in buffy coat cells, even from patients with positive lymph nodes.

The significance of one or more of these structures to the etiology of AIDS is unknown. A key question regarding our findings is whether the appearance of TRS alone or together with TRF antedates the development of AIDS in individuals at risk and thus serves as an important surrogate marker for this disease. At this institution, one AIDS patient with Kaposi's sarcoma had a TRS/TRF-positive lymph node over 1 month before a diagnosis of AIDS was made. Ewing et al. (Ewing EP Jr, Spira TJ, Chandler FW, et al: Lancet, 1983, 2:285) reported similar findings in four patients. Currently, four patients with TRF-positive specimens (6 buffy coats in one, 2 buffy coats in another, and single lymph nodes in two) are being followed for the possible development of AIDS. A longitudinal study is needed for comparing the presence of the various ultrastructural markers with levels of suggested biochemical markers, such as α-IFN (DeStefano E, Friedman RM, Friedman-Kien AE, et al: J Infect Dis., 1982, 146:451-455; Buimovici-Klein E, Lange M, Klein RJ, et al: Lancet, 1983, 2:344) and thymosin α1 (Biggar RJ, Taylor PH, Goldstein AL, et al: N Engl J Med., 1983, 309:49-50; Hersh EM, Reuben JM, Rios A, et al: N Engl J Med., 1983, 308: 45-46) in large numbers of persons at risk for developing AIDS. Buffy coats, which are readily available through venipuncture, are the ideal specimens for use in studying these patients.

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THYMOSIN α1 BUT NOT β2-MICROGLOBULIN IS ELEVATED IN HOMOSEXUAL MEN WHO ARE AT RISK FOR AIDS

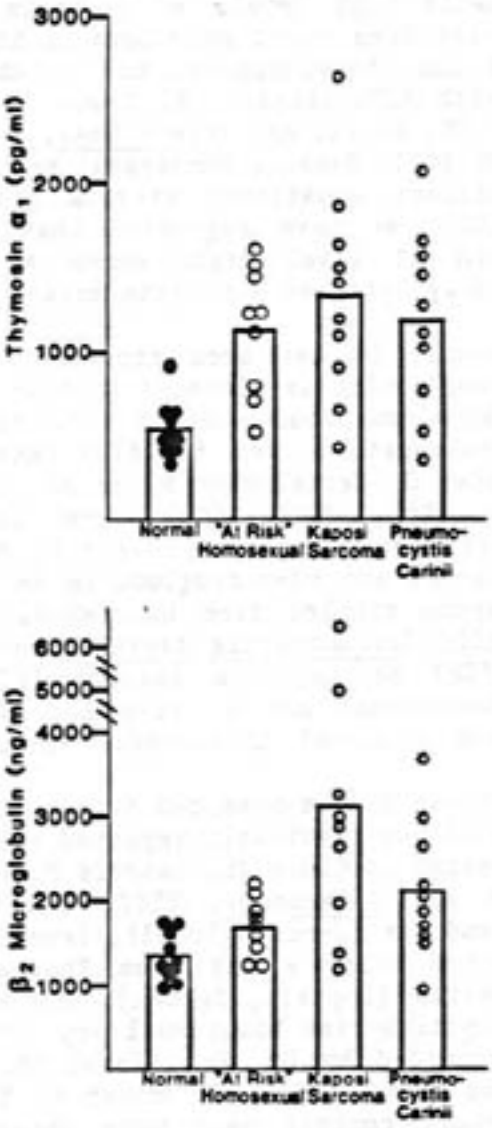
We have previously reported elevated levels of thymosin α1 in individuals with AIDS (Naylor PH, Goldstein AL: Clin Immunol Newsletter, 1983, 4(9):126-128). Abnormally high levels of thymosin α1 have also been found by others in homosexual men, hemophiliacs, and in children with AIDS (Kreiss JK, Lawrence DN, Kasper CK, et al: Ann Intern Med., 1984, 100:178-182). Because homosexual men and hemophiliacs constitute at-risk groups for AIDS, we have suggested that the thymosin α1 level might serve as an early diagnostic or surrogate marker for AIDS.

Recently it has been reported that β2-microglobulin is elevated in AIDS and that β2-microglobulin might also serve as a surrogate marker for AIDS (Bhalla RB, Safai B, Mertelsmann R, et al: Clin Chem., 1983, 29(8):1560). We have, therefore, evaluated the levels of both thymosin α1 and β2-microglobulin in the same serum samples from homosexual men with AIDS (Pneumocystis carinii pneumonia [PCP] or Kaposi's sarcoma [KS]), from homosexual men at risk for AIDS, and from a normal heterosexual control group.

Thymosin α1 was measured by a modification of our previously reported radioimmunoassay (McClure JE, Lameris N, Wara DW, et al: J Immunol., 1982, 128:368-375), and the β2-microglobulin level was determined using a kit from Pharmacia Diagnostics (Uppsala, Sweden). The sera from the high-risk homosexual population were provided by Dr. Evan Hersh (M. D. Anderson Cancer Center, Houston, TX). The normal control sera were obtained from the Red Cross Blood Center (Washington, DC). Sera from the AIDS patients

were provided by Dr. A. Friedman-Kien (New York University, New York, NY).

The results (Figure) confirm previous reports of elevations of thymosin α1 levels in high-risk homosexual men and in AIDS patients. Many individuals with frank AIDS (KS or PCP) also had elevated β2-microglobulin levels. However, β2-microglobulin levels were not elevated in the high-risk homosexual population.



Thymosin α1 and β2-Microglobulin Levels in Four Populations

Although the β2-microglobulin level was elevated in a significant number of patients with AIDS, the level was not elevated in at-risk homosexual men at a time when the thymosin α1 level was clearly elevated. While elevation of β2-microglobulin could precede the initial diagnosis of AIDS, it does not occur prior to the elevation of thymosin α1. Thus, thymosin α1 may be an earlier marker of blood suspect for AIDS than is β2-microglobulin.

It is not surprising that a significant number of patients with AIDS have elevated serum levels of β2-microglobulin. β2-Microglobulin is elevated in a number of clinically abnormal states. In addition, most hemophiliacs as well as individuals with hepatitis antigen have elevated levels of β2-microglobulin.

To date, the events which cause thymosin α1 levels to be elevated in homosexual men and hemophiliacs who are at risk for AIDS and in adult and pediatric AIDS patients have not been elucidated. We suggest that longitudinal studies in large populations of individuals at risk for AIDS are warranted to determine whether serum levels of surrogate markers such as thymosin α1 and β2-microglobulin will be of use in identifying individuals who might be asymptomatic carriers of AIDS.

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HIGH INCIDENCE OF LYMPHADENOPATHIC KAPOSI'S SARCOMA IN AUTOPSY SERIES

Data released by the Centers for Disease Control (CDC) (see page 23) indicate that only about one-third of AIDS patients suffer from Kaposi's sarcoma (KS). Our experience with biopsy and autopsy specimens suggests that KS is far more frequent than that, raising the possibility that KS may be the common denominator of AIDS from a pathologic standpoint.

Between April 16, 1980 and October 15, 1983, we performed complete autopsies on 55 patients who died of AIDS as defined by strict CDC criteria (Morb Mort Weekly Rep., 1982, 31:507-514). Fifty-three were selected for analysis of KS lesions. The types of KS were divided into two categories: (1) classical (CKS) or familiar and (2) "inflammatory" (IKS). IKS has been described in the literature under a variety of terms (Tedeschi CG: Arch Pathol., 1958, 66: 656-684; Lubin J: Arch Pathol., 1971, 92:338-341).

Gross and microscopic examinations showed one or both types of KS lesions in 87% of lymph nodes and in 73% of spleens examined. KS lesions were also found in lung (28%), skin (26%), alimentary tract (25%), and liver (15%). In all, lesions of KS were found in 94% of patients in this series. Except for the central nervous system and the myocardium, virtually every type of tissue was at risk. In 10% of the cases, KS was considered to be the proximate cause of death; the other 90% died of a variety of opportunistic infections.

All of the patients with KS had IKS; only a third had CKS. Every patient with CKS also had IKS either in association with CKS or independent of CKS. Morphologic intermediates of the two forms of KS were readily identifiable, but it was impossible to establish that sequential evolution had occurred. Review of serial biopsies available in several cases did not clarify this association, since CKS and IKS were found both early and late in the disease.

We believe that the IKS lesions are bona fide manifestations of KS. The frequency of IKS lesions is three-fold higher than the frequency of CKS lesions. Based on our biopsy analyses of specimens from AIDS patients, we do not believe that our results can be dismissed as artifacts of autopsy procedures.

IKS was a rare manifestation of KS before the epidemic of AIDS. In our opinion, it is the commonest manifestation of KS in AIDS. Others have described in different terms lesions in lymph node biopsies that we would probably call IKS (Harris NL: N Engl J Med., 1984, 310:462-463; Guarda LA, Butler JJ, Mansell P, et al: Am J Clin Pathol., 1983, 79(5):559-568; Brynes RK, Chan WC, Spira TJ, et al: JAMA, 1983, 250(10): 1313-1317; Ioachim HL, Lerner CW, Tapper ML: Am J Surg Pathol., 1983, 7(6):543-553). In these reports, the patients with marked vascular proliferation in lymph nodes had a poor prognosis.

The possibility has been raised that KS is not a neoplasm (Costa J, Rabson AS: Lancet, 1983, 1:58). Many apparently doubt that IKS is neoplastic in nature. However, our autopsy results suggest to us that both IKS and CKS in AIDS patients are highly malignant neoplasms. None of the patients survived longer than 3 years after diagnosis. Many who survived more than a year after diagnosis and those who experienced opportunistic infections but died of KS were cachectic.

We believe the true incidence of IKS in this series of patients may have been underestimated, because IKS is sometimes

impossible to distinguish from an inflammatory process. It is possible that lymphadenopathic KS is present in all cases of AIDS and that decreases in T cell numbers result from destruction of T cell domains in lymph nodes and spleens by the neoplasm.

If KS is ubiquitous in AIDS, earlier diagnoses of AIDS in the absence of opportunistic infections might be made by pathologists. Consideration could then be given to treating KS as the underlying disease in AIDS.

A detailed report of the autopsy findings has been submitted for publication.

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INTERFERON IN KAPOSI'S SARCOMA--HOW IMPORTANT ARE IMMUNOLOGICAL MEASUREMENTS?

Epidemic Kaposi's sarcoma (KS) is a frequent accompaniment of AIDS (Fauci AS: Ann Intern Med., 1984, 100:92-106; Longo DL: Ann Intern Med., 1984, 100: 96-98). Impaired immune function is felt to be an important component in the causation of this malignancy. Interferon (IFN) has been found to exert a therapeutic effect in such patients, although the long-term effects of IFN therapy are not yet known (Krown SE, Real FX, Cunningham-Rundles S, et al: N Engl J Med., 1983, 308:1071-1076).

Two KS patients were treated with recombinant alpha-2 IFN, and their clinical responses and various immunologic parameters were evaluated. Both patient A (a 32-year-old man) and patient B (a 25-year-old man) suffered from widespread progressive KS. In each case a diagnosis of KS was proven by multiple biopsies of skin lesions (stage II A). Both men were otherwise healthy, and neither had suffered from opportunistic infections. Both had been working regularly at the time IFN therapy was started.

Thirty million units of recombinant alpha-2 IFN (Schering Corp., Kenilworth, NJ) were injected subcutaneously three times a week. Within 4 weeks, patient A appeared to be in complete remission with complete disappearance of all skin lesions. Biopsy 10 weeks after institution of IFN therapy proved this to be the case. The therapy was stopped and patient A returned to work. Clinical relapse was suggested by the reappearance of subcutaneous nodules 16 weeks later. For patient B, skin lesions completely disappeared after 18 weeks of therapy, except for a discolored area on the forearm. Biopsy revealed residual KS cells. The dose of IFN was reduced to 15 million units per injection to reduce fatigue, and patient B was able to return to work. No new lesions and no opportunistic infections appeared in either patient at any time during therapy.

Both patients had occasional fevers and flu-like symptoms. Patient A had an OKT4:OKT8 ratio of 0.71 with 487 helper-inducer cells/mm^3 at the start of therapy. When therapy was stopped, the OKT4:OKT8 ratio was 0.04 with only 25 helper-inducer cells/mm^3. The lymphocyte proliferative capacity (measured as a response to phytohemagglutinin) was impaired at each testing. In contrast, all immunological studies of patient B have been normal both before and during his treatment.

These two patients with KS had very different levels of immune functioning, yet both responded to IFN. In fact, patient A, with the greatest abnormalities

in tests of immunity, responded faster to therapy than did patient B. The toxicity of the drug was not noticeably different in the two patients. Both patients have already outlived the mean time to death for patients with AIDS in our region (Louisiana Department of Health and Human Resources, January 1984). Such findings suggest a need for better, perhaps more representative, immunoregulatory studies to assess the effects of therapy and prognosis in immunodeficient patients.

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HEMOPHILIA AND AN UNUSUAL CANCER

Immunoregulatory abnormalities, including AIDS, have been noted in patients with hemophilia (Daly HM, Scott GL: Lancet, 1983, 2:1190; DeShazo RD, Andes WA, Nordberg J, et al: Ann Intern Med., 1983, 99:159-164). The causes of the abnormalities have not been determined but may be related to transfusion of blood products (Curran JW, Lawrence DN, Jaffe HW, et al: N Engl J Med., 1984, 310:69-75). The affected hemophiliacs are not generally exposed to other risk factors associated with AIDS (DeShazo RD, Andes WA, Nordberg J, et al: Ann Intern Med., 1983, 99:159-164). We report the development of an aggressive lung cancer in a patient with hemophilia 5 months after intensive exposure to cryoprecipitate (but not factor VIII concentrate) prepared from the blood of voluntary donors.

The patient was a 54-year-old white male physician transferred to the Tulane Medical Center in May 1983 following an episode of severe coronary insufficiency. Hemophilia A had been diagnosed in 1954 after excessive postoperative bleeding complicated a routine appendectomy. He received 6 units of whole blood and an unknown quantity of lyophilized plasma. Subsequently, the patient developed hepatitis. The patient did not recall receiving blood products at any other time.

The patient was married, had two children, and practiced medicine in a small, middle-class community. He had no history of homosexuality, drug abuse, recent foreign travel, or contact with patients with AIDS. He had smoked a few cigarettes per day for less than 3 years and had not worked with silica or asbestos.

Physical examination was unremarkable and laboratory studies indicated a normal blood count and chest x-ray. The template bleeding time was 8 min (normal = 2-10 min), the factor VIII coagulant activity (FVIII:C) was 12% of normal, and the factor VIII related antigen level was 132% of normal.

After coronary arteriography revealed multiple high-grade stenoses of both right and left coronary arteries, the patient underwent quadruple aorto-coronary artery bypass grafting without complication. The patient was prepared for surgery with cryoprecipitate to achieve 100% FVIII:C levels. Postoperatively, cryoprecipitate was continued twice daily to keep the FVIII:C between 50% and 100%. The postoperative course was uneventful, and cryoprecipitate was discontinued on the seventh postoperative day. The patient returned home 4 days later. During the hospitalization, the patient received a total of 250 bags of cryoprecipitate, 10 units of random-donor platelets, 4 units of fresh-frozen plasma, and 7 units of

packed red blood cells. All blood was from voluntary donor sources.

The patient did well until September 1983 when he noted a small mass in the right side of his neck. One week later he developed hoarseness due to a paralyzed right vocal cord and was readmitted to the hospital. Physical examination revealed an ill-appearing man with fever, tachypnea, and an indurated mass in the right side of his neck. Chest x-ray revealed interstitial infiltrates in the lower fields of both lungs.

Adequate factor VIII levels were attained without difficulty using cryoprecipitate. The patient developed progressive hypoxemia with rapidly worsening interstitial infiltrates in both lung fields and an expanding right paratracheal mass. Thoracotomy with biopsy of a 5 × 4 cm mass in the right side of the neck and biopsy of a large mediastinal mass revealed metastatic, poorly differentiated adenocarcinomas, with frequent mitoses and blood vessel invasion. The same type of tumor was present in the lung with lymphangitic spread. No evidence of Pneumocystis carinii infection or cytomegalovirus infection was found. There was rapid worsening of respiratory distress and rapid enlargement of the tumor mass. Death from intractable respiratory failure occurred within 5 days of lung biopsy and within 5 months of the cardiac surgery.

Tests for the presence of various hepatitis antibodies and antigens were performed. Tests for HBcAB, HBsAB, and HBVAB were positive; tests for HBeAG, HBeAB, and HAVAB-IgM were negative. Three days before the patient's death and 3 days after the lung biopsy, an unusual pattern of lymphopenia was found in immunologic studies (Table). Peak lymphocyte mitogen responses to phytohemagglutinin were suppressed to 66% of normal when compared with the responses of simultaneously tested controls.

This patient had a rapidly fatal carcinoma of the lung. He had very few risk factors for such a malignancy. The unusual course of his disease and the

MONONUCLEAR CELLS IN A HEMOPHILIAC WITH AN UNUSUAL CANCER

Cell Subset	Monoclonal Specificity	Absolute No. Cells/mm^3	Patient	Control
			(%)	(%)*
T_{11}	Pan T (E rosette receptors)	360	16	60 ± 18
T_4	T helper-inducer	202	9	25 ± 8
T_8	T suppressor-cytotoxic	0	0	22 ± 9
Ia^+	Monocytes, activated T	405	18	27 ± 7
T_7	Natural killer	23	1	9 ± 6
B	B	36	16	11 ± 6

*Mean ± SD.

types of immunological impairments which developed suggest that he may have had an illness related to AIDS. Although reduced ratios of helper:suppressor T lymphocytes have been seen in patients who have undergone open heart surgery (Brody JI, Pickering NJ, Behr D, et al: Blood, 1983, 62:A109), this appears to be a transient phenomenon which returns to normal within 24 hr. Our patient's coronary bypass surgery had occurred 5 months earlier. Our patient was exposed to large amounts of cryoprecipitate and other blood products but was not exposed to commercial coagulation factor concentrate at the time of surgery.

No increases in malignancies in patients with hemophilia have been reported in the literature. However, there have been recent descriptions of immune changes in such patients (Ballard JO, Kelly GA, Kukrika MD, et al: Cancer, 1981, 48:686-690; Gordon EM, Berkowitz RJ, Strandjord SE, et al: J Pediatr., 1983, 103:75-76; Bart RS, Kopf AW: J Dermatol Surg Oncol., 1980, 6:894-895). Cases of hemophilia and hepatoma, Burkitt's lymphoma, and basal cell carcinoma have been reported, but descriptions of the transfusion histories and immune functions of the patients have not always been available. All patients with hemophilia who have developed AIDS have used coagulation factor concentrates; opportunistic infections have been widespread in these patients and are indicative of immune dysfunctioning. The follow-up of patients with hemophilia whose immune dysfunctions have been documented has been short and has not allowed for a determination of the frequency with which such abnormalities are associated with the development of (B cell?) lymphomas, carcinomas, or Kaposi's sarcomas (such as those seen in homosexual patients) (Fauci AS: Ann Intern Med., 1984, 100:92-106; Longo DL: Ann Intern Med., 1984, 100:96-98; Gascon P, Zoumbos NC, Young NS: Ann Intern Med., 1984, 100:173-177; Irwin LE, Begandy MK, Moore TM: Ann Intern Med., 1984, 100:158).

Close scrutiny of patients receiving blood transfusions (Gascon P, Zoumbos NC, Young NS: Ann Intern Med., 1984, 100:173-177) may provide a better understanding of the disease seen in our patient. Evaluation of the effects of therapy for hemophilia should perhaps be extended to the use of cryoprecipitate as well as commercial coagulation factor concentrates. Careful analysis of the status of patients receiving various blood products may be of use in determining the safest therapy for hemophilia and for other patients requiring blood transfusions.

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INFECTIOUS COMPLICATIONS IN AIDS: EXPERIENCE AT THE NEW YORK HOSPITAL-CORNELL MEDICAL CENTER

We reviewed the records of all patients admitted to The New York Hospital-Cornell Medical Center in whom the diagnosis of AIDS had been made. The CDC criteria were used for diagnosis (Morb Mort Weekly Rep., 1982, 31:507-514).

Stool specimens were taken from patients with diarrhea. Bacterial, viral, and fungal cultures were grown by the hospital diagnostic microbiology laboratory. Specimens were examined for ova and parasites and for cryptosporidia. Cryptosporidia were identified in the stools using a three-step procedure.

This includes the Sheather's sugar coverslip flotation technique for concentration, an iodine stain, and a modified Kinyoun acid-fast stain (Bates DV, Macklen PT, Christie RV: in Respiratory Function in Disease, 2nd ed, WB Saunders Co., Philadelphia, 1971).

Patients with pulmonary disease were studied in several ways: chest radiography, arterial blood gas analyses, sputum analyses (when sputum samples were available), pulmonary function tests, and, if indicated, bronchoscopy and/or open lung biopsy (Stover DE: Ann Intern Med., 1984, in press). Bronchial washings were obtained randomly in the airways by instilling and suctioning back 5-10 cc of normal saline. Bronchoalveolar lavage was accomplished by wedging the fiber optic bronchoscope into an involved segment of the lung and instilling a total of 210-280 cc of normal saline in 30 aliquots. Each aliquot was [illegible]trated back by general manual suction. The amount of lavage fluid used depended on the clinical situation. Transbronchial brushings and biopsies were performed under single plane fluoroscopic control. Brushings, washings, and lavage fluid were processed with bacterial, fungal, and viral stains and were also cultured for these organisms. In addition, lavage specimens were tested for Legionella antigen and antibody using direct immunofluorescence techniques.

Ninety patients with AIDS were admitted to The New York Hospital by December 1983 (Table 1). Since no patient had been seen only in the out-patient department, this number represents the total number of patients observed in this center. Eighty patients were diagnosed as having AIDS with opportunistic infections (OI) (alone, with Kaposi's sarcoma [KS], or with lymphoma); three other patients had KS alone, and seven had lymphoma alone.

TABLE 1
PATIENT POPULATION WITH AIDS

Diagnosis at Presentation	No. of Patients
OI	52
OI and KS	20
OI and lymphoma	8
Total OI	80
KS alone	3
Lymphoma	7
Total patients	90

Abbreviations: OI, opportunistic infection; KS, Kaposi's sarcoma.

Figure 1 shows the admission dates for all patients seen since 1979. In the first 6 months of 1979, a single pa-

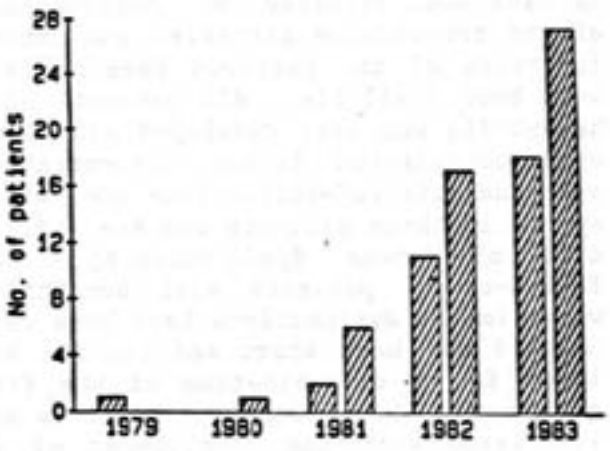

Fig. 1. AIDS--Opportunistic Infections by Admission Date

tient with AIDS was admitted. None were seen in the last 6 months of 1979 and the first 6 months of 1980. A second patient was seen in the fall of 1980. In the spring of 1981, two patients were observed, and six were seen in the fall of that year. The number of patients seen has progressively increased; in the last 6-month period, 27 new patients have been admitted.

The frequencies of the various opportunistic infections in our study population of 80 patients are given in Table 2.

TABLE 2
FREQUENCY OF
OPPORTUNISTIC INFECTIONS

Infection	No. of Infections
Pneumocystis carinii pneumonia	59
Candidiasis	
Thrush and/or esophagitis	57
Disseminated	5
Disseminated CMV (12/32 at post mortem)	32
Herpes simplex virus (perirectal)	14
Mycobacterium avium intracellulare	18
Cryptococcosis	6
Cryptosporidiosis	8
Toxoplasmosis	4
Salmonella bacteremia	4
Aspergillosis (4/4 at post mortem)	4

Abbreviation: CMV, cytomegalovirus.

The most common infections were Pneumocystis carinii pneumonia, candidiasis, and disseminated CMV.

Most patients had several infections. The number of patients showing from one to six infections is given in Table 3.

TABLE 3
MULTIPLICITY OF
OPPORTUNISTIC INFECTIONS

No. of OI	No. of Patients with Indicated No. of OI
1	16
2	29
3	12
4	14
5	6
6	2

Abbreviation: OI, opportunistic infection.

Fifty-seven and one-half percent (46/80) of the total patient population had died by December 31, 1983. Figure 2 shows the time of death after the onset of OI for the 46 patients who died. A more accurate estimate of the true mortality is given by the statistic that 97.2% (35/36 patients) with disease onsets before December 31, 1982 had died by December 31, 1983.

OI are the most frequent of the clinical manifestations of AIDS. Their presence also constitutes one of the methods of diagnosis of the disease. Scattered reports dealing with specific clinical aspects of AIDS have appeared previously. The perspective gained by evaluation of a large series of patients studied in a single institution has been reported in this paper.

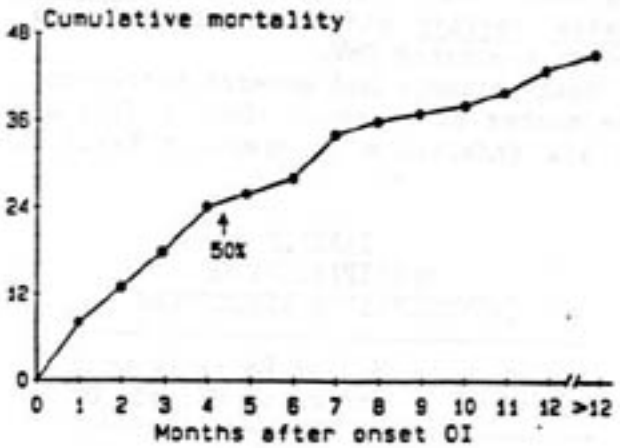

Fig. 2. Mortality After Onset of Opportunistic Infections, 1978-1983

R. G. Douglas, Jr., R. B. Roberts, P. Romano, C. Metroka, J. Amberson, R. Soave, and D. Stover, Department of Medicine, Cornell University Medical College, The New York Hospital, New York, New York 10021.

UPCOMING AIDS MEETING

Symposium: Critical Gay and Lesbian Health Problems
August 22-25, 1984
Marriott Hotel
Chicago, Illinois

Scientific Program Co-Sponsored by American Association of Physicians for Human Rights and National Coalition of Gay Sexually Transmitted Diseases Services in association with the annual meeting of the AAPHR

Information/Registration:
Mr. Doug Carner
AAPHR, P.O. Box 14366 .
San Francisco, CA 94114
(415) 558-9353

Topics: Etiology, Diagnosis, Immunology, Therapeutic Trials and Alternative Treatments, Psychological Aspects, and Sociology of AIDS; Lymphadenopathy Syndrome and Its Relationship to AIDS; The Hepatitis B Vaccine and AIDS; Hepatitis B Infection in Gay Men; Overview of NIH's AIDS Research Programs; Gay Community Medical Organizations in AIDS Research and Prevention; Intestinal Syndromes in Gay Men; Lesbian Health Issues; Helping Gay and Lesbian Youth Attain Positive Self Images; Stages of Gay and Lesbian Relationships; Impaired Gay and Lesbian Physicians; Gay Parenting; Social and Political Barriers to Gay and Lesbian Healthcare.

Speakers: Drs. R. Krause, R. Enlow, W. Blumenthal, P. Volberding, K. Mayer, W. Siroty, S. Follansbee, M. Forstein, D. Abrams, E. Harrison, M. Kirkpatrick, K. Sell, C. Stevens, T. Quinn, R. Bolan, S. Nichols, J. Sonnabend, P. Robertson, D. Ostrow, D. McWhirter, D. Mattison, N. Schram, D. Martin, M. Ross, M. Pohl, E. Hetrick, D. Stewart, P. Paroski, and M. Schneider.

AIDS CASES REPORTED TO THE CENTERS FOR DISEASE CONTROL AS OF April 23, 1984

UNITED STATES CASES

DISEASE	CASES	PERCENT OF TOTAL	DEATHS	PERCENT DEAD
KS without PCP	1043	25.0	255	24.4
PCP without KS	2166	51.9	1017	47.0
Both KS and PCP	278	6.7	175	63.0
OI without KS or PCP	690	16.5	360	52.2
TOTAL	4177	100.0	1807	43.3

KS = Kaposi's sarcoma
OI = Opportunistic infection
PCP = Pneumocystis carinii pneumonia

	MALES		FEMALES		TOTAL	
RISK GROUPS*	CASES	% OF TOTAL	CASES	% OF TOTAL	CASES	%
Homosexual or bisexual	2999	76.9	0	0.0	2999	71.8
IV drug user	580	14.9	154	55.8	734	17.6
Haitian	143	3.7	24	8.7	167	4.0
Hemophiliac	30	0.8	0	0.0	30	0.7
No apparent risk group or unknown	149	3.8	98	35.5	247	5.9
TOTAL	3901	100.0	276	100.0	4177	100.0

* The risk groups listed are hierarchically ordered; cases with multiple risk factors are tabulated only in the risk group listed first.

INSTRUCTIONS FOR AUTHORS CONTRIBUTING TO THE AIDS MEMORANDUM

Content: Articles published in the AIDS Memorandum must have obvious relevance to AIDS. They can describe clinical or experimental findings. Letters and other types of commentary are also welcome. All manuscripts should be typed double spaced.

References: References should be integrated into the text in parentheses. Each citation should include the names of up to three authors, the journal title, the year of publication, volume and issue numbers, and inclusive page numbers. Citations from books should include the names of up to three authors, book title, editor(s), publisher, publisher's location, year of publication, and relevant page numbers.

Tables and Figures: Whenever possible, data should be organized into tables. Figures should be clear and no wider than 3¼ inches.

Announcements of Meetings: Announcements of upcoming AIDS meetings should include meeting title, location, and date and the name, address, and telephone number of the organizer of the meeting.

Further Information: For further information call the AIDS Memorandum office at (301) 496-9537.

Mailing Instructions: Manuscripts for the AIDS Memorandum should be sent to this address:

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AIDS
MEMORANDUM
Acquired Immune Deficiency Syndrome

National Institute of Allergy and Infectious Diseases

Volume 1, Number 6 June 1984

IN THIS ISSUE

GROUND RULES FOR USE OF THE AIDS MEMORANDUM

The AIDS Memorandum serves as a forum for the rapid exchange of new information and ideas among clinicians and scientists involved in AIDS research and management. Material contained in the Memorandum can be of several kinds: positive and/or negative results, clinical and/or experimental findings, preliminary and/or validated data, observations, questions, theories, commentaries, and others. This material is not subjected to peer review. Therefore, users of the Memorandum must agree to treat all material as privileged information and to consider it as tentative and subject to change prior to formal publication in a refereed journal.

Users must agree not to cite material from the Memorandum without first obtaining the consent of the author(s), and, with author permission, to cite information only as a personal communication. Author addresses are provided for this purpose.

Users must agree to contribute data or ideas to the Memorandum at least once a year. On an annual basis, the names of individuals who have not contributed to the Memorandum will be culled from the mailing list, so as to limit circulation of the Memorandum only to individuals actively working in the field.

Finally, users must agree to share material in the Memorandum only with other individuals willing to honor these ground rules.

CORRELATION BETWEEN EXPOSURE TO HTLV-III AND THE DEVELOPMENT OF AIDS

Epidemiologic data and other kinds of evidence have accumulated which indicate that AIDS is caused by an infectious T lymphotropic agent transmitted by intimate contact, whole blood, or separated blood components (Curran JW, Lawrence DN, Jaffe H, et al: N Engl J Med., 1984, 310:69-75; Scott GB, Buck BE, Letterman JG, et al: N Engl J Med., 1984, 310:76-81). We originally proposed that members of the human T cell leukemia-lymphoma virus (HTLV) family of human retroviruses were prime candidates for the cause of AIDS (Gallo RC, Sarin PS, Gelmann EP, et al: Science, 1983, 220 (4599):865-867). Of these, HTLV-I was the most frequently isolated and best characterized. It and its variants are endemic in Africa and may have originated there (Gallo RC, Sliski A, Wong-Staal F: Lancet, 1983, 2:962-963). Africa may also be the location of origin of AIDS (Ibid).

These human retroviruses are T lymphotropic, preferentially infect cells with a helper phenotype (OKT4/leu3a$^+$), and, under natural conditions, are transmitted from person to person by intimate contact or in blood or blood products (Gallo RC: in Franks LM, Wyke LM, Weiss RA (Eds): Cancer Surveys, Oxford University Press, Oxford, 1984, in press). Like some other retroviruses, such as feline leukemia virus, HTLV isolates can have direct effects on T lymphocyte functional properties. In addition, HTLV-infected cells produce many cell-regulating factors, including those having suppressive effects (Salahuddin SZ, Markham PD, Lindner SG, et al: Science, 1984, 223(4637):703-707).

Numerous isolates of retroviruses which were T lymphotropic but which, in preliminary experiments, did not have significant immunological cross-reactivity with type-specific antibodies to HTLV-I and HTLV-II (the first two HTLV subclasses characterized) have been made in our laboratory from patients with AIDS and pre-AIDS since November 1982. Characterization of these viruses, named HTLV-III, remained laborious because of the cytopathic effects of the viruses on infected cells. Recently, permissive subclones of a permanently growing cell line were established which yielded virus in large amounts. Consequently, large quantities of HTLV-III could be made and reagents--proteins, immunological products, and nucleic acids--could be developed for characterizations and comparisons (Popovic M, Sarngadharan MG, Read E, et al: Science, 1984, 224(4648): 497-500).

Samples of peripheral blood, bone marrow, and serum from a large number of AIDS and pre-AIDS patients were collected, processed, and tested for the presence of HTLV-III or the presence of antibodies to viral proteins (Gallo RC, Salahuddin SZ, Popovic M, et al: Science, 1984, 224(4648):500-503). ELISA and Western blot procedures were used for detecting anti-HTLV-III antibody in sera and/or plasma from patients and controls (Sarngadharan MG, Popovic M, Bruch L, et al: Science, 1984, 224 (4648):506-508).

As summarized in Table 1, the retrovirus, HTLV-III, was isolated from the cells of a large proportion of the AIDS patients examined (30-50%) and from an even higher number of the pre-AIDS samples tested (87%). On the other hand, HTLV-III was isolated from only one of 26 nonpromiscuous homosexual donors; this was the one person in this group who later developed AIDS. HTLV-III was not found in 125 samples from normal heterosexual donors. The incidence of

virus isolations from the AIDS samples is an underestimate of the true frequency with which the virus is associated with AIDS, since many tissue specimens, particularly those received from terminal AIDS patients, had a low viable cell number.

TABLE 1
HTLV-III ISOLATES FROM AIDS AND PRE-AIDS PATIENTS AND CONTROLS

Donor Diagnosis	Number Tested	% Retrovirus Positive
Adult AIDS with opportunistic infection	25	50
Adult AIDS with Kaposi's sarcoma	43	30
Juvenile AIDS	8	30
Pre-AIDS, chronic lymphadenopathy	30	87
Mothers of juvenile AIDS	4	75
Clinically normal nonpromiscuous homosexuals	26	4
Clinically normal heterosexuals	125	0

Table 2 shows the frequency with which antibody to HTLV-III was detected in sera of various test groups. Exposure to the virus was apparent in almost all of the AIDS and lymphadenopathy patients, in a high proportion of intravenous drug users, and in many homosexual men. Normal controls and controls ill with diseases unrelated to AIDS showed no evidence of exposure to the virus.

TABLE 2
ANTIBODY TO HTLV-III DETECTED IN SERA OR PLASMA FROM AIDS AND PRE-AIDS PATIENTS AND CONTROLS

Donor Diagnosis	Number Tested	% Positive
AIDS	49	88
Pre-AIDS, chronic lymphadenopathy	14	79
Intravenous drug abusers	5	60
Homosexual men (high-risk areas)	17	35
Normal donors	163	<1
Acute mononucleosis	4	0
Lymphatic leukemia	8	0

Like other members of the HTLV family, HTLV-III is an exogenous T lymphotropic retrovirus which appears to preferentially affect OKT4/leu3a$^+$ T cells. It contains a high molecular weight, Mg^{++}-requiring reverse transcriptase and other structural proteins similar in size to antigens of HTLV-I and HTLV-II (Schupbach J, Popovic M, Gilden R, et al: Science, 1984, 224(4648):503-505). Immunological comparisons have shown antigenic homologies among the three subgroups of HTLV (Sarngadharan MG et al, submitted), and recent molecular analyses of the genome of HTLV-III show that it contains nucleotide sequences which are homologous with sequences in the genomes of HTLV-I and HTLV-II (Arya S et al, submitted). Finally HTLV-III has the retrovirus-unique X sequence region at the 3' end of the genome. These findings clearly define HTLV-III as a member of the HTLV family.

Other retroviruses have been detected in cells of AIDS and pre-AIDS patients. The first member of the HTLV family which we identified in such cells belonged to the HTLV-I subgroup (Gallo RC, Sarin PS, Gelmann EP, et al: Science, 1983, 220(4599):865-867). HTLV-I proviral DNA was detected in T lymphocytes from two additional AIDS patients (Gelmann EP, Popovic M, Blayney D, et al: Science, 1983, 220(4599):862-865), and HTLV-I-related antigens were found in T cells from several other patients (unpublished observation). Exposure to HTLV-I was detected in sera of about 15% of AIDS patients (>100 patients were tested) in experiments using either proteins from disrupted HTLV-I or the purified structural protein, p24, to detect specific antibodies (Robert-Guroff M, Schupbach J, Blayney D, et al: in Gallo RC, Essex M, Gross L (Eds): Human T Cell Leukemia Viruses, Cold Spring Harbor Press, New York, 1984, in press). A much higher correlation between exposure to HTLV-related viruses and the development of AIDS was reported in another study in which sera from ~40% of AIDS and pre-AIDS donors had antibody which reacted with HTLV-I-infected cells. We now believe that this activity results from an antigenic cross-reactivity with HTLV-III envelope antigens (Essex M, McLane MF, Tachibana N, et al: in Gallo RC, Essex M, Gross L (Eds): Human T Cell Leukemia Viruses, Cold Spring Harbor Press, New York, 1984, in press). Virus belonging to the HTLV-II subgroup has been isolated from cultured lymphocytes from an AIDS patient (Popovic M et al, in preparation). This association of HTLV-I and HTLV-II with AIDS materials could be more than coincidental, since both can have effects on immune cell functions.

In addition to our observations, a retrovirus, LAV, was observed in cultured lymphocytes from a patient with lymphadenopathy (Barre-Sinoussi F, Chermann JC, Rey F, et al: Science, 1983, 220(4599):868-871), and additional virus isolates, called IDAV, have been made from other patients with AIDS (Montagnier L, Chermann J, Barre-Sinoussi, et al: in Gallo RC, Essex M, Gross L (Eds): Human T Cell Leukemia Viruses, Cold Spring Harbor Press, New York, 1984, in press). The relationships of these viruses to members of the HTLV family remain to be determined.

We have been able to isolate HTLV-III from the lymphocytes of a large number of AIDS and pre-AIDS patients and have been able to transmit the virus transiently to fresh human T cells and to cell clones of an established cell line. A high correlation was found between exposure to HTLV-III, as detected by antibodies to HTLV-III in patient sera, and the development of AIDS. Based on these observations, we conclude that HTLV-III is the primary cause of AIDS.

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THYMIC TRANSPLANTATION IN AIDS PATIENTS

The course of AIDS, once established, appears to be irreversible. Spontaneous recovery of immunocompetence has never been documented. Marked thymic dysplasia--manifested by destruction of epithelial thymic cells, relative or total absence of Hassall's corpuscles, plasma cell infiltration, and fibrosis--has been observed in autopsy analyses of 19 AIDS patients (Elie R, Laroche AC, Arnoux E, et al: N Engl J Med., 1983,

308:841-842; Seemayer TA, et al: Hum Pathol., 1984, in press). These findings led to the hypothesis that AIDS may be caused by a virus which is harbored by and replicates in the thymus and thymus-derived T cells. A consequence of the viral presence would be that specific populations of cells within the epithelial thymus as well as peripheral T cells would be destroyed.

Given the irreversibility of the immunodeficiency and the alterations observed in thymus tissue, therapeutic attempts with thymus transplants were initiated in June 1983. To date, 12 patients with AIDS have received thymus grafts. Three of these, grafted in Haiti, have been lost to follow up. Data from nine patients grafted in Canada are presented here. Eight of these have been followed at monthly intervals for periods of 1-7 months; one of these patients was lost to follow up.

Thymic epithelial cells and thymic explants used for transplantation were derived from normal thymic tissues excised from infants at cardiac surgery. The tissues were cultured for 2-3 weeks. Each patient received 2.5×10^7-10^8 isolated thymic epithelial cells and $1\text{-}3 \times 10^3$ thymic explants from a single donor. These were injected (1) intraperitoneally and intramuscularly in the deltoid area (four patients), or, more recently, (2) intrahepatically via the umbilical vein and under the capsule of the rectus abdominus muscle (five patients). Immune reconstitution was assessed clinically with sequential physical examinations, by delayed hypersensitivity skin tests, by enumeration of lymphocyte subpopulations, by measurements of serum interferon levels, and by mitogen stimulation tests. In addition, biopsy samples were taken at the injection sites 2 months after transplantation.

Thymic transplantation was well tolerated in every case. Manifestations of graft-versus-host reactions were never observed. Of the nine patients grafted in Canada, two died, one at 8 weeks and the other at 4½ months after transplantation. Because the former was lost to follow up, the circumstances of death are unknown. The latter died from cerebral hemorrhage shortly after a brain biopsy for the diagnosis of cerebral toxoplasmosis. During the follow-up period, the seven surviving patients have remained stable or have improved clinically. In none of these patients have new opportunistic infections occurred.

Delayed hypersensitivity skin tests remained negative and mitogen stimulation responses and interferon levels did not change significantly. A marked increase occurred in the total number of blood lymphocytes in all patients 2 months after transplantation. There was an increase in total T ($T3^+$ phenotype) lymphocytes; this was due to an increase of $T8^+$ but not of $T4^+$ cells.

Thymic epithelial cells could not be identified histologically with hematoxylin and eosin staining of biopsy samples taken from the injection sites. The apparent absence of thymic tissue 2 months after grafting remains unexplained. It could be due to (1) difficulty in distinguishing thymic cells using standard staining procedures, (2) rejection (a host-versus-graft reaction) mediated by immunological mechanisms and/or by an "F1 hybrid" resistance (NK-like) phenomenon, or (3) thymic cell destruction by the same process (possibly viral) that initially destroyed the thymus. Currently, monoclonal antibodies to thymic epithelial cells are being used to better define the events occurring at the graft sites.

J. M. Dupuy, H. Goldman, C. Tsoukas, P. Gold, N. Gilmore, Y. Thibodeau, G. Francois, L. Pelletier, M. Joly, E. Gresseau, and R. Duperval. Institut Armand-Frappier, Université du Québec; Montreal Children's Hospital, Montreal General Hospital, and Royal Victoria Hospital, McGill University; Jean-Talon Hospital; Fleury General Hospital; Centre Hospitalier Universitaire de Sherbrooke; Canada.

REPORT OF A LONGITUDINAL PROSPECTIVE STUDY OF A HEALTHY HOMOSEXUAL MALE COHORT IN ROME

A multidisciplinary study was conducted to evaluate the epidemiologic, virologic, and immunologic features of a healthy homosexual male population. The cohort consisted of 55 homosexual men, the members of a cultural club in Rome.

Epidemiologic information collected concerned past medical history (surgery, transfusions, sexually transmitted diseases, diarrhea, viral hepatitis); sexual behaviors (initial sexual activity, kinds of sexual activities, number of sexual partners for each year and in the past year); and use of drugs and medication (alcohol, cigarettes, antibiotics, corticosteroids, street drugs, inhalants).

The following laboratory tests were carried out: (1) isolation of cytomegalovirus (CMV) from urine and semen, (2) detection of anti-CMV antibodies, (3) measurement of T4:T8 lymphocyte ratios, (4) detection of DNA sequences homologous to human T leukemia virus (HTLV) in circulating lymphocytes, (5) detection of hepatitis B virus (HBV) markers, and (6) serologic testing for syphilis.

All subjects underwent clinical examinations. Ages ranged from 21-58 (mean = 30.4) years. Sexual partners per year are shown in the Table. A statistical analysis comparing sexual partners per year and each component of the past medical history did not show any significant associations. However, a high percentage of subjects had positive anamnestic responses for sexually transmitted diseases.

SEXUAL PARTNERS PER YEAR

No. of Subjects	No. of Partners/Year
11	<5
8	6-10
6	11-20
14	21-50
11	51-100
2	101-200
—	201-300
1	301-500
1	>500

In laboratory tests, antibodies against CMV were detected in 81.8% of the sera; CMV was isolated from the urine of four subjects (7.3%) and from the semen of one subject (1.85%). These five patients were all less than 30 years old. HBV markers were present in a greater number of individuals in the study group than in the overall population of the same Italian geographical area (60% vs. 10.5%) (Pasquini P, Kahn HA, Pileggi D, et al: Am J Epidemiol., 1983, 118:699-709). Carriage of HBsAg was very low (1.92%).

HTLV DNA was not found in T cells. T4:T8 ratios ranged from 1.1-2.3 (mean = 1.56).

So far this high risk population has shown neither signs nor symptoms of AIDS. A follow-up study is in progress to promptly catch any changes which may

occur in the health status of these subjects.

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HERPES ZOSTER AND AIDS IN HOMOSEXUAL MEN

I should like to report an epidemic of herpes zoster in homosexual men at risk for AIDS. My private practice consists of approximately 2000 patients. About 90% of my patients are homosexual men. Since 1980, I am aware of 45 patients who have developed AIDS. To date, there have been 18 deaths.

Since April 1982, I have identified 42 new cases of herpes zoster from patients already established in my practice. All of these zoster cases occurred in homosexual men. Most of these men were in their mid-30s. To date, only one of the new zoster cases has developed AIDS, as defined by the Centers for Disease Control (Morb Mort Weekly Rep., 1982, 31:507-514). His zoster was particularly severe; it involved three thoracic dermatomes which took over 12 weeks to heal.

Two of the new zoster cases occurred in men whose lovers had AIDS. At least six of the new zoster cases also had oral thrush at the time of their initial zoster outbreak. In most instances, the thrush has been chronic, persisting long after the zoster has healed. The majority of these new zoster cases have had chronic lymphadenopathy. In many patients, levels of β2-microglobulin were elevated, and the total white cell counts were depressed.

Of the 45 patients who have developed AIDS, four had herpes zoster before the onset of AIDS. Zoster preceded AIDS by 5, 17, 24, and 26 months in these patients.

When specific serologic tests for AIDS are developed, it will be possible to determine which patients with herpes zoster are infected with the AIDS agent. The appearance of a zoster epidemic in the same group of homosexual men at high risk for developing AIDS suggests that an association may exist between the zoster agent and the AIDS agent.

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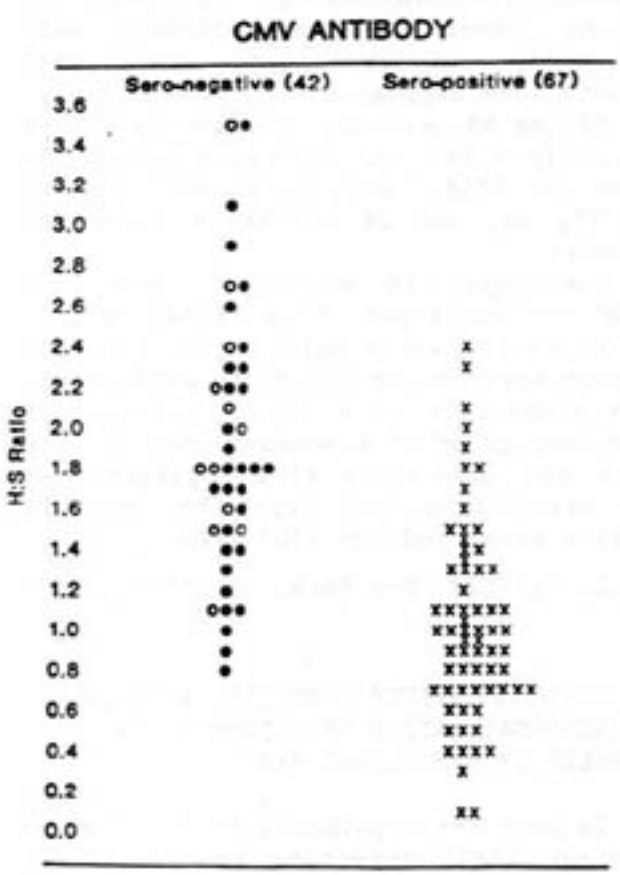
IS CYTOMEGALOVIRUS INFECTION A CAUSE OF ABNORMAL RATIOS OF T LYMPHOCYTE SUBSETS IN HOMOSEXUAL MEN?

To test the hypothesis that cytomegalovirus (CMV) infection is a critical factor in the development of the progressive immunosuppression which eventuates in AIDS, we compared helper:suppressor (H:S) subset ratios with the presence or absence of CMV antibody in homosexual men.

H:S ratios below 1.0 were found in two of 42 (<5%) seronegative men and in 33 of 67 (49%) seropositive men ($p < 0.001$) (Figure).

The results to date of a prospective study of 34 homosexual men seronegative for anti-CMV antibody at the start of the study are summarized in the Table. Nine of the 34 have converted to seropositive, and all have developed H:S ratios <1.0 following acquisition of CMV infections. Two of three seroconverters who have been followed for ≥16 months



Ratio (H:S) of OKT4 or leu3$^+$ (helper) lymphocytes to OKT8 or leu2$^+$ (suppressor, cytotoxic) lymphocytes in homosexual men with and without CMV antibody. •, x = Individuals referred to the U. C. Immunology Laboratory to "rule out AIDS." o = Healthy homosexual men screened at the San Francisco VD Clinic or Health Fair.

have maintained ratios persistently <1.0. Of 23 CMV seronegative individuals who had initial H:S ratios >1.0 and who have remained seronegative, only one has had an H:S ratio <1.0. Only two of nine seroconverters have had any symptoms attributable to the infection.

Two tentative conclusions are suggested by the data presented. (1) Abnormally low T lymphocyte H:S ratios occur almost exclusively in homosexual men who have been infected with CMV and are rarely seen in those who have never been infected with this virus. (2) Asymptomatic CMV infections induce marked and persistent H:S T lymphocyte abnormalities in homosexual men.

These findings do not prove that CMV infections are responsible for immune abnormalities in homosexual men. Those who have escaped infection with CMV may also have avoided exposure to the putative AIDS agent. Since CMV seropositivity in homosexual men correlates with receptive anal intercourse (men who have never been the receptive partner have no greater CMV prevalence than heterosexual men) (Mintz L, Drew WL, Miner RC, et al: Ann Intern Med., 1983, 99:326-329), those who lack CMV antibody may also have avoided exposure to the AIDS agent introduced by the same route.

The observation of a highly significant association between CMV infection and abnormal ratios of T cell subsets is an additional provocative link between CMV and AIDS. CMV infection may be necessary for the development of AIDS, acting as a co-factor in one of several ways. For example, primary CMV infection may induce a transient immunosuppression, permitting subsequent reinfection by other different strains of "wild-type" CMV. Each subsequent CMV infection induces further immunosuppression, ultimately disposing the patient to the development of opportunistic infections or Kaposi's sarcoma. Alternatively, primary CMV infection may induce a transient immunosuppression which permits subsequent infection by the putative AIDS agent. Finally, a preceding

PROSPECTIVE STUDY OF HOMOSEXUAL MEN INITIALLY NEGATIVE FOR CMV ANTIBODY

	H:S Ratio >1.0 Prior to Seroconversion	Average Follow-up Period (mo)	H:S Ratio <1.0 During Follow-up Period
Seroconverters (9)	9/9	6.3	9/9
Persistent seronegatives (25)	23/25	6.6	3/25*

Abbreviations: CMV, cytomegalovirus; H:S, helper:suppressor.

* Includes 2/25 whose ratios were <1.0 in their initial evaluation and have remained <1.0.

infection by another virus, for example, human T cell leukemia virus, may alter the way in which an individual "handles" subsequent CMV infections.

W. L. Drew, J. Mills, J. Dylewski, C. Cassavant, A. J. Ammann, H. Brodie, and T. C. Merigan. Biskind Pathology Research Laboratory, Harold Brunn Institute for Medical Research, Department of Pathology and Laboratory Medicine, Department of Medicine, Mount Zion Hospital and Medical Center, San Francisco, California 94115; Infectious Disease Division, Department of Medicine, San Francisco General Hospital, San Francisco, California 94110; Departments of Clinical Pathology and Laboratory Medicine; Immunology Division, Department of Pediatrics; University of California, San Francisco, California 94117; Infectious Disease Division, Department of Medicine, Stanford School of Medicine, Stanford, California 94305.

INVESTIGATION OF AIDS PATIENTS FOR EVIDENCE OF INFECTION WITH THE HUMAN PARVOVIRUS

In 1975, a virus with the morphology of a parvovirus was found in the serum of asymptomatic blood donors (Cossart YE, Field AM, Cant B, et al: Lancet, 1975, 1:72-73). Recent physicochemical studies of the genome of this agent (Summers J, Jones SE, Anderson MJ: J Gen Virol., 1983, 64:2527-2532) and of its polypeptides (Clewley JP: J Gen Virol., 1984, 65:241-245) have shown that this agent fulfills the requirements for classification as an autonomous member of the Parvoviridae family.

Initially, infection with this human parvovirus (HPV) was believed to be largely asymptomatic or associated with nonspecific febrile illnesses (Shneerson JM, Mortimer PP, Vandevelde EM: Br Med J., 1980, 280(6231):1580). Currently, evidence is accumulating to suggest that the common clinical manifestation of primary HPV infection is erythema infectiosum or Fifth disease (Anderson MJ, Jones SE, Fisher-Hoch SP, et al: Lancet,

1983, 1:1378; Anderson MJ, Lewis E, Kidd IM, et al: J Hyg., 1984, in press). The severe complication of HPV infection in individuals with chronic hemolytic anemia, aplastic crisis, is now well recognized (Rao KRP, Patel AR, Anderson MJ, et al: Ann Intern Med., 1983, 98:930-932; Anderson MJ, Davis LR, Hodgson J, et al: J Clin Pathol., 1982, 35:744-749; Kelleher JF, Luban NLC, Mortimer PP, et al: J Pediatr., 1983, 102:720-722; Duncan JR, Cappellini MD, Anderson MJ, et al: Lancet, 1983, 2:14-16).

Parvoviruses are probably ubiquitous among mammalian species. They have an absolute requirement for host cells to be in S phase of growth, and this has been demonstrated frequently in tissue culture. It is also reflected in the pathogenesis of the disease in host animals, where tissues composed of dividing cells constitute the target organs. Thus, in patients with chronic hemolytic anemia, infection of the red cell precursors in the hyperactive bone marrow leads to severe anemia. In both canine and feline species, transient leucopenia is a feature of infection. A similar phenomenon may occur in human infections (Shneerson JM, Mortimer PP, Vandevelde, EM: Br Med J., 1980, 280(6231):1580). These observations, together with the fact that HPV has been shown to be transmissible in blood and blood products (Mortimer PP, Luban NLC, Kelleher JF: Lancet, 1983, 2:482-484), prompted us to investigate AIDS patients for evidence of infection with HPV.

The study group comprised 50 patients with AIDS from St. Luke's-Roosevelt Hospital Center in New York City. Control groups comprised 20 heterosexual controls, 10 homosexual men with lymphadenopathy, 20 asymptomatic homosexual men, and 10 male homosexuals with chronic diarrhea of 3 months or more duration. Serum specimens were stored at -70°C prior to testing. Sera were examined for parvovirus DNA by the "dot blot" method (Mason WS, Aldrich C, Summers J, et al: Proc Natl Acad Sci., 1982, 79:3997-4001) using a ^{32}P-labeled cloned portion of HPV genome as probe (Anderson MJ, Jones SE, Minson AC, manuscript in preparation). This test is capable of detecting 10^3 genome copies in serum specimens. Sera were also examined for parvovirus-specific IgM (Cohen BJ, Mortimer PP, Pereira MS: J Hyg., 1983, 91:113-130).

HPV DNA was not detected in any specimen. Only one specimen contained detectable IgM antibody. This was a specimen obtained from a homosexual man in the control group. Thus, no evidence of current or recent infection with HPV was found among the AIDS cases.

In order to evaluate past exposure of AIDS patients and controls to HPV, sera were examined for parvovirus-specific IgG (Ibid) (Table 1). Anti-parvovirus IgG antibody was less common among AIDS patients than controls, and the titers in the AIDS group were, on the whole, lower. A history of parvovirus infection thus appeared less common among AIDS patients than among controls. The observation that mean titers were lower in AIDS patients raised the possibility of virus-specific immunosuppression in these patients.

To investigate this possibility, all sera were tested for the presence of rubella-specific antibody by hemolysis in gel (Kurtz JB, Mortimer PP, Mortimer PR, et al: J Hyg., 1980, 84:213-222) (Table 2). The pattern of results for anti-rubella antibodies was similar to the pattern for anti-parvovirus antibodies: both types of antibodies were less common and the mean titers were lower in AIDS patients than in controls.

The rubella virus is not considered a good candidate etiologic agent for AIDS.

TABLE 1

IgG ANTIBODY TO HUMAN PARVOVIRUS

Group	Number	Neg	Percent with Stated Amount of Antibody			
			1.3-3.7*	3.8-11	11.1-33	30-100
AIDS	50	36	24	28	12	—
Homosexuals (lymphadenopathy)	10	20	20	60	—	—
Homosexuals (diarrhea)	10	30	20	10	30	10
Homosexuals (asymptomatic)	20	20	20	45	15	—
Heterosexual controls	20	15	30	25	15	15

* Antibody measured in radioimmunoassay and expressed in arbitrary units.

TABLE 2

IgG ANTIBODY TO RUBELLA VIRUS

Group	Number	Neg	Percent with Stated Amount of Antibody			
			8-9*	10-11	12-13	14-15
AIDS	50	22	22	28	26	2
Homosexuals (lymphadenopathy)	10	10	—	20	60	10
Homosexuals (diarrhea)	10	—	10	30	40	20
Homosexuals (asymptomatic)	20	10	5	25	55	5
Heterosexual controls	20	10	—	35	45	10

* Hemolysis zone: diameter in mm.

The similarities in patterns of anti-rubella and anti-parvovirus antibody prevalences and titers suggest, by analogy, that infection with the human parvovirus is not etiologically associated with the development of AIDS.

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AIDS CASES REPORTED TO THE CENTERS FOR DISEASE CONTROL AS OF May 28, 1984

UNITED STATES CASES

DISEASE	CASES	PERCENT OF TOTAL	DEATHS	PERCENT DEAD
KS without PCP	1153	25.0	279	24.2
PCP without KS	2403	52.1	1129	47.0
Both KS and PCP	299	6.5	193	64.5
OI without KS or PCP	760	16.5	398	52.4
TOTAL	4615	100.0	1999	43.3

KS = Kaposi's sarcoma
OI = Opportunistic infection
PCP = Pneumocystis carinii pneumonia

	MALES		FEMALES		TOTAL	
RISK GROUPS*	CASES	% OF TOTAL	CASES	% OF TOTAL	CASES	%
Homosexual or bisexual	3328	77.3	0	0.0	3328	72.1
IV drug user	621	14.4	172	55.3	793	17.2
Haitian	154	3.6	27	8.7	181	3.9
Hemophiliac	33	0.8	0	0.0	33	0.7
No apparent risk group or unknown	168	3.9	112	36.0	280	6.1
TOTAL	4304	100.0	311	100.0	4615	100.0

* The risk groups listed are hierarchically ordered; cases with multiple risk factors are tabulated only in the risk group listed first.

AIDS
MEMORANDUM
Acquired Immune Deficiency Syndrome

National Institute of Allergy and Infectious Diseases

Volume 1, Number 7 August 1984

IN THIS ISSUE

GROUND RULES FOR USE OF THE AIDS MEMORANDUM

The AIDS Memorandum serves as a forum for the rapid exchange of new information and ideas among clinicians and scientists involved in AIDS research and management. Material contained in the Memorandum can be of several kinds: positive and/or negative results, clinical and/or experimental findings, preliminary and/or validated data, observations, questions, theories, commentaries, and others. This material is not subjected to peer review. Therefore, users of the Memorandum must agree to treat all material as privileged information and to consider it as tentative and subject to change prior to formal publication in a refereed journal.

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Users must agree to contribute data or ideas to the Memorandum at least once a year. On an annual basis, the names of individuals who have not contributed to the Memorandum will be culled from the mailing list, so as to limit circulation of the Memorandum only to individuals actively working in the field.

Finally, users must agree to share material in the Memorandum only with other individuals willing to honor these ground rules.

FELINE LEUKEMIA VIRUS: AN OVERVIEW

The feline leukemia virus (FeLV) is the etiologic agent of the most important fatal infectious disease complex affecting American cats. FeLV is a horizontally transmitted and vertically transmitted retrovirus. The in vivo host spectrum appears to be restricted to members of the family Felidae and includes domestic breeds as well as certain small exotic cats. Sophisticated molecular studies have demonstrated relationships between FeLV and some retroviruses of rodents; these and other data suggest that an ancient rodent virus may have been transferred in some manner to an ancestor of the domestic cat millions of years ago, and, from this progenitor, FeLV evolved.

Excretion of FeLV occurs primarily in salivary secretions. Virus may also be present in respiratory secretions, feces, urine. The social grooming habits (licking and biting), sneezing, and the common urban practice of providing shared litter pans and feeding bowls for pet cats are probably the major means by which FeLV is spread. In addition, the exposure of kittens to the virus may be effected by an infected queen or by close contact with other carrier cats: in utero transfer of virus across the placenta and excretion of FeLV in colostrum are both known to occur. Prolonged close contact (days to weeks) probably is required for effective transmission of FeLV. Virus can also be transmitted in blood transfusions from viremic cats and possibly also by the bites of hematophagous arthropods, such as fleas. The time period between initial exposure to an infective dose of FeLV and the development of either persistent viremia or immunity is quite variable and may be dependent in part on the route of virus transmission.

Through recent studies, some of the early steps in the interactions of host tissue and virus during FeLV infection have been identified. Following infection of the lymphoid tissues surrounding the site of initial virus penetration, a low-grade (transient) viremia occurs involving small numbers of mononuclear leukocytes. Virus is transported to other regions of the body, especially to systemic lymphoid tissues, the intestinal tract, and the bone marrow--all areas containing populations of rapidly dividing cells where FeLV replication can be enhanced. This occurs within 2 weeks of the initial viral exposure. Infections of both polymorphonuclear leukocyte and platelet precursor cells in the bone marrow and the subsequent release of infected cells into the circulation result in a second, more profound (persistent) viremia.

In those cats which resist the widespread replication and dissemination of FeLV, virus containment occurs in the early lymphoid stage of infection following transient viremia. In those animals destined to be viremic persistently, infection proceeds and extensive involvement of the bone marrow, pharynx, esophagus, stomach, bladder, respiratory tract, and salivary glands occurs. All cats with persistent viremia are excretors of infectious FeLV and probably remain excretors for the rest of their lives. They then serve as the primary reservoirs of infectious viruses and can transmit infection to healthy, uninfected, susceptible cats with which they come into contact.

The age of the host at the time of infection and the amount and strain of the infective dose of virus transmitted are important determinants of the outcome of any FeLV challenge. Whereas most kittens exposed to FeLV develop persistent viremia, most cats over 6 months of

age resist persistent viremia, suggesting that age-related maturational changes in the immune system are involved. Evidence indicates that the pertinent maturational changes occur in cats between 2 and 4 months of age. However, some older animals may develop persistent viremia if the duration of exposure to FeLV is very long (years).

Cats with persistent viremia can develop a number of disease entities that are either directly or indirectly caused by FeLV. Among the conditions directly caused by FeLV are lymphoid malignancies (lymphosarcoma, lymphocytic leukemia), a number of myeloproliferative disorders, several types of anemia, panleukopenia-like and thymic atrophy syndromes, glomerulonephritis, certain reproductive disorders, and several other conditions. Diseases indirectly caused by FeLV include myriad conditions that can develop secondary to FeLV-induced immunosuppression. The prognosis for survival of cats with persistent infections is exceedingly poor: approximately 50% die within 6 months of infection and over 80% die within 3 years of infection.

Suppression of the normal protective immunologic responses is unquestionably one of the most important consequences of persistent FeLV infection and is especially pertinent to researchers studying AIDS. Both the humoral and cellular arms of the immune system are affected by the virus. A major cause of FeLV-induced immunosuppression appears to be a specific structural protein, p15(E), that is associated with the viral envelope. Both intact and disrupted virus particles retain immunosuppressive capabilities. An array of secondary disease entities is associated with persistent FeLV infection. It has been estimated that nearly 50% of all cats with severe bacterial infections or hemobartonellosis and 75% of cats with toxoplasmosis have an underlying FeLV infection. In addition, FeLV-induced immunosuppression has been associated with chronic stomatitis and gingivitis, poorly healing or recurrent abscesses, pyoderma, chronic respiratory infections, acute colitis, severe otitis, and feline infectious peritonitis (a lethal, systemic coronavirus disease of both domestic and exotic cats). FeLV-induced immunosuppression probably contributes also to the development of FeLV-induced malignancies.

Research into the development of a safe, protective FeLV vaccine has progressed slowly over the past several years, despite increases in our understanding of the biological behavior of FeLV and the pathogenesis of FeLV infection. Several strategies for FeLV immunization have been investigated, including use of inactivated virus vaccines, tumor cell vaccines, envelope glycoprotein vaccines, and live virus vaccines. Recently, a soluble tumor-cell antigen vaccine (STAV) has been developed by a research team headed by Dr. Richard Olsen, College of Veterinary Medicine, Ohio State University. This vaccine contains neither tumor cells nor FeLV; it is a subunit vaccine composed of immunogenically important antigens naturally released from FeLV-induced lymphosarcoma cells grown in vitro. Studies have shown that adult cats as well as kittens vaccinated with STAV produce protective antiviral and antitumor antibodies and that most are protected against the development of FeLV-induced lymphoid malignancies. In addition, although STAV contains the p15(E) protein, its immunosuppressive action is apparently not exerted in vaccinated animals. Further work is currently in progress to evaluate this highly promising form of immunization.

Local control of FeLV has been achieved through the removal of carrier cats with persistent viremia from multiple-cat households in which they are living. The FeLV test-and-removal program uses an immunofluorescence assay (IFA) for detecting FeLV antigen in infected leukocytes and platelets. In a survey of 45 households from which 159 cats with persistent viremia were removed, 99.5% of the FeLV-negative cats not removed (561/564) remained negative on retesting. Multiple-cat households in which FeLV test-and-removal has not been implemented may experience infection rates over 40 times greater than the rates experienced by households in which the program has been successfully introduced. This program and the IFA procedure it employs were developed by a team of researchers headed by Dr. William D. Hardy, Jr. of the Memorial Sloan-Kettering Cancer Center.

The public health significance of FeLV including, most importantly, the qu[illegible]n of the oncogenic potential of FeL[illegible]umans is still largely unknown[illegible]s which were designed to determi[illegible]evalent circulating FeLV and/or anti[illegible] FeLV are in human sera have produ[illegible] conflicting results over the years. Most surveys have failed to find evidence of FeLV infection in humans, even in individuals with lymphoid or other malignancies. However, most cats with FeLV-induced malignancies similarly have little or no circulating virus-neutralizing antibody, and 10-50% are FeLV negative. Until a more complete understanding of the public health implications of FeLV is obtained, the author considers it prudent to restrict as much as possible human exposure to carrier cats with persistent viremia. It must be emphasized, however, that, as of this writing, there is no conclusive evidence that any human illness (including cancer) has ever been caused by FeLV.

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AIDS-RELATED COMPLEX: A DEFINITION

The National Cancer Institute/National Institute of Allergy and Infectious Diseases Extramural AIDS Working Group consists of a sizable number of investigators who receive funding from the National Institutes of Health specifically for AIDS research. Members of the Group see a large number of patients with AIDS and with AIDS-related conditions. In the summer of 1983, selected members of the Group formulated criteria to describe the "Lymphadenopathy Syndrome" or "AIDS Prodrome." Participants in this exercise were Drs. D. Abrams (UCSF), E. Hersh (MD Anderson), J. Allen (CDC), D. Armstrong (Memorial Sloan-Kettering), A. Friedman-Kien (NYU), M. Gottlieb (UCLA), G. Copley (NCI), J. Killen (NCI), and R. Edelman (NIAID). A considerable amount of time was devoted to finding a name for the syndrome. All agreed that the name chosen should not imply a prodromal condition to overt AIDS, considering both the limits of our current level of understanding of the disease and the variety of psychosocial and medical/financial risks which such a name would impose on the patient. The compromise term, AIDS-related complex (ARC), was finally adopted by consensus and used in Group discussions.

In establishing a definition of ARC, the Group used an approach similar to that used by the American Rheumatism Association for developing a standard diagnosis for rheumatoid arthritis. The

diagnosis of ARC depends upon the finding of any two clinical plus any two laboratory abnormalities in a patient with no underlying infectious cause who is in a high risk group for AIDS.

Clinical Signs/Symptoms (minimum duration 3 months): (1) Fever: >100°F, intermittent or continuous, no infectious cause. (2) Weight loss: unexplained, >10% or ≥15 lbs. (3) Lymphadenopathy: ≥2 extrainguinal areas. (4) Diarrhea: intermittent or continuous, no other cause. (5) Fatigue: unexplained and causing decreased physical or mental function. (6) Night sweats: intermittent or continuous, no infectious cause.

Laboratory Abnormalities: (1) Leukopenia, or thrombocytopenia, or anemia, or absolute lymphopenia. (2) Depressed helper:suppressor T cell ratio (≥2 SD). (3) Depressed absolute number of T helper cells (≥2 SD). (4) Depressed blastogenesis (pokeweed and phytohemagglutinin). (5) Elevated serum globulins. (6) Cutaneous anergy.

This definition encompasses the entire ARC syndrome, because enough information was not available at the time to further stratify ARC into logical clinical subcategories. This definition and minimum data set are subject to change based upon new findings. Indeed, both the discovery of a role for HTLV-III in AIDS and the additional insight which has been gained recently concerning the natural history of ARC and its many clinical expressions have forced us, only 9 months after the definition was first formulated, to reconsider the name and the definition. The results of this second consensus effort, just undertaken by the Group, will be published as soon as possible, assuming that a consensus can be reached.

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THYMOPENTIN TREATMENT IN AIDS AND AIDS-RELATED COMPLEX

Many immunomodulators are currently under investigation in AIDS patients. Thymopentin (TP5) is a synthetic pentapeptide. It has been used successfully in the treatment of various congenital immunodeficiency disorders (Aiuti F, Fiorilli M, Quinti I: Lancet, 1983, 1: 551). Its biological activity is similar to that of thymopoietin which induces the maturation of thymocytes and affects the regulation of the immune system (Goldstein G, Scheid MP, Boyse EA et al: Science, 1979, 204:1309-1310). A recent report showed that levels of serum thymic factor were lowered in patients with AIDS (Dardenne M, Bach JF, Safai B: N Engl J Med., 1983, 309:48). We therefore decided to evaluate whether thymopentin could improve the clinical status and alter immunologic parameters of patients with AIDS (Clumeck N, Sonnet J, Taelman H: N Engl J Med., 1984, 310: 492-497) or with the prodrome of AIDS, AIDS-related complex (ARC). This report describes the results of a study of African patients, five with full-blown AIDS and 11 with ARC. ARC was characterized by generalized lymphadenopathy (100% of cases), weight loss (90%), chronic diarrhea (82%), fever (73%), and T cell ratios (OKT4:OKT8) less than 0.5 (91%; mean ratio = 0.20).

The five patients with AIDS received 50 mg TP5 three times a week for 1 month by slow intravenous (IV) infusion (Group A). Six patients with ARC received 50 mg TP5 three times a week by IV bolus for 1 month followed by 50 mg TP5 by slow IV infusion for an additional month (Group

B). The other five ARC patients received 15 mg TP5 three times a week subcutaneously for 1 month (Group C). Various immunological tests were performed on all patients before, during, and after therapy. These included in vitro studies of T cell functions, studies of the blastogenic responses of lymphocytes to PHA, and in vivo evaluations of the cutaneous responses to five test mitogens (PPD, candidine, varidase, PHA [1 μg], and PHA [10 μg]).

Immunologic parameters tested in all of the patients in Group A deteriorated during the course of therapy. The number of OKT4 cells dropped from 7% (±8) to 1% (±1) and the number of OKT8 cells increased from 52% (±10) to 58% (±60). The OKT4:OKT8 ratio dropped from 0.15 (±0.18) to 0.03 (±0.03). The response to PHA decreased from 33,186 cpm (±34,142) to 9617 cpm (±8479). All patients were anergic before treatment and remained anergic even after therapy. Clinically, all five patients grew worse during the course of the study. All died, two from infections during the course of therapy and three within 2-8 months after therapy.

The results of immunological evaluations of the six ARC patients in Group B at various times before and during treatment are summarized in the Table. After IV bolus administration of TP5, there was a significant increase in the percent of total (OKT3) T cells, due mostly to an increase in the number of suppressor/cytotoxic (OKT8) cells. After slow infusion of additional TP5, there was significant improvement in the in vitro response to PHA over the pre-therapy value and over the post-bolus value. This was associated with an improved in vivo response: skin tests, all of which were negative before therapy, became positive in five patients after TP5 therapy. All patients also gained weight and subjective reports indicated

OLOGIC PARAMETERS IN GROUP B AIDS-RELATED COMPLEX PATIENTS
ECEIVING THYMOPENTIN BY TWO ROUTES OF ADMINISTRATION

	Mode of Administration			
	1 Before Treatment	2 Intravenous Bolus	3 Infusion	P*
Lymphocytes (cells/μl)	2,000 ± 1,069	2,167 ± 1,314	2,253 ± 1,575	NS
OKT3 (%)	70 ± 5	79 ± 8	73 ± 12	0.03 (1 vs. 2)
OKT4 (%)	6 ± 3	10 ± 5	7 ± 6	NS
OKT8 (%)	65 ± 8	74 ± 8	66 ± 16	0.01 (1 vs. 3)
PHA (cpm)	45,182 ± 42,300	61,311 ± 51,228	116,362 ± 75,866	0.05 (1 vs. 3) 0.02 (2 vs. 3)

All results are expressed as mean ± standard deviation. Abbreviations: cpm, counts per minute; NS, not significant; PHA, phytohemagglutinin.

* T test on paired samples.

improvement. After 8 months observation, immunological and clinical improvement persisted in four patients. One patient developed cutaneous Kaposi's sarcoma (KS) at 7 months. One patient developed opportunistic infections (OI) (Pneumocystis carinii pneumonia (PCP), esophagitis, candidiasis) and disseminated KS at 3 months. (This patient was the one showing no response to mitogens during TP5 therapy.)

The five patients in Group C showed only one common modification following TP5 therapy--a significant decrease of OKT3 cells. For one patient, subjective reports indicated improvement and weight gain was recorded. This patient developed positive skin tests, an increased OKT4:OKT8 ratio (from 0.3-0.8), and a 20-fold increase in the in vitro response to mitogens. Three patients developed OI during TP5 therapy: herpes zoster (two cases), PCP (one case), and oral candidiasis (two cases).

This preliminary study confirms a previous report (Mascart-Lemone F, Huygen K, Clumeck N: Lancet, 1983, 2: 735-736) and suggests that IV infusion with TP5 may be useful in treating patients with ARC. No effect of TP5 was noted in patients with full-blown AIDS. It is possible that in these patients the pool of lymphocytes is too seriously depleted for stimulation to occur.

The mode of administration of TP5 is important. The same dose administered in different ways can produce opposite effects (Audhya T, Goldstein G: Int J Pept Protein Res., 1983, 22:187). In addition, it has been shown in the guinea pig that, at equivalent doses, the effect of TP5 on neuromuscular transmission is higher by slow IV infusion (Ibid, p 568). In our study, 50 mg administered by slow IV infusion appears to be more effective than other doses and other routes.

This study suggests that improvement of both the clinical and the immunological status of ARC patients may be possible through high-dose TP5 therapy. Long-term double-blind studies are needed to assess whether such therapy can interfere with the natural evolution of the disease.

This paper contains information which has been accepted for presentation at the Interscience Conference on Antimicrobial Agents and Chemotherapy to be held in Washington, D.C., October 1984.

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HYPOTHESIS: THE PATHOGENESIS OF AIDS INVOLVES ACTIVATION OF T AND B CELL CASCADES

The concept advanced in this paper is that viral infection of lymphocytes can produce proliferative or lytic responses depending on the circumstances of infection. In either case, infection of lymphocytes is followed by a cascade of secondary events. AIDS may result when an agent related to the human T leukemia/lymphoma virus (HTLV) produces a lytic response in T helper cells. The sequence or cascade of events in the T cell population following lysis of T4 helper cells in AIDS would include reactivation of Epstein-Barr viruses (EBV) with production of a secondary B cell cascade, reactivation of cytomegaloviruses (CMV) and the development of Kaposi's sarcoma in genetically susceptible individuals, and perhaps reactivation of other intracellular agents. Opportunistic infections also may occur.

The T Cell Cascade. That a virus might be capable of inducing a proliferative response in T lymphocytes was first suggested by the occurrence of lymphatic tumors in non-human primates and other animals infected with herpes viruses (Deinhardt F, Deinhardt J: in Epstein MA, Achong BG (Eds): The Epstein-Barr Virus, Springer-Verlag, New York, 1979, 374-415). More recent developments associate T tropic retroviruses with various diseases of humans. For example, both virologic and antibody data indicate that a human T cell leukemia virus (HTLV-I) is present in patients with human T cell leukemia or lymphomas (Reitz MS, Jr, Kalyanaraman VS, Robert-Guroff M, et al: J Infect Dis., 1983, 147:299-305; Blattner WA, Blayney DW, Robert-Guroff M, et al: J Infect Dis., 1983, 147:406-416; Hinuma Y, Nagata K, Hanaoka M, et al: Proc Natl Acad Sci., 1981, 78:6476-6480; Miyoshi I, Kubonishi I, Yoshimoto S, et al: Nature, 1981, 294:770-771). Most recently, strong evidence has been presented which implicates [illegible]ruses (HTLV-III, IDAV, and LAV) [illegible] etiology of AIDS (Barre-Sinous[illegible]ermann JC, Rey F, et al: Science, 1983, 220:868-871; Popovic M, Sarngadharan MG, Read E, et al: Science, 1984, 224:497-500; Gallo RC, Salahuddin SZ, Popovic M, et al: Science, 1984, 224:500-502; Schupbach J, Popovic M, Gilden RV, et al: Science, 1984, 224: 503-505; Sarngadharan MG, Popovic M, Bruch L, et al: Science, 1984, 224:506-508; Marx JL: Science, 1984, 224:475-477; Vilmer E, Barre-Sinoussi F, Rouzioux C, et al: Lancet, 1984, 1:753-757). The three AIDS-associated retroviruses are probably closely related to each other, if not identical.

Immunologically, AIDS is characterized by a reversal of the helper:suppressor (T4:T8) T-cell ratio (Kornfeld H, Vande Stouwe RA, Lange M, et al: N Engl J Med., 1982, 307:729-730). Reversal of this ratio is, however, also common in asymptomatic homosexuals (Ibid) and in members of other risk groups. B lymphocytes are also affected in AIDS, with the types of alterations seen suggesting that polyclonal activation of B cells may have occurred (Lane HC, Masur H, Edgar LC, et al: N Engl J Med., 1983, 309:453-458).

A virus capable of infecting T cells, especially helper T cells, could, in theory, initiate a sequence of events which could produce the various known signs and symptoms of AIDS as well as other effects. Figure 1 illustrates the steps in the hypothetical T cell cascade. The concept of a T cell cascade was originally suggested by Pagano (Pagano J: Presented at a conference on Epidemic Kaposi's Sarcoma and Opportunistic Infections in Homosexual Men, New York University, New York, March 17-19, 1983).

In theory, the infection of T4 cells by a retrovirus could initiate either a lytic response or a proliferative response (Blattner WA, Blayney DW, Robert-Guroff M, et al: J Infect Dis., 1983, 147:406-416). In the former instance, the outcome might be AIDS, while, in the latter instance, the outcome might be adult T leukemia/lymphoma (ATL). Factors which would facilitate the production of lytic effects could be different in different groups of affected individuals. These effects could be primary viral effects or secondary ones. Whatever their genesis, the lytic effects on helper T cells would impair a key link in the cell-mediated immune system. Then, impaired surveillance of malignant cells, reactivation of latent viruses, certain intracellular organisms, and other opportunistic agents, impairment of the primary immune response to these agents, and additional secondary effects could occur.

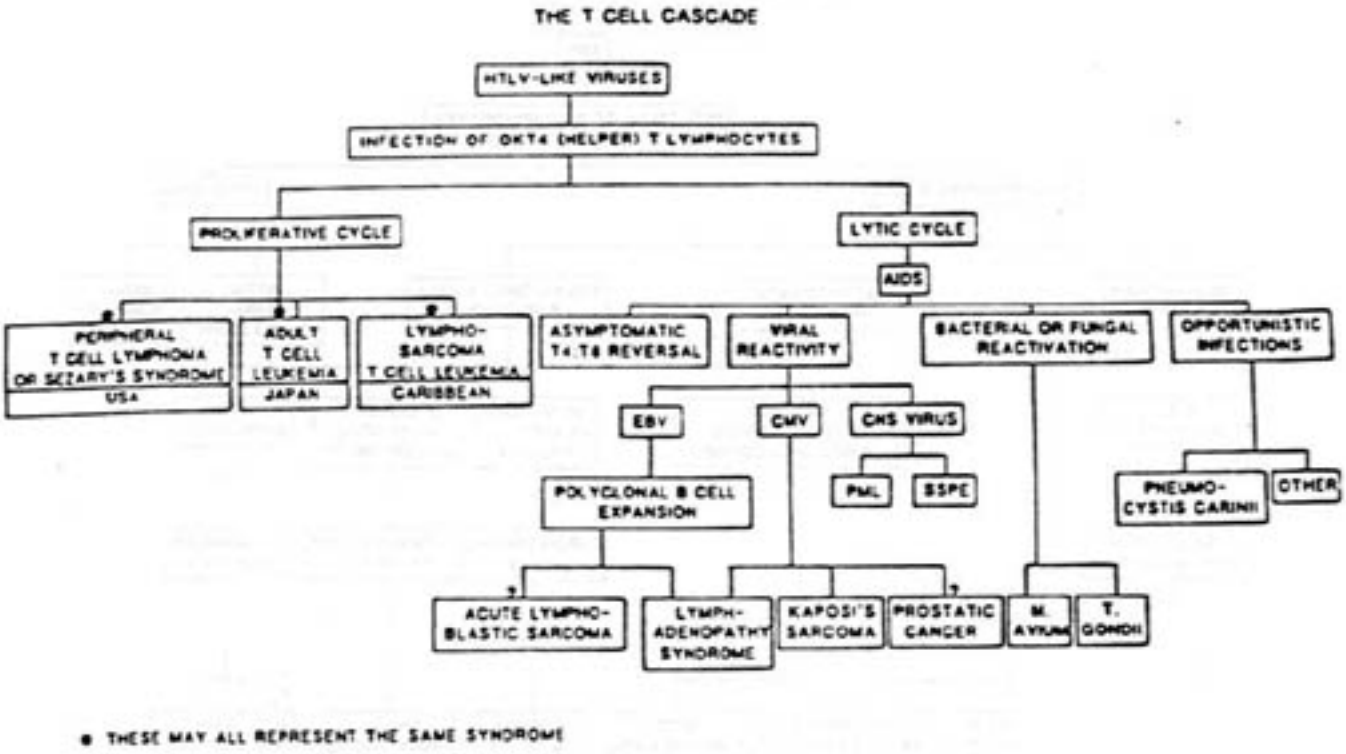

Fig. 1. Hypothetical sequence of events following infection of OKT4 (helper) T lymphocytes by a human T cell leukemia (HTLV)-like virus.

Reactivations of herpes viruses are of special interest. The reactivation of EBV in B lymphocytes can lead to polyclonal B cell proliferation (Lane HC, Masur H, Edgar LC, et al: N Engl J Med., 1983, 309:453-458), the production of high titers of EBV antibody, and the various effects listed in the B cell cascade (see below). CMV reactivation might be responsible for acute CMV mononucleosis, lymphadenitis, or, in a more chronic phase, Kaposi's sarcoma (Ibid). The total possible spectrum of acute and chronic consequences of the reactivation of various latent viruses is not fully known. Additional viral effects are expected to be recognized as more persons with T4:T8 disturbances are followed for longer periods of time.

The B Cell Cascade. Activation or reactivation of EBV in infected B cells could produce several kinds of effects as indicated in the cascade presented in Figure 2. This figure is derived from various data published previously (Evans AS, Neiderman JC: in Evans AS (Ed): Viral Infections of Humans. Epidemiology and Control, 2nd ed, Plenum Press, New York, 1982, 253-281; Evans AS: J Infect Dis., 1971, 124:330-337; Carter RL: Lancet, 1975, 1:846-855).

In the lytic cycle, anemia or hypogammaglobulinemia might result. In the proliferative cycle, transformation and

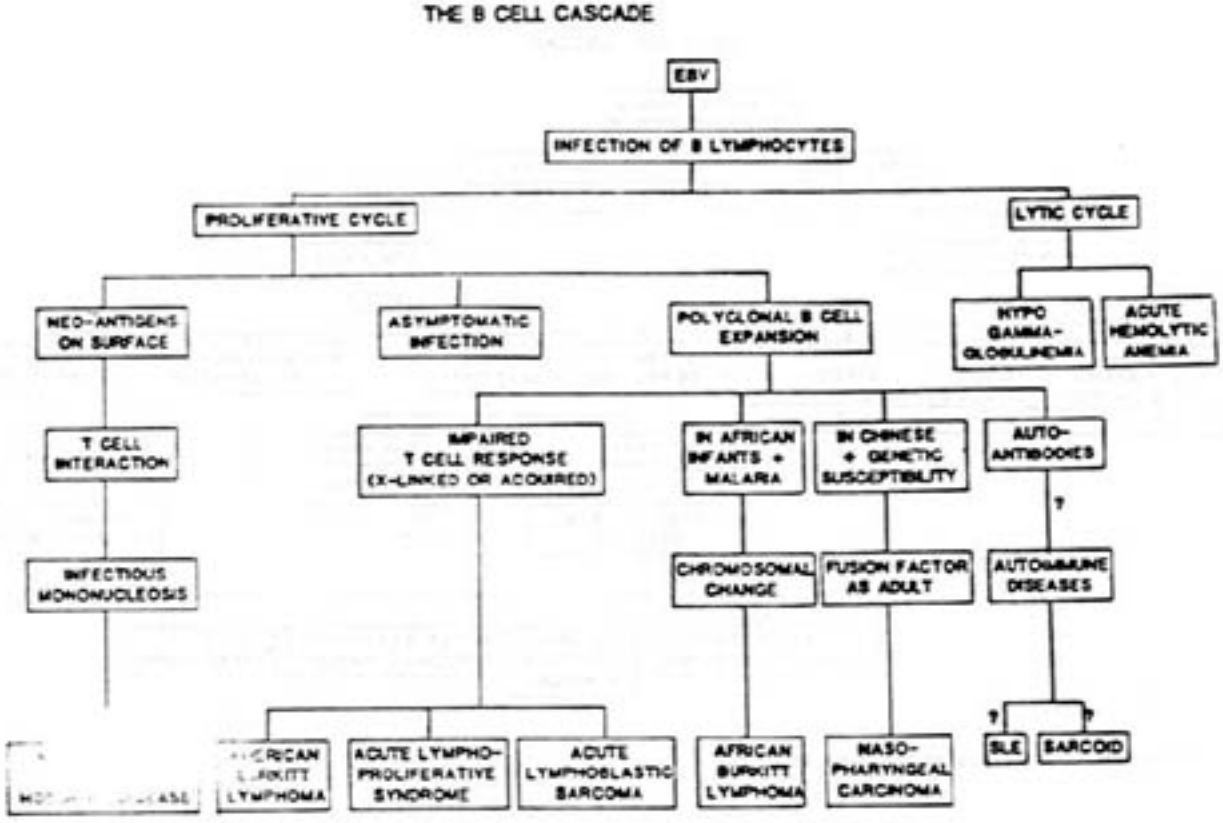

Fig. 2. Hypothetical sequence of events following infection of B lymphocytes by Epstein-Barr virus (EBV).

"immortalization" of B lymphocytes and polyclonal B cell expansion could occur. A wide spectrum of antibodies could be produced by EBV-activated B cells, including various heterophile, anti-EBV, and anti-self antibodies (Evans AS, Neiderman JC: in Evans AS (Ed): Viral Infections of Humans. Epidemiology and Control, 2nd ed, Plenum Press, New York, 1982, 253-281; Kano K, Milgrom F: Curr Top Microbiol Immunol., 1979, 77:43-69). The induction of new antigens on the surface of EBV-infected B cells can evoke vigorous T cell responses as in infectious mononucleosis in older children and young adults. Usually this is a benign and self-limited disease in which the proliferative events are brought under control through the activities of suppressor/cytotoxic and non-specific "killer" T lymphocytes early in disease (Evans AS, Neiderman JC: in Evans AS (Ed): Viral Infections of Humans. Epidemiology and Control, 2nd ed, Plenum Press, New York, 1982, 253-281; Thorley-Lawson DA, Chess L, Strominger JL: J Exp Med., 1977, 146:495-507; Tosato G, McGrath I, Koski I, et al: N Engl J Med., 1979, 301:1133-1137). However, when genetic (X-linked) or acquired defects in T cell responsiveness permit B cell proliferation to continue unchecked, acute lymphoblastic sarcoma may result (Purtilo DT, Hutt L, Bhawan J, et

al: Clin Immunol Immunopathol., 1978, 9:147-156; Robinson JE, Brown N, Andiman W, et al: N Engl J Med., 1980, 320:1293-1296; Snydman DR, Rudders RA, Daoust P, et al: Ann Intern Med., 1982, 96:737-742). EBV infections in Africa occurring in early infancy can lead to impaired cytotoxic and suppressor T cell responses and augmented B cell proliferation caused by holendemic malaria (de-The G, Geser A, Day NE, et al: Nature, 1978, 274:756-761). African Burkitt lymphoma can arise when chromosomal changes occur--specifically a translocation from chromosome 8 to chromosome 14--in the rapidly proliferating B cells (Miller G: in Evans AS (Ed): Viral Infections of Humans. Epidemiology and Control, 2nd ed, Plenum Press, New York, 1982, 599-619). EBV has also been associated with the development of nasopharyngeal cancer (de-The G, Ho JHC, Muir CS: in Evans AS (Ed): Viral Infections of Humans. Epidemiology and Control, 2nd ed, Plenum Press, New York, 1982, 621-652). High levels of EBV antibodies are produced in 30-40% of patients with Hodgkin's disease (Evans AS, Kirchhoff LV, Pannuti CS, et al: Am J Epidemiol., 1980, 112: 609-618; Henle W, Henle G: Int J Cancer, 1975, 16:323-328) even prior to diagnosis (Evans AS, Comstock GW: Lancet, 1981, 1:1183-1186), but viral genomes have not been demonstrated in malignant tissues (Pagano JS, Huang CH, Levine P: N Engl J Med., 1973, 289:1395-1399).

Proof that HTLV-related viruses are the etiologic agents of AIDS will involve establishment of close temporal associations between infection by the candidate agents and both clinical symptoms of AIDS and immunologic parameters. Infection with the candidate agents must precede these events and must be significantly higher in those who develop AIDS than in those who do not. Epidemiologic techniques which have been key in establishing a causal role for EBV in infectious mononucleosis (Evans AS: Presented at NIH Workshop on Epidemiology of AIDS, September 12-13, 1983; Hallee TJ, Evans AS, Neiderman JC, et al: Yale J Biol Med., 1974, 47:182-195) and in African Burkitt lymphoma (de-The G, Ho JHC, Muir CS: in Evans AS (Ed): Viral Infections of Humans. Epidemiology and Control, 2nd ed, Plenum Press, New York, 1982, 621-652) would be useful as models for establishing a causal relationship between HTLV-related viruses and AIDS.

The hypothesis presented in this paper is that an HTLV-like virus infects T4 cells causing lysis and/or suppression by T8 cells. These events initiate the reactivation of EBV, CMV, and other latent viral, bacterial, and fungal agents. Careful prospective serologic and immunological studies of susceptible persons who are at high risk are needed to associate causally the infection by candidate agents with various changes in the immune system, with changes in levels of various markers, and with the appearance of prodromal and early clinical features of AIDS.

An expanded paper including portions of this article will be published in the Yale Journal of Biology and Medicine, 1984, 57 (3).

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PREVALENCE OF KAPOSI'S SARCOMA IN AIDS PATIENTS REFLECTS DIFFERENCES IN RATES OF CYTOMEGALOVIRUS INFECTION IN HIGH RISK GROUPS

Higher morbidity due to Kaposi's sarcoma (KS) has been noted in the homosexual/bisexual AIDS risk group as compared to the heterosexual intravenous (IV) drug user risk group (DeJarlais DC, Marmor M, Thomas P, et al: N Engl J Med., 1984, 310:1119). Since several lines of evidence suggest that cytomegalovirus (CMV) may be related etiologically to KS (Giraldo G, Beth E, Henle W, et al: Int J Cancer, 1978, 22:126-131; Drew WL, Miner RC, Ziegler JL, et al: Lancet, 1982, 2:125-127), we have compared the prevalence of antibody to CMV in IV drug users with the prevalence of such antibody in homosexual men (Table).

Serum samples were collected from 94 male clients in methadone maintainence and drug detoxification programs in the San Francisco Bay area. Ninety-three percent of the subjects denied homosexual or bisexual activity. No cases of AIDS or AIDS-related complex were found. The mean duration of IV drug abuse was 10.6 years (±5.5 years SD). Ninety percent of the subjects admitted sharing needles with other drug abusers. Sixty-six percent of these subjects were seropositive for CMV antibody when evaluated by the fluorescence immunoassay (FIAX®) system of IDT, Inc. (Santa Clara, CA).

A similar study evaluating 49 patients in an out-patient drug rehabilitation program was conducted in New York City. Of the subjects in this group, 61.2% were seropositive for CMV antibody.

Previous studies have shown that 94% of homosexual men are seropositive for CMV (Drew WL, Mintz L, Miner RC, et al: J Infect Dis., 1981, 143:188-192).

These data indicate that the prevalence of CMV antibody is significantly greater in homosexual men than it is in intravenous drug abusers. The differences are statistically significant ($p < 0.001$) for both the San Francisco and New York City drug abuser groups when compared with homosexual men. If CMV contributes to the etiology of KS, the higher CMV infection rate in homosexual men may account for the greater prevalence of KS in homosexual patients with AIDS.

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POSITIVE AND NEGATIVE SEROLOGIC TESTS FOR ANTI-CYTOMEGALOVIRUS ANTIBODIES

	Intravenous Drug Users		
	San Francisco	New York	Homosexual Men
	Total = 94	Total = 49	Total = 139
CMV+	62 (66%)	30 (61.2%)	130 (94%)
CMV-	32 (34%)	19 (38.8%)	9 (6%)

AUTHOR ADDENDUM

In the AIDS Memorandum, Volume 1(5), 1984, "Reinfection with Cytomegalovirus in AIDS Patients" was contributed by W. L. Drew, E. Sweet, and E. Mocarski. Mount Zion Hospital and Medical Center, San Francisco, California 94120, and Stanford University School of Medicine, Stanford, California 94305.

AIDS IN CANADA: JULY 16, 1984

LCDC has received reports of 96 cases of AIDS in adults which comply with the case definition published by the Centers for Disease Control in Atlanta. In addition, seven cases in children have been reported but are not included in the tabulated statistics.

Age Group (years)	Male		Female		Total (% of Total)
	Alive	Dead	Alive	Dead	
Under 20	0	0	0	0	0 (0.0)
20-29	8	10	2	3	23 (23.9)
30-39	15	28	1	3	47 (49.0)
40-49	5	6	0	1	12 (12.5)
50 and over	4	9	0	1	14 (14.6)
Total (%)	32 (33.3)	53 (55.2)	3 (3.2)	8 (8.3)	96 (100.0)

Country of Birth	Alive	Dead	Total (% of Total)
Canada	24	34	58 (60.4)
Haiti	6	20	26 (27.1)
Other	4	4	8 (8.3)
Not known	1	3	4 (4.2)
Total (%)	35 (36.5)	61 (63.5)	96 (100.0)

AIDS IN CANADA

Sexual Orientation	Alive	Dead	Total (% of Total)
Homosexual/Bisexual	24	34	58 (60.4)
Heterosexual	10	22	32 (33.3)
Not Known	1	5	6 (6.3)
Total (%)	35 (36.5)	61 (63.5)	96 (100.0)

Primary Disease	Alive	Dead	Total (% of Total)
KS	9	11	20 (20.8)
PCP without KS	16	29	45 (46.9)
Both KS and PCP	3	2	5 (5.2)
Other OI	7	19	26 (27.1)
Total (%)	35 (36.5)	61 (63.5)	96 (100.0)

Abbreviations: KS, Kaposi's sarcoma; OI, opportunistic infection; PCP, Pneumocystis carinii pneumonia.

CLASSIFICATION OF CANADIAN CASES

A. Evidence of a Possible Means of Disease Acquisition	
Homosexual or bisexual practice	58
Intravenous drug abuse	1
Hemophilia	2
B. Exposure Factors	
Person of Haitian origin	24
Heterosexual partners of person(s) with AIDS or person(s) in group A	0
Recipients of blood transfusions/blood products (excluding hemophiliacs)	0
C. Children	
Infant (less than 12 months)	4
Child (1-15 years)	3
D. Person Diagnosed as Having AIDS But Not Fitting into A, B, or C Above	11

AIDS CASES REPORTED TO THE CENTERS FOR DISEASE CONTROL AS OF JULY 30, 1984

UNITED STATES CASES

DISEASE	CASES	PERCENT OF TOTAL	DEATHS	PERCENT DEAD
KS without PCP	1290	23.9	351	27.2
PCP without KS	2869	53.2	1400	48.8
Both KS and PCP	339	6.3	226	66.7
OI without KS or PCP	896	16.6	485	54.1
TOTAL	5394	100.0	2462	45.6

KS = Kaposi's sarcoma PCP = Pneumocystis carinii pneumonia
OI = Opportunistic infections

	MALES		FEMALES		TOTAL	
RISK GROUPS*	CASES	% OF TOTAL	CASES	% OF TOTAL	CASES	%
Homosexual or bisexual	3877	77.0	0	0.0	3877	71.9
IV drug use	748	14.9	202	56.0	950	17.6
Haitian	178	3.5	30	8.3	208	3.9
Hemophiliac	41	0.8	0	0.0	41	0.8
No apparent risk group or unknown	189	3.8	129	35.7	318	5.9
TOTAL	5033	100.0	361	100.0	5394	100.0

* The risk groups listed are hierarchically ordered; cases with multiple risk factors are tabulated only in the risk group listed first.

AIDS
MEMORANDUM
Acquired Immune Deficiency Syndrome

National Institute of Allergy and Infectious Diseases

Volume 1, Number 8 October 1984

IN THIS ISSUE

GROUND RULES FOR USE OF THE AIDS MEMORANDUM

The AIDS Memorandum serves as a forum for the rapid exchange of new information and ideas among clinicians and scientists involved in AIDS research and management. Material contained in the Memorandum can be of several kinds: positive and/or negative results, clinical and/or experimental findings, preliminary and/or validated data, observations, questions, theories, commentaries, and others. This material is not subjected to peer review. Therefore, users of the Memorandum must agree to treat all material as privileged information and to consider it as tentative and subject to change prior to formal publication in a refereed journal.

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Users must agree to contribute data or ideas to the Memorandum at least once a year. On an annual basis, the names of individuals who have not contributed to the Memorandum will be culled from the mailing list, so as to limit circulation of the Memorandum only to individuals actively working in the field.

Finally, users must agree to share material in the Memorandum only with other individuals willing to honor these ground rules.

13-CIS RETINOIC ACID THERAPY FOR KAPOSI'S SARCOMA

13-cis retinoic acid (RA), a metabolite of vitamin A with potent biologic activity, has been used clinically for treatment of severe acne and for the chemoprevention of cancer (Peck GL, Olsen TG, Yoder FW, et al: N Engl J Med., 1979, 300:329-333; Elias PM, Williams ML: Arch Dermatol., 1981, 117:160-180). In addition to its effects on cellular differentiation, RA inhibits virus induction (Yamamoto N, Bister K, ZurHausen H: Nature, 1979, 278:553-554) and potentiates the T cell immune response (Lotan R: Biochim Biophys Acta, 1980, 605:33-91). For these reasons, we thought that RA might be useful in treating Kaposi's sarcoma (KS) associated with AIDS, and a pilot trial was begun in March, 1983.

Six patients received RA by mouth in a daily dose of 2.0 mg/kg. All were young homosexual men with biopsy-proven cutaneous KS who gave informed consent to the study. Each patient was monitored weekly for tumor response and possible drug toxicity. We considered 4 weeks of continuous therapy as an adequate trial.

The results of this study are shown in the table. All patients developed the expected desquamative dermatitis. It became necessary to discontinue the drug in patients 4, 5, and 6. While on therapy, two patients (1 and 4) developed oral lesions typical of those caused by Herpes simplex virus. One patient (5) developed Pneumocystis carinii pneumonia. These infections are typically associated with AIDS and were not attributed to RA toxicity. No patient exhibited tumor regression, and all adequately-treated patients developed new lesions during the trial.

We conclude from this pilot study that RA is not an effective drug for treating KS associated with AIDS and that the skin toxicity which was produced by RA at the dose used made it an unacceptable drug for this group of patients.

CIS-RETINOIC ACID THERAPY FOR KAPOSI'S SARCOMA

Patient	Duration of Therapy (Wk)	Response	Toxicity
1	12	Progression	Cutaneous
2	4	Progression	Cutaneous
3	4	Progression	Cutaneous
4	3	Progression	Cutaneous
5	1	—	Cutaneous
6	1	—	Cutaneous

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SIMIAN AIDS: AN OVERVIEW

An immunosuppressive disease which resembles human AIDS has recently been recognized among Macaca monkeys housed at several regional primate centers in the United States (Henrickson RV, Osborn KG, Madden DL, et al: Lancet, 1983, 1: 388-390; Hunt RD, Blake BJ, Chalifoux LV, et al: Proc Natl Acad Sci USA., 1983, 80:5085-5089; Stromberg K, Benveniste RE, Arthur LO, et al: Science, 1984, 224:289-292). Like human AIDS, the simian disease, SAIDS, is characterized by profound immunosuppression, mul-

tiple opportunistic infections, chronic wasting, in some instances malignancy, and a high rate of mortality (Henrickson RV, Osborn KG, Madden DL, et al: Lancet, 1983, 1:388-390; Hunt RD, Blake BJ, Chalifoux LV, et al: Proc Natl Acad Sci USA., 1983, 80:5085-5089; Stromberg K, Benveniste RE, Arthur LO, et al: Science, 1984, 224:289-292; London WT, Madden DL, Gravell M, et al: Lancet, 1983, 2:869-873; Gravell M, London WT, Houff SA, et al: Science, 1984, 223:74-76; Letvin NL, King NW, Daniel MD, et al: Lancet, 1983, 2:599-602). Some affected monkeys have developed transitory skin lesions which are histopathologically similar to the "patch" and "plaque" lesions of Kaposi's sarcoma seen frequently in human AIDS patients (London WT, Madden DL, Gravell M, et al: Lancet, 1983, 2:869-873). Because of the similarities in the clinical and pathological features of the human and simian diseases, studies of SAIDS, particularly those concerned with vaccination and treatment, may increase our understanding of and contribute to the control of human AIDS.

SAIDS has been experimentally transmitted to healthy rhesus monkeys (Macaca mulatta) by inoculations of unfiltered homogenates of tissues, whole blood, and serum from rhesus monkeys with advanced disease (Hunt RD, Blake BJ, Chalifoux LV, et al: Proc Natl Acad Sci USA., 1983, 80:5085-5089; London WT, Madden DL, Gravell M, et al: Lancet, 1983, 2: 869-873; Gravell M, London WT, Houff SA, et al: Science, 1984, 223:74-76; Letvin NL, King NW, Daniel MD, et al: Lancet, 1983, 2:599-602). Direct evidence implicating a virus as the causative agent of SAIDS first came from experiments in which the disease was transmitted to healthy juvenile rhesus monkeys using as an inoculum a cell-free filtrate of plasma or a homogenate of lymphomatous tissue from diseased animals (Gravell M, London WT, Houff SA, et al: Science, 1984, 223:74-76; Letvin NL, King NW, Daniel MD, et al: Lancet, 1983, 2:599-602). The pore size of the filters used in these studies was small enough to exclude free-living microorganisms.

More recently, we and others have reported that a type D retrovirus, related but not identical to Mason-Pfizer monkey virus (MPMV) (Chopra HC, Mason MM: Cancer Res., 1970, 30:2081-2086), the prototype of type D retroviruses, is the causative agent of SAIDS (Gravell M, London WT, Hamilton RS, et al: Lancet, 1984, 1:334-335; Marx RA, Maul DH, Osborn KG, et al: Science, 1984; 223:1083-1086). The p27 core polypeptide of MPMV was found by competition radioimmunoassay (RIA) to be antigenically closely related to the core polypeptide of the SAIDS retrovirus. However, antigenic differences existed between the envelope glycoprotein, gp70, of MPMV and that of the SAIDS retrovirus (Marx RA, Maul DH, Osborn KG, et al: Science, 1984; 223:1083-1086). The reverse transcriptases of the SAIDS retrovirus and of MPMV were also found to have similar characteristics (Colcher D, Schlom J: Biochim Biophys Acta, 1980, 607:445-456). Both showed a Mg^{++} preference with the synthetic templates poly(rA)·oligo$(dT)_{12-18}$ and poly(rC)·oligo$(dG)_{12-18}$ but a Mn^{++} preference with poly$(rC)_m$·oligo$(dG)_{12-18}$ (Gravell M, London WT, Hamilton RS, et al: Lancet, 1984, 1:334-335).

In our studies, SAIDS was transmitted to two healthy rhesus monkeys (E-247 and B-959) by inoculating them at the National Institute of Neurological and Communicable Disorders and Stroke with an isolate of the SAIDS retrovirus, IDB-1, from serum of rhesus monkeys which developed fatal SAIDS while housed at the California Primate Research Center

at the University of California at Davis (CPRC) (Gravell M, London WT, Hamilton RS, et al: Lancet, 1984, 1:334-335). The virus isolation was made in rhesus monkey primary bone marrow cultures. Prior to use in transmission studies, the isolate was passed four times in vitro in low-passage normal rhesus monkey fibroblasts and purified by discontinuous and continuous density gradient centrifugation in neutral sucrose (density 1.15-1.17 gm/cm^3). Fractions pooled for the inoculum showed peak absorbance at 254 nm and contained the reverse transcriptase activity. Only type D retrovirus particles were seen by electron microscopy in negative stains of the inoculum. Finally, in an RIA broadly reactive for type C virus of Colobus monkeys, CPC-1, and using specific antisera to purified core proteins of several type C retroviruses, no evidence was found that the virus inoculum was contaminated with type C retroviruses (L. O. Arthur, unpublished data).

Both of the inoculated monkeys developed early manifestations of SAIDS (neutropenia, lymphadenopathy, and splenomegaly) between 2 and 4 weeks after inoculation. More severe disease was noted in monkey E-427, and an enlarged right inguinal node was removed from this animal for histopathological examination 5 weeks after the experimental inoculation. The normal architecture of the nodular cortex was found to be effaced by extensive atypical proliferation of lymphoblasts and immunoblasts. A few subcapsular aggregates of small lymphocytes provided the only evidence of follicles. Plasma cells were rarely seen. This histopathology is consistent with that seen in previously studied animals with SAIDS in early-to-intermediate stages of disease. Both animals died 8 weeks after inoculation with diseases similar both clinically and pathologically to the disease described previously in experimentally and naturally infected rhesus monkeys with SAIDS (Henrickson RV, Osborn KG, Madden DL, et al: Lancet, 1983, 1:388-390; Hunt RD, Blake BJ, Chalifoux LV, et al: Proc Natl Acad Sci USA., 1983, 80:5085-5089). Death in both animals was attributed to pneumonia caused by an opportunistic invader, probably a virus.

The antibody responses in the two monkeys to the SAIDS virus were monitored by an enzyme-linked immunosorbent assay. No significant increase in IgG antibody to SAIDS virus was detected in serum samples taken from these animals at various intervals during the 8 weeks they lived after infection. Other rhesus monkeys infected with and showing titers of antibodies to cytomegalovirus (CMV) or simian adenoviruses prior to infection with SAIDS virus have shown a gradual loss of these antibodies as SAIDS progresses and have been found to have no antibody to CMV or simian adenoviruses at death. These results suggest that infection of rhesus monkeys with the SAIDS retrovirus can impair both their ability to mount a primary antibody response to the SAIDS agent and their ability to respond to antigens to which they previously were primed. Radial immunodiffusion studies show that concentrations of IgM, IgG, and IgA antibodies are very low in animals with advanced SAIDS. Histological examinations of lymph nodes of animals with SAIDS have shown diminished numbers of T and B cells in nodes (London WT, Madden DL, Gravell M, et al: Lancet, 1983, 2:869-873). In sum, the humoral immune responses in rhesus monkeys with SAIDS are severly impaired, more so than are the humoral immune responses of humans with AIDS (Gravell M, London WT, Houff SA, et al: Science, 1984, 223:74-76).

No inversions of T4:T8 helper:suppressor T cell ratios have been found in rhesus monkeys with SAIDS. This is the case regardless of the time after infection or the severity of the disease. In contrast, inverted T4:T8 lymphocyte ratios are common in humans with AIDS (Gravell M, London WT, Houff SA, et al: Science, 1984, 223:74-76).

Studies of the responses of lymphocytes from rhesus monkeys with SAIDS to stimulation with the mitogens, phytohemagglutinin, concanavalin A, and pokeweed mitogen, have shown that, in the early stages of the disease, lymphocyte responses are not impaired. However, in late stages of the disease, when animals are near death, stimulation indices are significantly lower than are those of controls (Gravell M, London WT, Houff SA, et al: Science, 1984, 223:74-76).

Using a type D SAIDS retrovirus grown in tissue culture, our collaborators from the CPRC have also transmitted fatal SAIDS to rhesus monkeys (Marx RA, Maul DH, Osborn KG, et al: Science, 1984, 223:1083-1086). Isolations of similar type D retroviruses have been made from macaque species with SAIDS housed at the New England and Washington Regional Primate Research Centers (Stromberg K, Benveniste RE, Arthur LO, et al: Science, 1984, 224:289-292; Daniel MD, King NW, Letvin NL, et al: Science, 1984, 223:602-605). However, transmission studies of SAIDS with viruses isolated from diseased animals and propagated in vitro at these centers have not been described. In 1975, Fine and coworkers (Fine DL, Landon JC, Pienta RJ, et al: J Natl Cancer Inst., 1975, 54:651-658) reported that newborn rhesus monkeys inoculated with MPMV died of an immunosuppressive disease having characteristics similar to those of SAIDS. These reports add credence to our conclusion that SAIDS is caused by a type D retrovirus related to MPMV.

We believe that contaminated saliva and urine may be vehicles for the natural transmission of SAIDS. In recent studies, we have isolated SAIDS retroviruses from saliva and urine of diseased rhesus monkeys and were successful in transmitting SAIDS with such viruses propagated in vitro.

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SUPPRESSION OF HUMORAL IMMUNITY IN RHESUS MONKEYS WITH SIMIAN AIDS

Simian AIDS (SAIDS) is a frequently fatal, naturally occurring disease of monkeys of the genus Macaca. Affected animals show signs of profound immunosuppression, can be infected with multiple opportunistic agents, and, in some instances, develop Kaposi's-like sarcoma lesions and other malignancies. We and others have reported that the etiologic agent of SAIDS is a type D retrovirus related to Mason-Pfizer monkey virus.

An enzyme-linked immunosorbent assay employing density gradient-purified SAIDS type D retrovirus as antigen was used to study the effect of SAIDS virus infection on the humoral immunity of rhesus monkeys. Two female juvenile rhesus monkeys, 17½ months of age, were inoculated with purified SAIDS-California virus (IDB-1 isolate). Each was monitored serially during the 2 month course of infection till death. No significant increase in antibody to the SAIDS virus was detected at any time during the course of the disease.

Rhesus monkeys infected with cytomegalovirus (CMV) or simian adenoviruses and having measurable titers of specific antibodies to these agents prior to infection with the SAIDS virus gradually lose these antibodies as SAIDS progresses. At death, no antibody to CMV or adenoviruses is detectable in such animals, suggesting that SAIDS causes a general decrease in humoral immunity.

Many different cell types have been found to be susceptible to infection by the SAIDS type D retrovirus. These include bone marrow cells, T cells from thymus and peripheral blood, fibroblasts, and kidney cells. We are endeavoring to determine the mechanism of humoral immune suppression in animals with SAIDS.

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COMPARISON OF THE CAUSATIVE AGENT OF SIMIAN AIDS AND MASON-PFIZER MONKEY VIRUS

We and others have reported that simian AIDS (SAIDS) is caused by a type D retrovirus similar to the Mason-Pfizer monkey virus (MPMV). Features of these two viruses are compared here.

The p27 core antigen of the SAIDS virus isolates originating from diseased monkeys from the California Primate Research Center at Davis has been found to be closely related to the core antigen of MPMV. However, antigenic differences were found between the gp70 polypeptide of the SAIDS-California isolates and the comparable polypeptide of MPMV.

The reverse transcriptase associated with the isolate of the SAIDS-California virus designated IDB-1 has a divalent cation preference of magnesium when tested with the synthetic template-primers poly(rA)·oligo$(dT)_{12-18}$ and poly (rC)·oligo$(dT)_{12-18}$. It has a manganese preference when tested with poly(rC_m)·oligo$(dT)_{12-18}$. The reverse transcriptase of MPMV has the same divalent cation preferences for these synthetic template-primers.

Our immunoprecipitation and polyacrylamide gel electrophoresis studies have shown that the IDB-1 isolate contains four polypeptides with the same molecular weights (10K, 20K, 27K, and 70K daltons) as those reported for MPMV. The 12K dalton and 14K dalton polypeptides reported for MPMV were not detected in immunoprecipitates of SAIDS virus but were seen in electropherograms of non-immunoprecipitated virus.

These studies provide additional information which suggests that the IDB-1 isolate of SAIDS-California virus is related to, but not identical to, MPMV.

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TRANSMISSION OF SIMIAN AIDS WITH TYPE D RETROVIRUS ISOLATED FROM SALIVA OR URINE

Saliva and urine specimens from rhesus monkeys with simian AIDS (SAIDS) were found to contain a type D retrovirus related to Mason-Pfizer monkey virus (MPMV). The virus has been linked etiologically to SAIDS. Virus isolates from

saliva and urine were shown to have the characteristics of the SAIDS agent in their reverse transcriptase divalent cation preference for synthetic template-primers, production of characteristic cytopathology in Raji cells, and antigenic relatedness to MPMV determined by an enzyme-linked immunosorbent assay and a competition radioimmunoassay. Electron micrographs of parotid tissue from an animal with SAIDS also showed budding particles with type D retrovirus morphology. When a virus isolate from the urine of an animal with SAIDS was grown in tissue culture and subsequently inoculated into two normal juvenile rhesus monkeys, SAIDS developed in both animals. Since saliva and urine of monkeys with SAIDS contain infectious SAIDS viruses, they are likely sources by which the disease is naturally transmitted. Thus, care should be taken to avoid contact between normal and infected animals.

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INTERLEUKIN 1 AND INTERLEUKIN 2 PRODUCTION BY PERIPHERAL BLOOD MONONUCLEAR CELLS OF HOMOSEXUAL MEN WITH ALTERED IMMUNITY

Interleukin 1 (IL-1) production has been less intensively studied in homosexual men with AIDS or AIDS-related complex (ARC) than has interleukin 2 (IL-2) production (Ciobanu N, Welbe K, Kruger G, et al: J Clin Immunol., 1983, 3:332-340). IL-1 is produced by mononuclear phagocytes from various sources (Dinarello, CA: Rev Infect Dis., 1984, 6(1):51-95). In patients with AIDS and opportunistic infections, the macrophages appear to function normally when assays involving myeloperoxidase staining, measurements of oxidative metabolism, phagocytosis, and antimicrobial activity are performed (Murray HW, Rubin BY, Masur H, et al: N Engl J Med., 1984, 310:883-889). Generally, IL-1 production has correlated with other parameters of monocyte activation (Dinarello CA: Rev Infect Dis., 1984, 6(1):51-95).

We evaluated IL-1 and IL-2 production in 12 homosexual men who did not have AIDS but who had cutaneous anergy and low levels of T-helper (Th) cells. Four of the patients had weight loss, fatigue, and diffuse lymphadenopathy, while eight were asymptomatic or had chronic lymphadenopathy only. Ten heterosexual men served as controls.

The number of Th cells for the study group was 481 ± 255 (mean ± SD)/mm^3 and the number of T-suppressor (Ts) cells was 827 ± 349/mm^3. Heterosexual controls had 963 ± 333/mm^3 Th cells and 671 ± 303/mm^3 Ts cells. Lymphocyte proliferative responses to two mitogens, phytohemagglutinin (PHA) and concanavalin A, were depressed in homosexual men, but the differences from the results obtained for heterosexual controls were not significant.

The IL-1 production by adherent peripheral blood mononuclear cells stimulated by lipopolysaccharide was measured by a lymphocyte activating factor assay. The results are expressed as counts per minute (cpm) of ^{3}H-thymidine (^{3}H-TdR) incorporated into mouse thymocytes. IL-2 production by non-adherent peripheral blood mononuclear cells induced by PHA was analyzed using a T-cell growth factor assay. Results are expressed in cpm for ^{3}H-TdR incorporated into IL-2-dependent CTLL-20 cells.

Production of both IL-1 and IL-2 was significantly depressed in homosexual men when compared with the production in heterosexual controls (Table). Seven of 12 homosexual men had IL-1 production at a level that was <500 cpm, whereas all heterosexual controls were at a level >3000 cpm. The IL-2 production in seven homosexual men was <150 cpm as compared to >400 cpm in all heterosexual controls. Five participants showed depressed production of both IL-1 and IL-2 (<500 cpm and <150 cpm, respectively).

The IL-2 production was similiar in those homosexual men with Th <400/mm^3 and those with Th >500/mm^3. Four homosexual men with low levels of monocytes (M) (<100/mm^3) had lower IL-1 production (367 ± 449 cpm) than did eight homosexual men with higher levels of M (1212 ± 1736 cpm). IL-1 and IL-2 production were similiar in symptomatic and asymptomatic homosexual men.

Peripheral blood mononuclear cells of homosexual men without AIDS but with evidence of immune dysregulation produce less IL-1 and IL-2 than do cells of heterosexual controls. The decrease in IL-1 production and the recent finding by Kaye and co-workers that IL-1 promotes expression of IL-2 receptors (IL-2R) on T helper cell surfaces in vitro may explain why there is reduced IL-2R expression by stimulated lymphocytes in some patients with AIDS and lymphadenopathy syndrome (Kaye J, Gillis S, Mizel SB, et al: J Immunol., 1984, 133:1339-1345; Prince HE, Kermani-Arab V, Fahey JL: J Immunol., 1984, 133:1313-1317). Many of the opportunistic infections in AIDS patients are caused by intracellular pathogens. Effective control and eradication of these organisms require intact cellular immunity. Further investigations of monocyte and lymphocyte interactions, particularly their mediation by monokines and lymphokines, are therefore warranted in ARC patients, since the deregulation of cellular immunity may be instrumental in the subsequent development of opportunistic infections.

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IL-1 and IL-2 PRODUCTION

	Homosexual Men with ARC (n = 12)	Heterosexual Controls (n = 10)	
IL-1 production*	1026 ± 1551	6719 ± 4010	p = 0.0002†
IL-2 production‡	281 ± 288	722 ± 232	p = 0.001

* cpm (mean ± SD)/10^6 assay cells.

† Student's two-sample t-test.

‡ cpm (mean ± SD)/10^4 assay cells.

DEFECTIVE FUNCTION OF ANTIGEN-PRESENTING CELLS IN AIDS

In a recent publication, Belsito and associates (Belsito DV, Sanchez MR, Baer RL, et al: N Engl J Med., 1984, 310: 1279-1282) reported that persons with AIDS or the AIDS-related complex had significantly fewer numbers of Ia-positive Langerhans' cells in their skin biopsies than did normal subjects. They suggested that this abnormality might be associated with defective antigen presentation by these cells in the skin and perhaps by other antigen-presenting cells elsewhere in the body.

We have had a unique opportunity to obtain data that support this proposal. One of our male patients with AIDS proved to be HLA-identical to his sister, and cells from these siblings were mutually non-responsive in mixed leukocyte cultures. Mononuclear cells from the patient and his sister were obtained by Hypaque-Ficoll centrifugation of peripheral blood. Cell preparations from both subjects contained 10% monocytes and 90% lymphocytes.

The T cell proliferative responses of the cells were assessed by culturing 2.5 × 10^5 lymphocytes from each subject in the presence or absence of candida antigen (20 µg protein/ml). After 6 days, the cells were labeled with tritiated thymidine to measure antigen-dependent DNA synthesis. Antigen presentation was assessed by incubating mononuclear cell preparations from each subject with or without candida antigen (20 µg/ml) for 120 minutes at 37°C. The cells were then irradiated (1500 R), washed, and mixed with equal numbers of potential responder cells from the sister. (The low numbers of cells from the patient precluded testing the patient's cells as responders in the second stage of the assay.) In these second stage cultures, therefore, the only antigen involved was that presented by cells from the first incubation. After 5 days, the cells were labeled with tritiated thymidine and harvested.

T cells from the sister responded to candida antigen with a proliferative response as measured by thymidine incorporation, but T cells from the patient did not (Table, part A). In the two-stage studies (Table, part B), antigen-pulsed cells from the sister were able to stimulate the incorporation of thymidine by other (responder) cells from the sister. By contrast, antigen-pulsed

T CELL RESPONSES TO CANDIDA

Experimental Design	Cells from	Candida	cpm	Stimulation Index
A. Antigen present throughout experiment	AIDS patient	–	201	—
		+	241	1.2
	Sister	–	754	—
		+	6183	8.2
B. Antigen presented by antigen-pulsed cells to sister cells in second stage culture	AIDS patient (1° culture)	–	669	—
		+	899	1.3
	Sister (1° culture)	–	1727	—
		+	8927	5.2

cells from the patient did not stimulate a proliferative response by a responder cell preparation from the sister.

The well-recognized immunologic components of AIDS include profound depletion of T lymphocytes, especially helper T cells, and marked immunodeficiency. Our observations and the report that Ia-positive Langerhans' cells are deficient in patients with AIDS raise the possibility of yet another immunologic abnormality—a defect in antigen presentation. The existence of such a defect, if confirmed, could severely limit the efficacy of certain forms of immunotherapy for AIDS patients.

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MEDICAL RESEARCH COUNCIL WORKING PARTY ON AIDS

A Working Party on AIDS was set up by the Medical Research Council (MRC) in the United Kingdom (UK) in the autumn of 1983. The mandate for the Working Party was threefold: (a) to review scientific understanding of and research on AIDS in the UK and abroad, (b) to encourage contact and co-operation between researchers in the field, and (c) to advise the MRC as to the current status of knowledge in the field and about topics of interest for research.

The first meeting was held in October, 1983. Clinical, epidemiological, etiological, and pathogenetic aspects of AIDS were reviewed. The Working Party then went on to consider what opportunities for research would be unique or special to the UK. That the epidemic was lagging some 3 years behind the epidemic of AIDS in the United States meant that the background against which AIDS develops might be delineated, and the emergence of AIDS and AIDS-related conditions in high risk groups might be observable. The pattern of disease in the UK seemed somewhat different from the pattern observed elsewhere and needed careful documentation.

The structure of venereology in the UK was considered such that the highest risk group (homosexual men) could be studied in a small number of well-equipped centers with good contact with their communities. The position of gastroenterology in the UK was thought to be such that opportunities would be available for AIDS research. The system for hemophilia treatment and for blood product organization in the UK would make possible detailed studies of hemophilia-associated cases. The organization of epidemiology in the UK was thought well-suited for studying the AIDS problem. The close links between clinical and laboratory workers in immunology in the UK were considered an asset. Finally, it was felt that particular opportunities to pursue carefully controlled and monitored therapeutic trials were available. On the other hand, there appeared to be no unique virology facilities in the UK, nor was there special expertise in genetic engineering that was not available in other countries. The meeting concluded after considering three grant proposals that were to be forwarded to the Systems Board of the MRC for further consideration.

The second meeting of the Working Party was held in December, 1983. Reports from several meetings on AIDS that had been held in various parts of the world were given. The major focus of the meeting involved further discussion of those areas proposed for future research in the UK.

The third meeting was held in April, 1984. A document had been prepared outlining the possibilities for research. Eight conclusions and recommendations were made. (a) The national surveillance system for AIDS, which was based mainly on voluntary reporting of cases, should be extended. (b) Detailed studies of AIDS occurring in hemophiliacs should be carried out. (c) Longitudinal studies of homosexual men attending clinics (particularly St. Mary's and Middlesex Hospitals in London) should be undertaken, and such studies should be continued for at least 3 years. (d) All cases of AIDS should be studied clinically and documented completely, and studies of the pathophysiology of diarrhea and malabsorption should be encouraged. (e) New therapeutic methods should be evaluated by local groups on a few patients in pilot studies and followed up in larger trials if promising results were obtained. (f) All microbiological possibilities for an etiologic agent could not be adequately pursued. Because a viral etiologic agent seemed very likely, groups of workers with enthusiasm and skill for studying candidate viruses should be encouraged to do so. The MRC was already supporting a restriction endonuclease mapping survey of the cytomegaloviruses isolated. In addition, a search was underway for human T leukemia/lymphoma and related viruses and antibodies against them. (g) A good deal of work has already been done on immunological changes in AIDS but not on immunohistopathological changes. The reagents and facilities for studying the latter are excellent in the UK and these studies should be pursued. (h) Useful surrogate tests should be developed for studying blood sample donations.

After the report was considered, three grant proposals were discussed. The meeting was followed by a press briefing. The fourth meeting of the Working Party is scheduled for the autumn of 1984.

Members of this Party are D. A. J. Tyrrell, D. Taylor-Robinson, A. J. Pinching, M. W. Adler, A. L. Bloom, N. S. Galbraith, J. R. W. Harris, P. J. Lachman, H. P. Lambert, K. Murray, J. G. P. Sissons, R. S. Tedder, A. D. B. Webster, and R. Weiss.

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U.S. AIDS CASES REPORTED TO THE CENTERS FOR DISEASE CONTROL AS OF OCTOBER 1, 1984

DISEASE	CASES	PERCENT OF TOTAL	DEATHS	PERCENT DEAD
KS without PCP	1475	24	432	29
PCP without KS	3309	54	1659	50
Both KS and PCP	377	6	252	67
OI without KS or PCP	1021	17	559	55
TOTAL	6182	100	2902	47

KS = Kaposi's sarcoma PCP = Pneumocystis carinii pneumonia
OI = Opportunistic infection

	MALES		FEMALES		TOTAL	
PATIENT GROUPS*	CASES	% OF TOTAL	CASES	% OF TOTAL	CASES	%
Adult/Adolescent						
Homosexual or bisexual men	4503	78	—	—	4503	73
IV drug user	835	14	226	57	1061	17
Haitian	195	3	35	9	230	4
Hemophiliac	42	1	0	0	42	1
Heterosexual contact†	2	0	44	11	46	1
Transfusions with blood products	42	1	30	8	72	1
None of the above	164	3	64	16	228	4
TOTAL	5783	100	399	100	6182	100
Pediatric‡						
Parent with AIDS or at increased risk of AIDS	21	53	23	79	44	64
Hemophiliac	4	10	0	0	4	6
Transfusion with blood products	10	25	2	7	12	17
None of the above	5	13	4	14	9	13
TOTAL	40	100	29	100	69	100

* The risk groups listed are hierarchically ordered; cases with multiple risk factors are tabulated only in the risk group listed first.
† With a person with AIDS or at risk for AIDS.
‡ Includes patients under 13 years of age at time of diagnosis.

AIDS
MEMORANDUM
Acquired Immune Deficiency Syndrome

National Institute of Allergy and Infectious Diseases

Volume 1, Number 9 December 1984

IN THIS ISSUE

GROUND RULES FOR USE OF THE AIDS MEMORANDUM

The AIDS Memorandum serves as a forum for the rapid exchange of new information and ideas among clinicians and scientists involved in AIDS research and management. Material contained in the Memorandum can be of several kinds: positive and/or negative results, clinical and/or experimental findings, preliminary and/or validated data, observations, questions, theories, commentaries, and others. This material is not subjected to peer review. Therefore, users of the Memorandum must agree to treat all material as privileged information and to consider it as tentative and subject to change prior to formal publication in a refereed journal.

Users must agree not to cite material from the Memorandum without first obtaining the consent of the author(s), and, with author permission, to cite information only as a personal communication. Author addresses are provided for this purpose.

Users must agree to contribute data or ideas to the Memorandum at least once a year. On an annual basis, the names of individuals who have not contributed to the Memorandum will be culled from the mailing list, so as to limit circulation of the Memorandum only to individuals actively working in the field.

Finally, users must agree to share material in the Memorandum only with other individuals willing to honor these ground rules.

A METHOD FOR INACTIVATING LIPID-CONTAINING VIRUSES IN PLASMA PRODUCTS WITHOUT LOSING THE BIOLOGICAL ACTIVITY OF THE PRODUCT

Commerical plasma products such as factor VIII and factor IX have proven effective and practical for treating life-threatening clotting deficiencies. These products have, however, continued to be sources of infectious hepatitis viruses and, more recently, have been implicated in the transmission of the AIDS virus. Infections with these viruses following infusion of plasma products are not rare: over 60% of hemophiliacs have evidence of infection with hepatitis B virus, non-A,non-B hepatitis agents, and LAV/HTLV-III (the retrovirus that is the putative etiologic agent of AIDS). Probably all commercial lots of clotting factors are contaminated with one or more of these viruses. Even when a serologic screening test for the virus is available (as in the case of the hepatitis B virus), the infectious agent has not been eliminated from commercial lots. The inherent limitations of serologic tests, human error, and the ability of a single virus-positive unit to contaminate a very large pool of plasma such as that employed for fractionation of plasma derivatives may all contribute to this sustained contamination.

Numerous attempts to inactivate viruses contaminating plasma products have met with little success. The failure of the various inactivation procedures attempted has stemmed from the relative resistance of the agents to physical or chemical inactivation and the relative lability of the plasma products to the same inactivation procedures. Procedures used to stabilize the biological potency of the plasma products have produced concomitant stabilizations of the contaminating viruses.

One characteristic shared by bloodborne hepatitis viruses and retroviruses is the presence of essential lipids in the virions. Removal or disruption of the lipids inactivates both types of viruses. Both organic lipid solvents and detergents have been used successfully to inactivate lipid-containing viruses; different members of each of these classes of chemicals vary greatly in the efficiency with which they remove or disrupt lipids. Previous studies showed that diethyl ether could inactivate virtually all lipid-containing viruses except the pox viruses which proved to be highly resistant (only approximately one $\log_{10}$ of virus was inactivated). Chloroform was subsequently found to be a more efficient lipid solvent: with chloroform, over two $\log_{10}$ of vaccinia virus infectivity could be destroyed consistently. Poxviruses, especially vaccinia viruses, are, therefore, the most suitable agents for use in tests of virus inactivation by lipid solvents.

Tests of the lipid solvent sensitivity of viruses are usually performed in a two-phase water-solvent system; this system also denatures labile proteins. Similarly, certain detergents denature some proteins: those which are relatively ineffective in removing lipids are also the least effective in denaturing proteins, and those which are the most effective in removing lipids are most effective in protein denaturation.

Experiments were designed to develop virus inactivation procedures for labile proteins using chloroform. A model lipid-containing virus (vaccinia) was added to commercial factor VIII. The contaminated factor VIII was lyophilized and extracted in the dry state with chloroform. In preliminary studies, significant inactivation of vaccinia virus was achieved with essentially 100%

recovery of biological potency of the product. Subsequent experiments yielded erratic results including incomplete inactivation of the vaccinia virus.

We suspected that residual moisture content of the chloroform and/or the plasma product might play a role in the efficient inactivation of lipid-containing viruses in lyophilized plasma products. Therefore, an additional set of experiments was carried out to determine the ability of increasing concentrations of water in chloroform to potentiate inactivation of vaccinia virus. As shown in Table 1, 100% saturation of chloroform with water yielded significant inactivation of lyophilized vaccinia virus, while full biological potency of lyophilized factor VIII was retained. Chloroform completely saturated with H_2O existed as a single-phase liquid that could be manipulated conveniently and removed from the lyophilized product by evaporation. In contrast to these results, two-phase chloroform-water extraction resulted in complete inactivation of vaccinia virus but also significant loss of factor VIII activity, probably through denaturation of labile proteins at the chloroform-water interface (Table 1).

Since the solubility of water in chloroform can be increased by adding ethanol or by increasing the temperature, the effects of variations in these parameters on virus inactivation and retention of biological potency respectively were examined (Table 2). The saturation of chloroform with water at elevated temperature (37°C) or after the addition of 2% or 5% ethanol yielded a reagent at least as effective in inactivating virus while protecting biological potency of the product as was chloroform saturated with water under standard conditions. However, small differences in virus inactivation could not be evaluated in this experiment, since water-saturated chloroform, not further modified, completely inactivated the vaccinia virus at room temperature.

Although in our studies significant losses of biological potency were observed when two-phase chloroform-water systems were used for the extraction procedures, other studies have shown that more highly purified factor VIII preparations can be treated in this way with only minimal loss of biological potency. The ease with which a single-phase organic solvent system can be

TABLE 1

Treatment*	Vaccinia Titer ($TCID_{50}$)†	Factor VIII Level (% of Control)
100% H_2O saturated $CHCl_3$	$10^{2.25}$	105
75% H_2O saturated $CHCl_3$	$10^{4.75}$	100
50% H_2O saturated $CHCl_3$	$10^{4.25}$	100
25% H_2O saturated $CHCl_3$	$10^{4.75}$	110
Dry fresh $CHCl_3$	10^{4}	110
H_2O + $CHCl_3$ (2 phase)	0	14
H_2O only	$10^{4.5}$	100

* Extraction with shaking at 20°C for 4 hours. $CHCl_3$ removed by evaporation (single-phase) or centrifugation (two-phase).

† TCID = 50% Tissue culture infective dose.

TABLE 2

Treatment*	Temp.	Vaccinia Titer ($TCID_{50}$)	Factor VIII Level (% of Control)
Dry $CHCl_3$	20°C	10^5	75
H_2O saturated $CHCl_3$	20°C	0	94
Dry $CHCl_3$	37°C	$10^{4.75}$	119
H_2O saturated $CHCl_3$	37°C	0	75
Dry $CHCl_3$-2% ethanol	20°C	10^5	100
H_2O saturated $CHCl_3$-2% ethanol	20°C	0	100
Dry $CHCl_3$-5% ethanol	20°C	$10^{4.75}$	119
H_2O saturated $CHCl_3$-5% ethanol	20°C	0	96
$CHCl_3$+ H_2O (2-phase)	20°C	0	0.3
$CHCl_3$+ H_2O (2-phase)	37°C	0	0.3
H_2O only (control)	20°C	$10^{5.5}$	100
H_2O only	37°C	$10^{5.5}$	15

* Extraction and removal of solvent as in Table 1.

manipulated and the negligible effect of this system on biological potency would seem to make such a system the method of choice for inactivation of lipid-containing viruses in labile biological products.

Certain lipid solvents can efficiently inactivate lipid-containing viruses without altering the biological potency of labile proteins, thus providing a differential inactivating effect. Other chemicals--such as formaldehyde and beta-propiolactone--or physical agents--such as heat--produce parallel inactivation of viruses and blood products. The plasma derivatives of therapeutic interest generally do not contain essential lipids. Some undesirable biological substances, such as certain endotoxins, probably are inactivated by extraction with lipid solvents under these conditions.

Since the poxviruses are widely recognized as the lipid-containing viruses most resistant to inactivation by extraction with lipid solvents, all other classes of such viruses can be expected to be inactivated efficiently by the procedures described above. Among these viruses are the hepadnaviruses, the hepadnavirus-associated delta agent, herpes viruses, togaviruses, bunyaviruses, retroviruses, orthomyxoviruses, paramyxoviruses, rhabdoviruses, arenaviruses, coronaviruses, and other unclassified lipid-containing viruses such as the non-A, non-B hepatitis viruses.

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PORPHYRIA CUTANEA TARDA IN AN AIDS PATIENT

A 32-year-old white male was successfully treated for Pneumocystis carinii pneumonia in April, 1984, with a 28-day course of oral trimethoprim/sulfamethoxazole. Five weeks after the completion of all antibiotic therapy, the patient began to develop painless, bullous lesions on the dorsa of his arms, hands, and chest. The lesions ranged in size up to 1-1.5 cm. Lesions did not appear in "crops" but formed constantly. These lesions subsequently healed, leaving hypopigmented areas on the skin.

Biopsy of one lesion indicated that the lesion contained no giant cells, Tzanck cells, or viral inclusion bodies. The pathology was interpreted as nondiagnostic. No organisms were cultured from the lesion.

At this time, the patient's clinical course was marked by fevers rising occasionally to 102°F, oral candidiasis, herpes simplex infection in the perianal area, and herpes zoster infection in the right thoracic dermatomes (6th-8th). Laboratory data did not change from the baseline findings of mild leukocytopenia, anemia, and thrombocytopenia. Liver function tests, normal at diagnosis, gave evidence of inflammation (SGOT = 78 IU/L, GGT = 125 IU/L, LDH = 267 IU/L). Markers of hepatitis B infection remained negative. The cytomegalovirus antibody titer was low and viral cultures were negative. Repeat gallium scans at this time demonstrated no pulmonary uptake; moderate diffuse hepatosplenomegaly was indicated.

Over the next 2 months, new bullous lesions continued to develop and to heal. Liver enzyme elevations continued to increase, with the SGOT level measuring as high as 364 IU/L. A percutaneous liver biopsy demonstrated minimal increased iron and mild fatty metamorphosis. There were no inflammatory infiltrates and no granulomata. Acid fast and Gomori's methenamine-silver stains were negative.

At this point the patient mentioned that his urine had been turning red. A 24-hour urine collection demonstrated 1642 mcm of coproporphyrins and 6355 mcm of uroporphyrins. The urine fluoresced. A diagnosis of porphyria cutanea tarda (PCT) was made. There was no family history of PCT. There was also no known exposure to hepatotoxins or exogenous estrogens, and the patient's ingestion of alcohol was not significant. The alpha-fetoprotein level was less than 2 ng/ml. The number of new lesions has diminished with restricted exposure to the sun. However, the usual forms of therapy for PCT, such as phlebotomy or hydroxychloroquine, have been judged inappropriate for this patient.

While a number of dermatologic lesions besides Kaposi's sarcoma have been seen in AIDS patients, most have been associated with viral, bacterial, or fungal infections. This case illustrates that not all lesions may be signs of infections in AIDS patients. The etiology of the marked liver function abnormalities in this patient remains to be determined.

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GENERALIZED LYMPHADENOPATHY IN HYPERTRANSFUSED PATIENTS WITH SICKLE CELL DISEASE

We are caring for two boys, DB and NS, ages 13 and 18, who have sickle cell disease. Both have been receiving hyper-

transfusion therapy consisting of 2 units of packed red blood cells every month as treatment for previous cerebrovascular accidents. Although they appear healthy otherwise, each has developed generalized lymphadenopathy. Neither is Haitian. Neither has a history of homosexual activity or intravenous drug use. Immunological evaluations indicate several abnormalities: increased serum IgG levels, decreased lymphocyte blastogenic response to the mitogen PHA (NS), decreased percentages of T-helper lymphocytes (T4), an increased percentage of T-suppressor lymphocytes (T8) (DB), and decreased T4:T8 ratios. Specific data are presented in the table.

DB has high levels of antibody to HTLV-III. NS has yet to be tested for HTLV-III antibodies. We feel certain that both boys have AIDS-related lymphadenopathy. We have, therefore, studied seven other patients without lymphadenopathy who have sickle cell disease and are being hypertransfused (HT) and seven who do not require hypertransfusion (NHT). Both groups of sickle cell patients (HT and NHT, respectively) had lower percentages of T4 cells (32 ± 4; 27 ± 3) and T8 cells (22 ± 5; 16 ± 5) when compared with controls. Since T4 and T8 cells were both decreased, the resultant T4:T8 ratios (1.63 ± 0.3; 1.91 ± 0.4) were not significantly different from control values. The lymphoproliferative responses to PHA were decreased in the NHT group (69,970 ± 938). Responses in the hypertransfused group, although slightly lower (104,595 ± 12,311) than control values, were not significantly different from controls.

We thus conclude that these two hypertransfused boys with sickle cell disease and lymphadenopathy have unique immunological abnormalities distinct from those found in other patients with sickle cell anemia without lymphadenopathy. We wish to alert others to the possibility that children with sickle cell anemia who require transfusions may be at risk for AIDS-related conditions.

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IMMUNOLOGICAL PARAMETERS IN SICKLE CELL DISEASE PATIENTS

Patient	Age (Yr)	Duration of Hypertransfusion Therapy	Duration of Lymphadenopathy	Serum IgG ng/ml	PHA (cpm) 20 µg/ml	T4 %	T8 %	T4:T8
DB	13	4 yr	17 mo	6180	22,141	24	36	0.67
NS	18	9 yr	7 mo	4060	7,583	19	22	0.86
25 Controls	14-27	None	None	1012 ± 68	111,691 ± 4,780	35 ±1	23 ±2	1.76 ±0.2

A STUDY OF IN VIVO IMMUNOMODULATION BY CIMETIDINE IN PATIENTS WITH AIDS AND THE AIDS-RELATED COMPLEX

Cimetidine is known to act as a histamine antagonist. It binds specifically to H-2 receptors present on suppressor T cells. The immunomodulatory effects of cimetidine were studied in vivo in seven patients with AIDS and in four patients with AIDS-related complex (ARC). All patients had been stable clinically for at least 4 weeks before the initiation of therapy.

Cimetidine (Smith Kline and French Laboratories, Philadelphia, PA) was administered in doses of 300 mg four times per day for 4 weeks to patients who had given written informed consent. Blood samples were drawn just before treatment began, on the 14th and 28th days of therapy, and 14 days after the completion of therapy. T cells were analyzed phenotypically for OKT4 and OKT8 markers. Lymphocyte proliferative responses to mitogens--phytohemagglutinin (PHA), concanavalin A (con A), and pokeweed mitogen--were quantitated before therapy, on the 28th day of therapy, and 14 days after completion of therapy.

There was no significant association of cimetidine treatment with alterations of OKT4:OKT8 ratios in any subject. Similarly, there were no significant changes or enhancements of lymphocyte proliferative responses to mitogens in any of the patients during or following therapy. In the seven patients with AIDS, the mean lymphocyte proliferative response to PHA was 23,952 (±8,759) CPM (counts per minute) on completion of therapy compared to 39,149 (±15,304) CPM before therapy. The mean response to con A was 16,939 (±6,625) on completion of therapy compared to 14,645 (±5,643) CPM prior to therapy. Similarly, the mean lymphocyte proliferative response to PHA in the four patients with ARC was 61,713 (±4,324) CPM at completion compared to 77,076 (±32,829) CPM before therapy. The mean con A response was 50,010 (±5,232) CPM after therapy compared to 62,562 (±36,848) CPM at baseline. In addition, none of the patients in either group provided evidence suggestive of clinical improvement.

This pilot study suggests that the administration of oral cimetidine is not associated with apparent immunologic improvement in patients with AIDS and ARC.

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DISSEMINATED VARICELLA-ZOSTER COMPLICATED BY COMPLETE HEART BLOCK IN A PATIENT WITH AIDS: SUCCESSFUL TREATMENT WITH ACYCLOVIR

The very severe suppression of cell-mediated immunity (CMI) associated with AIDS predisposes patients to multiple opportunistic infections. Reactivation of a varicella infection presenting as localized or disseminated herpes zoster (HZV) is not surprising in this setting and has been reported previously (Quinnan GV, Masur H, Rook AH, et al: JAMA, 1984, 252:72-77). This report describes a case of disseminated HZV in an AIDS

patient. A severe myocarditis developed and required the chronic administration of acyclovir for its control.

A 29-year-old hispanic woman with no risk factors for AIDS presented in May, 1984, with Campylobacter enteritis and cryptosporidiosis. In June, 1984, she developed esophageal candidiasis and a severe HZV lesion on her posterior chest wall. Very severe T cell suppression was documented (22 T4 positive cells/µl of blood; normal in our laboratory = 567 ± 250/µl). The diagnosis of AIDS was supported by the finding of anti-HTLV-III antibody in her serum. Mycobacterium avium-intracellulare was cultured from her duodenum and urine. The zoster responded slowly to intravenous acyclovir but cleared by August, 1984. Two weeks after discharge, the patient developed severe herpetic lesions on her buttocks. These coalesced into a necrotic ulcer. Herpetic outbreaks occurred on her face, chest, and extremities. At this time she had a heart rate of 44 and blood pressure of 90/60. She was not orthostatic. An EKG revealed third degree heart block. Her chest x-ray was normal. Intravenous acyclovir was recommended and a temporary pacemaker was inserted. An echocardiogram of the heart and a multigated acquisition scan (MUGA) and a gallium scan were all normal. Her condition was complicated by rapid deterioration in renal function which had previously been normal. Creatinine rose steadily to 4.4 mg/dl, while creatinine clearance fell to 15 ml/min. As much as 14 gm of protein were excreted in the urine per day. After 7 days of treatment, skin lesions had cleared but the heart block persisted. A permanent pacemaker was inserted.

In September, 1984, the patient developed left-sided heart failure. A MUGA demonstrated an enlarged and hypokinetic left ventricle. Intravenous acyclovir was again started and heart failure was controlled with Lasix and digoxin. Since then, two further admissions for severe HZV infection have been necessary. After controlling an exacerbation of zoster with intravenous acyclovir in October, 1984, the patient was discharged on oral acyclovir (400 mg five times per day). The patient has been free of zoster lesions for 3 months. Coincident with the chronic oral administration of acyclovir, left ventricular function improved and became almost normal by November, 1984. The complete heart block persists. Renal function has steadily improved and is now almost normal.

HZV may involve the nervous system, eye, lung, and liver. Myocarditis, though rare, has been reported (Moore CM, Henry J, Benzing G III, et al: Am J Dis Child., 1969, 118:899-902; Morales AR, Adelman S, Fine G: Arch Pathol., 1971, 91:29-31). Clearly, HZV can be a persistent and serious infection for patients with AIDS. We believe that this virus damaged the heart and perhaps the kidneys of the patient described in this report. Because there was no evidence for right ventricular involvement, we did not obtain an endomyocardial biopsy. Left ventricular biopsies are more dangerous, and the lesions in HZV myocarditis are focal (Kereiakes DJ, Palmley WW: Am Heart J., 1984, 108:1318-1326). Nevertheless, the concomitant occurrence of widespread cutaneous zoster with acute deterioration in cardiac function responding to acyclovir strongly suggested that a zoster infection of the heart had developed.

Cytomegalovirus (CMV) and atypical Mycobacterium infections can each produce cardiac disease in patients with AIDS (Guarda LA, Luna MA, Smith J. Jr,

et al: Am J Clin Pathol., 1984, 81:549-557; Cantwell AR Jr: Growth, 1984, 47: 129-134). Neither was a likely cause in this case: no CMV was isolated from urine or saliva and the patient improved on acyclovir at a time when her antimycobacterial therapy had been withdrawn. While our patient's serum contained a high titer of antibody to HTLV-III virus, this agent has not been reported to infect the heart and does not respond to acyclovir.

HZV has been reported to cause tissue damage to host tissue by provoking an immune response. In addition, a direct cytopathic effect of the virus on infected cells has been reported (Kereiakes DJ, Palmley WW: Am Heart J., 1984, 108:1318-1326). With immunosuppression as profound as that seen in our patient, the latter effect is far more likely. As in this case, HZV has been reported to have a propensity for conduction rather than contractile tissue (Morales AR, Adelman S, Fine G: Arch Pathol., 1971, 91:29-31).

HZV skin lesions are common when CMI is suppressed in the elderly, in patients with Hodgkin's disease, or in recipients of renal allografts (Wang DT, Peary OL: Med Clin North Am., 1983, 67: 1075-1092). In the latter group, continued immunosuppression can result in persistent infection. With suspension of immunosuppressive treatment, the lesions frequently clear (Gallagher JG, Merigan TC: Ann Intern Med., 1979, 91: 842-846). The depression of CMI in patients with AIDS is currently irreversible; patients must depend on the antiviral properties of acyclovir, a drug which is frequently effective against HZV (Balfour HH Jr, Bean B, Laskin OL, et al: N Engl J Med., 1983, 308:1448-1453). We have administered oral acyclovir chronically to keep this patient free of HZV lesions, using the approach reported for treatment of chronic herpes simplex infections (Straus SE, Scidlin M, Takiff H, et al: Ann Intern Med., 1984, 100:522-524). When zoster infection occurs in advanced cases of AIDS, it is likely to disseminate dangerously. The long-term administration of oral acyclovir may prove to be valuable in the control of this problem in such patients.

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GUIDELINES FOR CONFIDENTIALITY IN RESEARCH ON AIDS

The identification of AIDS 3 years ago created a crisis of confidence. Persons with AIDS and others who might be research subjects recognized that research was essential for understanding, treating, and preventing this devastating disease. However they also were concerned that information disclosed for research purposes might be used in ways that could be detrimental to their own interests. Unless these individuals can have confidence in the systems designed to protect their privacy and in the people to whom personal information is entrusted, they will face a difficult choice--either to provide inaccurate or incomplete data, thus compromising the validity of the research, or to give accurate and full data, thus placing themselves at risk. The dilemma, then, has become the following: What procedures and policies will both protect the privacy of research subjects and enable research to proceed expeditiously? Now that major research efforts

are being undertaken to tackle the many puzzling aspects of AIDS, this question has become an urgent one.

While in part a technical and administrative problem, the issue has important ethical, legal, and social aspects as well. Ethically, a balance must be struck between the principle of respect for persons (which requires that individuals should be treated as autonomous agents who have the right to control their own destinies) and the pursuit of the common good (which requires maximizing possible benefits and minimizing possible harms to society as well as to individuals). Legally--by statute, policy, and regulation--subjects, researchers, and institutions must be protected from involuntary disclosure of information. Those entrusted with confidential information must be prohibited by law from unjustifiable voluntary disclosure. As a society, we must express our moral commitment to the principle that all persons are due a full measure of compassion and respect.

Any investigation involving a disease which is possibly communicable poses a tension between an individual's desire to control personal information and the desire of others to have access to that information. Although this tension is not unique to AIDS, it is particularly sharply drawn in this case, because those groups that have been identified as at high risk are also highly vulnerable socially, economically, and politically. Because of the unknown factors that are involved in AIDS, researchers may have to explore many intimate aspects of an individual's medical, social, and behavioral history. Further, these data will have to be kept for an extended period. Investigators may seek information that reveals, for example, that a subject has engaged in homosexual or other sexual practices that are illegal in many states and are subject to social stigma, has injected drugs obtained illegally, has engaged in criminal activities, such as prostitution, or has entered the country illegally.

Furthermore, disclosure of a diagnosis of AIDS, or perhaps even involvement in AIDS research, carries a stigma that can adversely affect a person's interests socially, politically, and economically. Potential subjects, either individually or through organizations representing their interests, have sought recognition of these risks and assurances that appropriate measures will be taken to protect their privacy.

For these reasons, we believe that special guidelines are necessary for AIDS research. The guidelines which we have developed are concerned with the protection of the privacy of persons with AIDS and their families and friends, with the confidentiality of information collected about them, and with the security of data systems in which this information is stored. However, research into other diseases also carries risks for subject populations. We hope that guidelines on AIDS will stimulate an examination of the general problem of protecting the confidentiality of research records.

AIDS research is conducted in a context of standards already set by law and regulation, professional practice, and agency policy. In some cases, these standards provide only minimal protection. The guidelines, which were developed by a multidisciplinary group representing diverse professional, public and social interests, are intended to strengthen existing protections and procedures. They are directed at several audiences: researchers, public health officials, legislators, members of institutional review boards, subjects, and

organizations that represent subjects' interests.

Thirteen topics and broad issues are addressed in the guidelines. They are the following: (1) What activities are covered by the guidelines? (2) For whom is confidentiality protection necessary? (3) What kinds of information are researchers likely to need and what are the likely sources? (4) When are identifiers needed in research and what precautions should be taken? (5) Who should have access to personally identifiable information obtained in research or surveillance? (6) Who should NOT have access to personally identifiable information obtained in research or surveillance? (7) What are the current legal protections? (8) What steps should be taken to enhance the legal protections available to research subjects? (9) What standards should institutional review boards follow? (10) When is consent required? (11) The need for consistency. (12) The need for a continuing advisory board. (13) Communication and education.

A copy of the guidelines proposed and the recommendations of the committee can be obtained by writing to: AIDS Guidelines, IRB Hastings Center Report 6/6, 360 Broadway, Hastings-on-Hudson, New York, 10706.

R. Bayer, C. Levine, and T. H. Murray. The Hastings Center, Hastings-on-Hudson, New York 10706.

PSYCHOSOCIAL AND PSYCHIATRIC ASPECT OF AIDS

The AIDS epidemic has produced profound psychosocial and medical impacts since it was first recognized in the United States in 1979. The illnesses of AIDS patients and also of the much larger number of individuals diagnosed as having AIDS-related complex (ARC) have affected not only the patients but also a significant number of family members, friends, spouses, lovers, healthy members of high risk groups, health care professionals who care for AIDS patients, and members of the general population. AIDS has had a much greater psychosocial impact than would be expected based solely on the numbers of diagnosed patients or the numbers of people who have died from AIDS.

Many factors contribute to the great psychosocial impact of AIDS: its newness, its high two-year mortality rate, its transmissibility, its long incubation period, its resistance to effective treatment, its early association with stigmatized population groups, and its predominance in young adults and in children. This paper addresses psychosocial and psychiatric issues for diagnosed AIDS patients and also briefly discusses psychosocial effects on other groups of "AIDS-affected" individuals.

Any disease can affect not only an individual's biological functioning but potentially also his/her personal activities (routine self care, mobility, and physical activities), psychological well-being, general health perceptions, social functioning, and role functioning (work, social interactions, leisure activities) (Ware JE: Cancer, 1984, Suppl 53:2316-2323.) AIDS is an extremely "psychosocially malignant" illness. The biomedical effects of AIDS and the social and psychological effects of this transmissible, life-threatening illness often seriously damage all of the levels of individual functioning just enumerated.

Concepts which have previously proven useful in understanding the psychosocial impacts of numerous serious medical ill-

nesses also are applicable to AIDS. These include the life cycle phase of the individual (the psychosocial impact on the patient and members of his/her social network varies dramatically when 5, 35, or 65 year olds are compared), the patient's previous patterns of coping with stressful events including illnesses, the sources, types, and adequacy of social supports currently being given by others, the degree and sources of ongoing current psychological distress, the extent to which the illness has resulted in functional losses and has brought on a grief reaction, the manner in which the illness is conceptualized by the patient (for example, as punishment), the effects of the illness on the patient's positive personal identity (for example, enforced dependence on others may result in feelings of worthlessness), and the extent to which the illness threatens a hoped-for future.

The feeling of helpless vulnerability--that one can do nothing to affect the course of one's illness--is a common and powerful source of distress for AIDS patients. AIDS is currently a highly stigmatizing illness. The social support received from others can be undermined when others fear contracting AIDS through interactions with the AIDS patient.

Clinically, there are phases of the psychosocial response to AIDS (Nicholls SE: Psychosomatics, 1983, 24:1083-1089; Forstein M: Semin Oncol., 1984, 11:77-82). These are like the four phases commonly encountered in cancer. Weisman has defined these phases as existential plight (the acute, intense, often chaotic early psychological response to the diagnosis of a life-threating illness), accommodation and mitigation (the process of resolving the acute psychological crisis and achieving a new, relatively stable, psychological equilibrium), recurrence and relapse (the response to the realization that cure is no longer likely and that this disease is likely to cause one's death), and deterioration and decline (the preparation for imminent death when the terminal phase of illness is entered). The phases of existential plight and recurrence and relapse are usually characterized by the most intense psychological distress and are the phases during which there is the greatest risk that psychiatric symptoms will develop (Weisman AD: Gen Hosp Psychiatry, 1979, 1:187-195).

Hospitalization often produces added stresses. In hospitals, individuals experience lengthy periods of social isolation. In addition, they may be deprived of direct physical contact with others when infection control procedures are being enforced.

AIDS patients quite frequently develop psychiatric syndromes. Some patients completely deny illness and refuse appropriate treatment. Anxiety states, panic attacks, severe reactive depressions, brief stress-induced reactive psychoses lasting a few hours or days, marked preoccupation with physical symptoms (hypochondriasis), and chronic insomnia have all been observed. Some patients engage in highly dangerous risk-taking behaviors. Suicidal crises and successful suicides appear to be more frequent in patients with AIDS than in cancer patients.

Central nervous system (CNS) diseases, which are usually associated with organic mental disorders, are very common in AIDS patients. The neuropsychiatric syndromes common in AIDS include delirium, organic personality disorders and/or affective disorders, and dementia. Localizing neurologic signs may be present in AIDS patients with CNS dis-

ease. In one report, 50/160 AIDS patients (31%) had evidence of neurologic disease prior to death. The CNS problems in AIDS patients include syndromes secondary to infections (subacute encephalitis often probably due to cytomegalovirus, cryptococcal and other meningitides, toxoplasmosis and other infectious cerebral mass lesions), neoplasms (CNS Kaposi's sarcoma, immunoblastic lymphoma), and cerebrovascular disease (Snider WD, Simpson DM, Nielsen S, et al: Ann Neurol., 1983, 14:403-418). Other organ system disease states common in AIDS may also contribute to acute organic mental disorders, such as delirium. These include hypoxemia secondary to Pneumocystis carinii pneumonia, metabolic imbalance secondary to diarrhea, sepsis, and post-ictal states.

Because of the high incidence of CNS disease in AIDS patients and the frequency with which neurologic diseases present as psychiatric syndromes in general and because some CNS disease processes can be successfully treated, physicians should always consider that a psychiatric syndrome in an AIDS patient may have an underlying neurologic cause. AIDS has been reported in one study to present with neurologic symptoms (Levy RM, Pons VG, Rosenblum ML: J Neurosurg., 1984, 61:9-16).

Members of the high risk groups (particularly homosexual men) and people with ARC have shown a significant incidence of anxiety and depression related to concern about AIDS. This is to be expected in individuals who feel they are at increased risk for developing a life-threatening illness. AIDS patients in different high risk groups may experience group-related specific psychosocial problems.

In homosexual men, the diagnosis of AIDS may precipitate a unique psychological crisis, if family members and friends did not previously know of, and accept, the patient's sexual orientation. Many homosexual AIDS patients who have been estranged from their families may experience uncertainty about whether, and how, to reestablish ties with family members. In addition, internalized negative feelings about homosexuality often are aroused or reawakened in newly-diagnosed male homosexual AIDS patients. Anxiety and guilt about the possibility of transmitting AIDS through sexual activity are also frequent sources of stress.

Some hemophiliac patients have apparently changed their patterns of factor VIII use in response to the AIDS epidemic. Tremendous stress becomes associated with factor VIII usage which is at once acutely life-saving and at the same time potentially life-threatening.

Little has been published concerning the psychiatric effects of AIDS in children, although many apparently come from fragmented families with limited economic and psychosocial resources. The adverse effects of fatal illnesses in children on the physical health, psychological status, and social functioning of other family members have been documented in families of children with cancer (Kaplan DM, Smith A, Grobstein R, et al: Social Work, 1978, 18:60-69).

Some Haitians have been ostracized by their families after receiving a diagnosis of AIDS (Forstein M: Semin Oncol., 1984, 11:77-82). Little else has been written about the psychiatric effects of AIDS in Haitians or in intravenous drug abusers.

Family members, spouses, lovers, and close friends of AIDS patients face many stresses induced by the patient's progressive physical decline and eventual death. Physical and emotional exhaustion

and anticipatory grief are frequent. These may contribute to conflict and even to estrangement at a time when the patient most needs both the emotional support and practical assistance best provided by these intimate relationships. Health care professionals caring for AIDS patients may "burn out" as a result of the stresses they experience from the often intense needs of the patients with respect to both physical care and emotional support and from the recurring grief reactions they experience when AIDS patients (who are often previously healthy, young adults) die.

Psychosocial Interventions with "AIDS-Affected" Individuals

The components of an ideal program to meet the psychosocial and psychiatric needs of the "AIDS-affected" population are listed in the table. In general, brief individual psychotherapy, support groups (especially open-ended "drop in" groups), education, and psychopharmacologic therapy appear to be effective when used appropriately with AIDS patients. Health care professionals need to become aware of the unique psychosocial needs of AIDS patients from specific high-risk groups, of the psychosocial consequences of the lengthy periods of disability common in AIDS (particularly in patients with opportunistic infections), and of the psychiatric presentations of neurologic diseases seen in AIDS.

Psychological Stresses for Seropositive Blood Donors

Screening of potential blood donors for HTLV-III antibody has begun. This technical achievement has created ethical and psychological questions with regard to policies for informing seropositive donors of their status.

Longitudinal studies of sexually active seropositive homosexual males in New York City indicate that they are at risk for developing AIDS or ARC (Goedert JJ, Sarngadharan MG, Biggar RJ: et al: Lancet, 1984, 2:711-716). It is conceivable that currently healthy, but seropositive, individuals could, by altering their sexual behavior or engaging in other health-enhancing behaviors, preserve their immunocompetence and prevent the development of AIDS or ARC. They might also want to take measures to protect their acquaintances from exposure to HTLV-III.

Many studies have found that people are able to deny, minimize, or in some other way protect themselves psychologically from threatening information. People differ in whether they want to be informed of unpleasant information: most competently know in advance that they do or do not wish to receive potentially distressing information about their health status. Until the medical, ethical, legal, and confidentiality issues concerning seropositive individuals are identified and delineated, it might, therefore, be appropriate to ask those tested for HTLV-III seropositivity whether or not they wish to know the results. All those who have chosen to know their serologic status could then be informed by an identical procedure, regardless of the test results. The results could be given personally, by an individual who is medically knowledgeable and who is psychologically sensitive and empathic. Along with the test findings, medical information about the meaning of seropositivity could be given to seropositive individuals in a realistic, but hopeful manner. The accessible individual and group support resources available for seropositive individuals could be described at that times as

AN IDEAL COMPREHENSIVE PROGRAM TO MEET THE PSYCHOSOCIAL AND PSYCHIATRIC NEEDS OF "AIDS-AFFECTED" INDIVIDUALS

I. Care of individual AIDS or ARC patients

A. Longitudinal outpatient and in-patient care provided or coordinated by a primary physician throughout the illness.

B. Accurate and complete medical information presented as fully as desired by the patient. Presentation should be made empathically and with hope by the physician.

C. Patient participation in the decision-making process for treatment at all times as fully as s/he desires.

D. Provision of needed additional medical services by a multidisciplinary team, including mental health professionals knowledgeable about the psychiatric problems and needs of AIDS patients. Access to brief individual psychotherapeutic, support group, and psychopharmacologic interventions.

E. Provision of in-home care as needed.

F. Referral to community resources (such as AIDS Project/Los Angeles, Gay Men's Health Crisis, and others).

G. Routine (usually informal) screening of ARC patients or members of high risk groups for evidence of significant psychological distress. Referral for psychiatric or psychological services as indicated.

II. Care of family members, spouses, lovers, and close friends of AIDS or ARC patients

Informal screening for psychological support or for information. Provision of these services on an individual and/or group basis. Provision of post-bereavement support.

III. Support of health care professionals caring for AIDS and ARC patients

Regular and/or as-needed group meetings to provide information and to allow for expression of feelings engendered by patients' illnesses and deaths to minimize staff stress and to prevent chronic professional stress syndrome (burn out).

well, so that help will be provided for coping with any level of distress engendered by the test findings. Although such a program would be costly, requiring the services of highly skilled personnel, it might be effective not only in preventing and/or relieving psychological distress, but in lessening the human toll of the AIDS epidemic.

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BLOOD TRANSFUSION SAFETY STUDY

The National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health is sponsoring a contract held by the University of Southern California to establish a serum repository for collecting, labelling, and storing serum samples from 200,000 randomly selected volunteer blood donors. The blood will be tested for antibodies to HTLV-III. The consent form printed below was developed by the contractor in consultation with the NHLBI and is being used in four centers: Los Angeles Orange County Red Cross, Irwin Memorial Blood Bank of San Francisco, the New York Blood Center, and the South Florida Blood Service of Miami. Seropositive donors will be entered into a prospective study as will recipients of blood products from these donors.

Consent Form

I understand that, as part of a national research study of 200,000 volunteer blood donors, I am being asked to consent to having a small sample of my blood saved and possibly used for research. Some of the samples will be selected for future testing for infectious agents which may be transmitted by blood transfusion. This includes new tests for antibodies to indicate whether a virus has been or is present which is possibly related to AIDS or other diseases.

The significance of the presence of the antibodies and the reliability of the method used to detect them are not known at this time. If my blood is tested and if these antibodies are detected, I will be informed of the results and offered further testing to clarify their meaning. Even if antibodies are not detected, I may be contacted and asked to serve in a comparison group. I consent to be contacted for further tests.

I understand that I am free to decline to allow a sample of my blood to be saved for testing. If I do participate and am contacted in the future, I will be free to decline further testing at that time.

I further understand that results of the test will be treated with confidentiality. Only authorized staff of this institution and members of the research team are expected to have access to the information relative to my test; however, officials of the Food and Drug Administration or others authorized by law may require access to this information.

My entrance to this study is completely voluntary. If I decide not to participate I will not be denied any benefit to which I am otherwise entitled.

Any questions I may have about this study or my rights as a subject may be addressed to _____ who is fully acquainted with all of the details of this study.

F. A. Pitlick. National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland 20205.

GREEK WORKING PARTY ON AIDS

A Working Party on AIDS was set up by the Ministry of Health and Welfare of Greece in October, 1983. Its mandate included (a) advising the Ministry on the current status of understanding about AIDS and proposing measures to combat the disease, (b) organizing a nationwide epidemiology surveillance system, (c) organizing diagnostic facilities and periodically reviewing suspected cases, and (d) providing adequate information to hospitals and other health personnel and educating the public. Members of the Working Party are G. Papaevangelou, J. Papapanajotou, J. Iordanoglou, J. Stratigos, T. Mandalaki, J. Economidou, A. Kaloterakis, and Th. Stephanou.

The Working Party has met several times and, by ministerial decision, has declared AIDS a reportable infectious disease. It has established an epidemiological registry for reporting suspected cases and has issued specific instructions for recordkeeping. Guidelines have been issued for blood donors and precautions for health personnel caring for patients have been established.

Five cases of AIDS have been reported to date (Table). Lymphadenopathy associated syndrome (LAS) was diagnosed in six patients. All six had hemophilia. All had been heavily treated with factor VIII concentrates of commercial origin. Antibodies to LAV were detected in samples studied from almost all of these patients. In contrast, antibodies to LAV were not found in samples from patients with classical Kaposi's sarcoma. Some details of these studies have already been published (Papavangelou G, Economidou J, Kallinikos J, et al: Lancet, 1984, 2:642). Further studies of individuals in high risk groups are in progress.

In July, 1984, the Ministry of Research and Technology issued a call for research proposals on AIDS.

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CHARACTERISTICS OF AIDS PATIENTS IN GREECE

Patient No.	Origin	Sex	Age	Sexual Behavior	No. of T4 Cells/µl	Ratio T4:T8	Antibodies to LAV
1	Zambia	Male	26	Homosexual	0	0.00	+
2	Greece	Male	36	Bisexual	7	0.18	+
3	USA	Male	31	Bisexual	54	0.09	+
4	Burundi	Male	33	Heterosexual	158	2.0	+
5	Greece	Male	35	Homosexual	37	0.07	N.D.

NEW BOOK: AIDS, A BASIC GUIDE FOR CLINICIANS

The recently published volume, "AIDS, A Basic Guide for Clinicians" (P. Ebbesen, R.J. Biggar, and M. Melbye (Eds), Munksgaard, Copenhagen, 1984), consists of a series of short essays on various aspects of AIDS. The essays were written by individuals and groups with extensive experience dealing with different facets of this disease. As stated in the preface, the book is meant to provide a clinical and laboratory profile of AIDS which could serve as a ready reference to general physicians who find themselves responsible for the care of the occasional AIDS patient. Perhaps because of the very conciseness of the individual contributions, this purpose is generally well-served.

A basic philosphical question that must be asked about any book on a newly discovered disease (including AIDS) is how complete is the information that is presented and how long will that information remain current and useful. What can be said in the case of AIDS is that the biomedical community has moved with extraordinary rapidity to limn out the major features of the disease. As a result, barely 4 years after the description of the first case, we already have on hand a body of information which can reasonably form the basis of an organized and coherent compendium. Having said this, it is also fair to point out that any book on AIDS written at this point will become increasingly deficient as certain areas of information about AIDS expand. In particular, this book was written just a short time after the HTLV-III retrovirus was discovered. Consequently, the impact of knowing the identity of the agent which causes AIDS on our understanding of the epidemiology of the disease, on prevention of disease, and on certain clinical manifestations is not fully known and could not be reflected in the book.

It follows from all this that the individual chapters reflect the strengths and weaknesses of the knowledge base in each field. I felt that the clinically oriented chapters, which form the core of the book, were commendable because they contain all the essential elements necessary for the general physician, yet they were free of excess information likely to be of interest mainly to experts. Perhaps one exception here is the chapter on opportunistic infections which is excellent as a current guide to treatment but gives little information about the unique clinical aspects of such infections in AIDS. A very welcome feature of the book is the extensive collection of color photographs of various disease manifestations, histopathological findings, and other relevant bacteriological and diagnostic features. These photographs are well reproduced and cannot be found in other publications on AIDS.

The volume contains material that does not, strictly speaking, have a direct role in the care of AIDS patients but is, nevertheless, extremely valuable as background information on AIDS. For instance, the book provides up-to-date information about the epidemiology of AIDS, the pathology of AIDS, and some early but essential information about the virology of AIDS. In addition, there is a chapter on the immunology of AIDS which is quite clear and lays the groundwork for understanding the various immunologic dysfunctions occurring in AIDS. Again, this basic information about AIDS is subject to change, and one can expect significant new information to become available in the years ahead.

Finally, the book contains a well-indexed bibliography.

In all, this is a readable volume for any clinician who has need of an organized summary of the AIDS syndrome as we know it so far. It is not the definitive word on AIDS and as such is not likely to become a standard reference text. Nevertheless, it will find a useful place on many a shelf.

W. Strober. National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20205.

UPCOMING AIDS MEETING

International Conference on AIDS
Atlanta, Georgia
April 14-17, 1985

Information
AIDS Conference Office
Centers for Disease Control
Building 1, Room 2047
Atlanta, Georgia 30333

The purpose of the Conference is to exchange scientific information on the epidemiology, virology, immunology, hematology, oncology, clinical manifestations, and treatment of AIDS, on screening and diagnostic tests, on psychosocial and behavioral issues, and on strategies for the prevention and control of AIDS. Internationally recognized scientists will provide a comprehensive overview of the subject.

U.S. AIDS CASES REPORTED TO THE CENTERS FOR DISEASE CONTROL AS OF DECEMBER 17, 1984

DISEASE	CASES	PERCENT OF TOTAL	DEATHS	PERCENT DEAD
KS without PCP	1670	23	499	30
PCP without KS	4056	55	2040	50
Both KS and PCP	452	6	294	65
OI without KS or PCP	1230	17	665	54
TOTAL	7408	100	3498	47

KS = Kaposi's sarcoma PCP = Pneumocystis carinii pneumonia
OI = Opportunistic infection

	MALES		FEMALES		TOTAL	
PATIENT GROUPS*	CASES	% OF TOTAL	CASES	% OF TOTAL	CASES	%
Adult/Adolescent						
Homosexual or bisexual men	5329	78	—	—	5329	73
IV drug user	998	15	262	55	1260	17
Haitian	216	3	39	8	255	3
Hemophiliac	47	1	0	0	47	1
Heterosexual contact†	6	0	54	11	60	1
Transfusions with blood products	48	1	40	8	88	1
None of the above	201	3	78	16	279	4
TOTAL	6845	100	473	100	7318	100
Pediatric‡						
Parent with AIDS or at increased risk of AIDS	34	64	30	81	64	71
Hemophiliac	4	8	0	0	4	4
Transfusion with blood products	10	19	2	5	12	13
None of the above	5	9	5	14	10	11
TOTAL	53	100	37	100	90	100

* The risk groups listed are hierarchically ordered; cases with multiple risk factors are tabulated only in the risk group listed first.
† With a person with AIDS or at risk for AIDS.
‡ Includes patients under 13 years of age at time of diagnosis.