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INTER OFFICE MEMORANDUM

H.L.S. REC'D. 14 JAN 1983

TO : H. Kjellman

DATE: 11th January 1983

FROM : C.R. Bishop

SUBJECT : AIDS (ACQUIRED IMMUNE DEFICIENCY SYNDROME)

COPIES TO :

I. Regier
H. Townsend
H.L. Shaw
D.H. Ferguson
Master
File

Dear Hans,

I enclose for your information, articles relating to the above, and I would confirm to you that this is now of particular concern to clinicians in the U.K., particularly if it is felt that regular infusions of Factor VIII Concentrate are the prime cause of this associated immune deficieny syndrome.

Have you got any comments to make, and is it of equal concern elsewhere?

Regards,

GRO-C

C.R. Bishop.

RBC

RECEIVED
R.B.C.
24 JAN 1983
ACTION .....
.....

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T-LYMPHOCYTE SUBPOPULATIONS IN HOMOSEXUAL MEN

Hardy Kornfeld, M.D.,
Robert A. Vande Stouwe, M.D., Ph.D.,
Michael Lange, M.D.,
M. Mohan Reddy, Ph.D.,
and Michael H. Grieco, M.D.

In the past two years there has been an unprecedented outbreak of Kaposi's sarcoma, *Pneumocystis carinii* pneumonia, and other opportunistic infections in male homosexuals and, to a lesser extent, in drug addicts in the United States.[1,2] These cases have been concentrated in New York City and California, and as of January 13, 1982, 216 cases had been reported to the Centers for Disease Control.[3]

Nineteen cases with immunologic evaluation were reported in December 1981.[4-6] All patients had evidence of cellular immunodeficiency with cutaneous anergy, reduced numbers of T lymphocytes, and impaired lymphocyte transformation. Four patients described by Gottlieb et al.[4] had an altered distribution of T-cell subsets on immunofluorescent staining with monoclonal antibodies. The ratios of Leu-3 positive (helper/inducer) to Leu-2 (suppressor/cytotoxic) lymphocytes were reduced.

It is assumed that the opportunistic infections and Kaposi's sarcoma occurred in these patients as a consequence of acquired immunodeficiency analogous to the complications of treatment with immunosuppressive drugs.[7,8] If this is true then the number of persons at risk for serious illness may be larger than is indicated by the cases of Kaposi's sarcoma and opportunistic infections reported to date.

We have studied 81 male homosexuals in New York City and have found that a large proportion have an altered distribution of T-lymphocyte subpopulations similar to but less pronounced than that found in patients with Kaposi's sarcoma or opportunistic infection. Reduced ratios of OKT4 (helper cells) to OKT8 (suppressor cells)[9,10] were associated with the presence of certain symptoms and with sexual promiscuity but not with the use of inhaled nitrites.

From the Division of Infectious Diseases and Epidemiology and the Division of Allergy and Clinical Immunology, the Medical Service, St. Luke's–Roosevelt Hospital Center. Address reprint requests to Dr. Grieco at the Division of Allergy and Clinical Immunology, the Medical Service, St. Luke's–Roosevelt Hospital Center, New York, NY 10019.

Methods

Eighty-one healthy homosexual volunteers 34.9±8 years of age (mean ±S.D.) were recruited by advertising in gay newspapers and through a gay health clinic and a university gay student organization. Those with histories of serious systemic illness or immunosuppressive therapy were excluded. Twenty heterosexual men 30.7±5.4 years of age served as controls.

A questionnaire was administered by one of us (H.K.) for information regarding medical history as well as symptoms, drug use, and sexual practices within the previous 12 months. For purposes of standardization, a history of fever was defined as a temperature of 37.8°C or higher for more than one week, weight loss as the unintentional loss of 5 kg or more, and diarrhea as three or more unformed stools per day for more than one week. Lymphadenopathy was defined as persistently enlarged nodes outside the inguinal chains. Recurrent amebiasis was defined as a history of five or more successfully treated discrete episodes in the previous year, and persistent amebiasis as persistently positive stool examinations despite two successive standard treatment regimens.

Mononuclear cells were isolated from heparinized peripheral blood on Ficoll–Hypaque gradients. Monocytes were identified by latex-particle ingestion. After washing, lymphocytes were suspended in Roswell Park Memorial Institute 1640 medium containing 10 per cent heat-inactivated fetal calf serum. Lymphocytes positive for OKT4 and OKT8 (Ortho Diagnostic Systems, Raritan, N.J.) were identified by an indirect immunofluorescence assay with fluorescein-conjugated goat antimouse IgG (Meloy, Springfield, Va.) used as the developing antibody. Cells were mounted and slides were examined with a fluorescence microscope. Two hundred latex-negative cells were counted. Simultaneous complete blood counts and differential leukocyte counts were obtained.

Titers of cytomegalovirus antibody were determined by complement fixation.[11]

The means of the percentages and calculated absolute numbers of OKT4-positive and OKT8-positive lymphocytes and the OKT4/OKT8 ratios were compared in different patient groups using Student's t-test. The applicability of the t-test to the data was verified by F tests and graphic inspection of cumulative frequency distributions. Linear regression analysis was used to compare the OKT4/OKT8 ratios with the height of the titers of cytomegalovirus antibody.

Results

Of the 81 homosexual volunteers, 50 were asymptomatic and 31 had a history of one or more symptoms or signs according to the questionnaire. Within the symptomatic group, 2 had weight loss, 2 had thrush, 5 had diarrhea, 7 had fever, 11 had lymphadenopathy, 18 had amebiasis, and 11 had more than one disorder.

The distribution of T-cell subsets was abnormal in both groups of homosexuals as compared with controls, and it differed between the symptomatic and

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Table 1. Lymphocyte Subpopulations in Symptomatic and Asymptomatic Male Homosexuals and in Heterosexual Controls.*

Group	% OKT4	Absolute OKT4 Count	% OKT8	Absolute OKT8 Count	OKT4/OKT8 Ratio
		cells/mm³		*cells/mm³*	
Controls (n = 20)	36.6 ±1.0	813.3 ±60.6	20.5 ±0.8	454.0 ±37.3	1.8 ±0.1
Asymptomatic homosexuals (n = 50)	27.4 ±1.4	643.9 ±41.5	28.8 ±1.1	675.1 ±33.3	1.1 ±0.1
Symptomatic homosexuals (n = 31)	22.4 ±1.6	483.5 ±43.0	31.1 ±1.6	651.2 ±42.5	0.8 ±0.1

*Data are reported as means ±S.E.M. The percentages and absolute counts of OKT4 and the OKT4/OKT8 ratios were significantly different among all three groups ($P<0.05$ or less). The percentages and absolute counts of OKT8 in symptomatic and asymptomatic homosexuals were higher than in controls ($P<0.01$ or less) but did not differ from each other.

asymptomatic homosexuals as well (Table 1). The percentages and absolute counts of OKT4-positive lymphocytes and the OKT4/OKT8 ratios were lower in the homosexuals and were significantly different in all three groups as compared with one another. Of all 81 homosexuals tested, only 14 (17.3 per cent) had OKT4/OKT8 ratios within the control range of 1.4 to 2.8. Of these 14 subjects, 12 were in the asymptomatic group and 2 in the symptomatic group. Six asymptomatic and nine symptomatic subjects had OKT4/OKT8 ratios below 0.5. The percentages and absolute counts of OKT8-positive lymphocytes were significantly higher in homosexuals than in controls but did not differ between the two groups of homosexuals.

Tests for cytomegalovirus antibody were positive in 79 of 81 homosexuals, with titers above 1:16 in 63 (77.8 per cent). There was no correlation between titers of the antibody and OKT4/OKT8 ratios ($r = 0.02$). Five of 20 heterosexual controls (25 per cent) were positive for cytomegalovirus antibody — all with titers of 1:16 or less.

Sexual promiscuity was associated with reduced OKT4/OKT8 ratios (Fig. 1). Subjects reporting nine or fewer different sexual partners per year tended to have higher ratios than those reporting more sexual partners, although this difference became statistically significant ($P<0.05$) only in comparisons with subjects reporting 50 or more partners.

Long-term use of amyl and butyl nitrite was unrelated to OKT4/OKT8 ratios (Fig. 2). Six of 40 subjects (15 per cent) using nitrites at least once a week had normal ratios, whereas 18 of 23 subjects (78.3 per cent) who had never used these drugs had low ratios.

Discussion

Reduced OKT4/OKT8 ratios have been reported in a variety of diseases including cytomegalovirus-induced mononucleosis,[12] Epstein–Barr virus infection, influenza, acute and chronic hepatitis B infection, and primary biliary cirrhosis.[13,14] The cause of the reduced ratios in our homosexual subjects is unknown, and their possible relation to the outbreak of Kaposi's sarcoma and opportunistic infections will require longitudinal study. It must be stressed that immunofluorescence staining of lymphocyte subpopulations with monoclonal antibodies reveals only phenotypic cell-surface markers that may not correlate with functional abnormalities.

Prodromal symptoms or signs such as fever, weight loss, diarrhea, and lymphadenopathy for up to 12 months have been reported in many patients with the syndrome of acquired cellular immunodeficiency and Kaposi's sarcoma or opportunistic infection.[3] In this study both symptomatic and asymptomatic homosexuals had reduced OKT4/OKT8 ratios, and there was a significant trend toward lower ratios in the symptomatic subjects. Although the assessment of symptoms was subjective, we believe it is clinically relevant.

Sexual promiscuity as defined by the number of different sexual partners in the previous year was frequently but not invariably associated with low OKT4/OKT8 ratios. The only monogamous volunteer had a ratio of 1.0, whereas another subject, who reported having had more than 400 different partners in the previous year, had a ratio of 1.7. The reduced ratios in the promiscuous subjects may have been due to a higher frequency of sexually transmitted viral infections, particularly cytomegalovirus infection.[15,16] Other factors associated with homosexual practices include mucosal exposure to seminal plasma, which may have immunosuppressive properties,[17] exposure to foreign HLA determinants on spermatozoa, and the use of nitrites.

Goedert et al.[18] recently reported low OKT4/OKT8 ratios in 9 of 15 healthy homosexual men, 8 of whom used nitrites regularly. It was concluded that nitrites may have had a causative role in altering the T-cell subsets. Although we did not find this association in our subjects, this does not exclude a transient

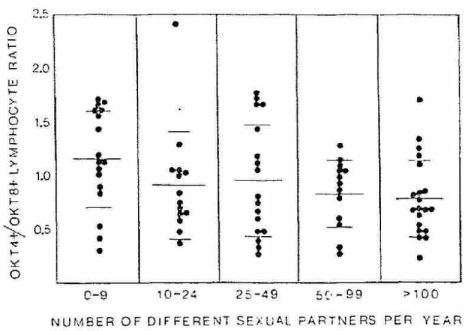

Figure 1. OKT4/OKT8 Ratios and Sexual Promiscuity in Homosexual Men.

The OKT4/OKT8 ratio was higher in subjects reporting nine or fewer different sexual partners per year than in those reporting 50 to 99 partners ($P<0.05$) or 100 or more partners ($P<0.01$) per year. Horizontal lines represent means ±S.D.

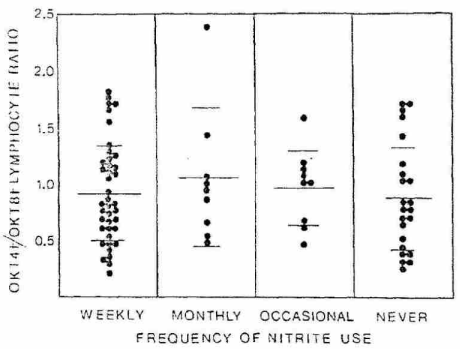

Figure 2. OKT4/OKT8 Ratios and the Use of Inhaled Nitrites in Homosexual Men.

The OKT4/OKT8 ratio was not related to the reported use of nitrites. Horizontal lines represent means ±S.D.

effect, since none of our subjects had taken these drugs within eight hours of testing. Furthermore, the lack of an association between nitrite use and altered T-cell subsets in our study does not exclude the possibility that these drugs have functional immunosuppressive properties.

Whatever the cause and the importance of the altered T-cell subsets in male homosexuals, the finding of a detectable abnormality in over 80 per cent of those tested suggests a greater public-health problem than is generally appreciated. Although the volunteers in this study may not be representative of the overall homosexual population in New York City, the strikingly high prevalence of reduced OKT4/OKT8 ratios in our subjects does suggest that this alteration may be present in a large number of homosexual men in the community.

We are indebted to the Columbia University Health Service, the Gay Men's Health Project, and the volunteers from Columbia University for their help; to Dr. Elena Klein for the serologic studies; to Ms. Mary Moriarty for technical assistance; and to Ms. Yolanda Sandoval for preparation of the manuscript.

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PERIPARTUM CARDIOMYOPATHY DUE TO MYOCARDITIS

KENNETH R. MELVIN, M.D.,
PETER J. RICHARDSON, M.R.C.P.,
ECKHARDT G. J. OLSEN, F.R.C.PATH.,
KIERAN DALY, M.R.C.P.I.,
AND GRAHAM JACKSON, M.R.C.P.

PRIMARY myocardial disease that develops during the course of pregnancy is a rare but exacting diagnostic problem. The variation in the time of onset of this disease from the second trimester of pregnancy until well into the puerperium has led to debate regarding terminology.[1,2] We refer to peripartum cardiomyopathy as the new presentation of primary myocardial disease during pregnancy or in the first five months after pregnancy.

In the evaluation of patients with peripartum cardiomyopathy it is necessary to exclude or identify myocarditis immediately because of the important therapeutic implications. We have included endomyocardial biopsy in the diagnostic workup of such patients because of the similarities in presentation between peripartum cardiomyopathy and viral myocarditis. We have previously shown transvenous endomyocardial biopsy to be a safe and valuable procedure in both acute and chronic disease states.[3-5]

We report on three consecutive patients with peripartum cardiomyopathy. Each patient had signs and

From the Cardiac Department, Kings College Hospital, Denmark Hill, London. Address reprint requests to Dr. Jackson at King's College Hospital, Denmark Hill, London SE5 9RS, England.

Supported by grants from the British Heart Foundation and the Ontario Heart Foundation.

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WORLD HEMOPHILIA AIDS CENTER
2400 South Flower Street
Los Angeles, California 90007 USA

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)
OR AIDS-RELATED COMPLEX (ARC)

CASE REPORT

SECTION I

Date of Report _____ (Day Month Year) WHAC Identification No. _____

Case of: AIDS ☐ ARC ☐ Date of Diagnosis _____ (Day Month Year)

Status of this Report: New Case ☐ Update ☐

REPORTING PHYSICIAN

Name of Physician _____ Title _____

Institution _____

Address _____

City _____ State/Prov/Dept. _____

Country _____ Postal Code _____

Has this case been reported to the U.S. Public Health Service Centers for Disease Control?

Yes ☐ No ☐ Date of Report _____

Has this case been reported to the WHO Centre for AIDS Surveillance in Paris?

Yes ☐ No ☐ Date of Report _____

PATIENT DATA:

Your patient's Identification No. _____ Age _____ Date of Birth _____ (Day Month Year) Sex ____ Race ____

County of Residence at onset of illness: _____

Any Risk Factors for AIDS other than Hemophilia (Homosexual/Bisexual, Intravenous Drug User, Resided in Haiti or Central Africa)? Yes ☐ No ☐

Type and Severity of Hemophilia:

A (Factor VIII) ☐ B (Factor IX) ☐ von Willebrand's Disease ☐

Other (please specify) _____ Unknown ☐

Severity: <1% (severe) ☐ 1-5% (moderate) ☐ >5% (mild) ☐ Unknown ☐

Inhibitor? Yes ☐ No ☐ Unknown ☐

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BLOOD PRODUCT USAGE

	Exposure Days Since 1 January 1979 ("Exposure Day" = any 24-hour period during which patient received blood or blood product, regardless of type or amount.)						
	0	1-10	11-50	51-100	101-1000	>1000	Unknown
Packed Red Cells or Whole Blood							
Cryoprecipitate							
Fresh Frozen Plasma							
Factor VIII Concentrate*							
Factor IX Concentrate*							

*Manufacturer(s) _____

Comments: _____

SECTION II

CLINICAL FINDINGS:

Patient Status: Alive ☐ Dead ☐ Date of Death: _____

Cause of Death: _____

Prior to onset of AIDS/ARC symptoms, did the patient:

- have any other known medical condition which might have caused immunosuppression, i.e. leukemia, Hodgkin's disease, Non-Hodgkin's lymphoma, multiple myeloma, diabetes mellitus (insulin-dependent), chronic renal failure, chronic hepatitis, congenital immune deficiency syndrome? Yes ☐ No ☐ Unknown ☐

  Other (specify) _____.

- receive systemic corticosteroid therapy? Yes ☐ No ☐ Unknown ☐

- receive other immunosuppressive or cytotoxic therapy? Yes ☐ No ☐ Unknown ☐

Please give details of immune studies: WBC and differential, platelets, lymphocyte subset analysis, and virology.

_____

_____

_____

_____

_____

*If you are reporting a patient with **ARC**, please go to Section III.*
*If you are reporting a patient with **AIDS**, please go to Section IV.*

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SECTION III

ARC CASE REPORT

AIDS-Related Complex Signs/Symptoms:

	Date of Onset	Duration (Months)
☐ Lymphadenopathy (Sites: _____)	_____	_____
☐ Weight loss (% of body weight _____)	_____	_____
☐ Fatigue/malaise	_____	_____
☐ Fever >39°	_____	_____
☐ Diarrhea	_____	_____
☐ Thrombocytopenia (_____ Platelets/cu.mm.)	_____	_____

Please describe clinical course, treatment results, and any other pertinent information in Section V.

SECTION IV

AIDS CASE REPORT

Medical Conditions Indicative of AIDS:

	Date of Diagnosis	Method of Diagnosis (Histology, cytology, endoscopy, autopsy, culture, serology)
☐ Kaposi's Sarcoma	_____	_____
☐ *Pneumocystis carinii* pneumonia	_____	_____
☐ Toxoplasmosis	_____	_____
☐ Disseminiated cytomegalovirus infection	_____	_____
☐ Cryptosporidiosis with diarrhea >1 month	_____	_____
☐ Primary lymphoma of brain	_____	_____
☐ Progressive multifocal leukoencephalopathy	_____	_____
☐ Candida esophagitis	_____	_____
☐ Atypical mycobacterial infection, disseminated	_____	_____
☐ Cryptococcal infection (other than pulmonary)	_____	_____
☐ Herpes simplex infection ulceration > 1 month	_____	_____
☐ Other opportunistic infections and cancers (describe fully)	_____	
	_____	

Please describe clinical course, treatment results and any other pertinent information in Section V.

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SECTION V

Please describe clinical course, treatment results, and any other pertinent information.

Can we be of help to you in the mangement of this patient? If so, how?

- ☐ Consultation regarding clinical management
- ☐ Review of diagnostic test results
- ☐ Other (please specify) _____