Epidemiologic and laboratory evaluation of homosexual males from an area of low incidence for acquired immunodeficiency syndrome (AIDS)[1]

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The northeastern Ohio area is currently one of low incidence for the acquired immunodeficiency syndrome (AIDS). From July through December 1983, 17 sexually active healthy homosexual males, 15 men with AIDS-related complex (ARC), and nine patients with AIDS were studied. In contrast to similar studies from high-incidence areas, healthy homosexuals did not have significant laboratory abnormalities, particularly of lymphocyte subpopulations, when compared with heterosexual controls. Epidemiologically, there were no significant differences detected based on travel to epidemic areas or sexual practices between healthy homosexuals and patients with ARC. Furthermore, ARC patients were significantly less sexually active than healthy homosexual controls. It appears that subclinical immunodeficiency is uncommon in areas of low attack rates for AIDS and that studies from low-incidence areas may shed light on the early events in the spread of AIDS.

Index term: Acquired immunodeficiency syndrome

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Though acquired immunodeficiency syndrome (AIDS) appears to have started simultaneously in the United States on the East and West coasts with geographic clustering around large urban coastal cities, it has now spread to nearly every state and over 20 foreign countries. Male homosexuals and bisexuals continue to constitute 75% of its victims and many of our current concepts regarding potential risk factors, modes of transmission, and immune dysfunction are derived from studies of these populations in areas where the incidence and prevalence of the clinical and subclinical disorder is high.[1] Although recent studies

indicate that a retrovirus (HTLV-III) is the etiologic agent,[2,3] many questions remain regarding individual host susceptibility factors and the clinical value of a growing number of laboratory tests used in the evaluation of individuals at high risk for AIDS.

With the remainder of the country now representing a relatively low-incidence area, it is not readily apparent that data derived from studies in high-incidence areas regarding risk factors (multiple sexual partners, sexual practices, etc.) are directly applicable. Similarly, laboratory testing of clinically normal homosexual and bisexual men from high-incidence areas has generally shown high frequencies of immunologic abnormalities.[4-6] Comparable studies from these now low-incidence areas are important for optimum care and counseling of high-risk individuals and for a better understanding of the overall nature of the epidemic. It is possible that such studies performed in low-incidence areas will provide insight into the early events in the spread of AIDS that can no longer be obtained in regions where the incidence and prevalence of the clinical and subclinical disorder are high.

Northeastern Ohio is populated by approximately 3.5 million people and by the end of the study period in January 1984, 10 cases of AIDS had been reported in homosexuals, an attack rate of approximately 1 per 350,000 per general population over three years. We have conducted an epidemiologic and immunologic study on healthy homosexuals, men with AIDS-related complex (ARC), and patients with AIDS, comparing our results with those previously reported.

Methods

Patients and controls

Four groups of patients were studied. Group I consisted of 17 healthy homosexuals who were solicited from two sources representing both public and private medical care facilities known for their high percentage of homosexual patients. These subjects were considered ineligible if they had significant lymphadenopathy, unexplained fever, significant weight loss, chronic diarrhea, thrush, or if they fulfilled the diagnostic criteria of AIDS as established by the Center for Disease Control (CDC). Group II consisted of 15 patients with ARC. These men were either homosexual or bisexual and were under the care of one of the authors (LC or BD). Each had lymphadenopathy that was persistent over at least a three-

month period with node size greater than 1 cm in diameter and involving two or more extrainguinal node-bearing areas regardless of the presence or absence of symptoms. Group III consisted of nine patients initially fulfilling the CDC definition of AIDS. Of this group five cases were reportable in the state of Ohio whereas the other four patients had not fulfilled residency requirements and their cases were reported elsewhere. No epidemiologic data were included on those cases not reported. During the study one Group II patient progressed to Group III. Group IV consisted of 20 heterosexual males selected for age to serve as controls for the lymphocyte subpopulation studies.

Studies

After informed consent was obtained, each study patient (Group I, II, III) completed an epidemiologic questionnaire (based on a questionnaire kindly provided by Dr. James Goedert, National Cancer Institute). This contained over 50 questions pertaining to personal sexual habits and practices, drugs, travel, and medical history, particularly over the past three years.

Complete blood counts with differential and platelet count, serum immunoglobulins, immune complexes by Clq binding, beta-2 microglobulin by solid-phase radioimmunoassay, T cell subsets utilizing the reagents OKT-3, OKT-4, and OKT-8 performed on a FACS-II flow cytometer, lymphocyte proliferative responses to concanavalin A (Con-A), pokeweed mitogen (PWM), and phytohemagglutinin (PHA), and detection and characterization of serum interferon (outlined below) were performed on each patient when possible.

Serum interferon (IFN) was assayed by a virus cytopathogenicity inhibition assay adapted from the procedure of Armstrong[7] and Jameson et al[8] using human lung carcinoma cells (strain A549). Rabbit antibodies to purified interferon alpha, beta, and gamma were used to confirm specific type; acid stability was determined by the procedure of DeStefano et al.[9]

HTLV-III antibody was detected by enzyme-linked immunoassay (Litton Bionetics, Inc.). The calculations of sensitivity, specificity, and predictive values were performed as previously described.[10] Receiver operator characteristic analysis was performed by plotting true-positive rates for varying values of each test versus false-positive rates for varying test values.[11]

Categorical data were analyzed using Fisher's

exact test or chi-square depending upon expected cell frequencies. Analysis of variance was conducted for the T cell subsets and other continuous laboratory measurements. When a significant F statistic was obtained by means of the analysis of variance, specific linear comparisons among groups were examined. Due to the multiple statistical tests performed in this study, values of $p < 0.01$ were considered to be significant. SAS was used to perform all statistical tests and for management of the data base.[12]

Results

Epidemiologic data

Epidemiologic questionnaires were completed by all patients in Group I and Group II, but unfortunately only two AIDS patients (Group III) were able to complete the questionnaire, and therefore they were not included in the statistical analysis.

As expected, there were significant differences between Group I and Group II with respect to swollen glands, unexplained fevers, and weight loss, but not for hepatitis, infectious mononucleosis, diarrhea, sore throat, pneumonia, or prior malignant disease during the preceding 12 months. The use of nitrate inhalants, marijuana, cocaine, and injectable drugs was not significantly different among the groups (data not shown).

A comparison of sexual activities among the study groups revealed an extremely wide range (*Table 1*). When grouped together by those having sex with more or less than 10 men per year, Group II appeared significantly less sexually active. Of the two AIDS patients one was basically monogamous while the other admitted to 100 different sexual contacts per year.

Table 1. Number of different men contacted sexually in a year

	Healthy homosexuals (Group I) ($n = 17$)*	ARC (Group II) ($n = 15$)*
Sexual contacts/1983	48.1 (S.D. = 62.1)	20.9 (S.D. = 22.3)
Median/1983	22	10
Range/1983	1–200	1–75
Sexual contacts/1982	47.3 (S.D. = 59.4)	9.4 (S.D. = 20.6)
Median/1982	20	12
Range/1982	1–200	1–75

S.D. = standard deviation.

* Group I & II differ significantly; $p < .04$ by chi square when compared on the basis of those having sex with > 10 men or < 10 men per year during the study period.

When the frequencies of a variety of sexual practices were investigated, there was no significant difference between active or passive (receptive) anal-genital sex or active or passive oral-genital sex in the study groups. Furthermore, there were no significant differences detected in the frequencies of active or passive oral-anal sex or the reception or insertion of a fist into the partner's rectum (data not shown).

A history of travel to epidemic areas during the preceding three years was considered an extremely important factor in this type of study, particularly travel associated with sexual contact with males from these areas. There were no important differences over the preceding three years between the frequency of travel and the number of men sexually contacted in New York, San Francisco, and Los Angeles. It is important to note in this situation that the numbers were so small that a valid statistical test could not be performed (data not shown).

Table 2. T cell subsets

Cells	Healthy heterosexuals ($n = 20$) (cells/mm³, mean ± S.D.)	Healthy homosexuals (Group I) ($n = 17$) (cells/mm³, mean ± S.D.)	ARC (Group II) ($n = 12$) (cells/mm³, mean ± S.D.)	AIDS (Group III) ($n = 9$) (cells/mm³, mean ± S.D.)
OKT-3	1274 ± 390	1507 ± 568	1146 ± 361	511 ± 398*†
OKT-4	860 ± 290	894 ± 348	413 ± 233*	52 ± 45*†
OKT-8	400 ± 121	554 ± 232	572 ± 136*	320 ± 260†
T4/T8	2.2 ± 0.6	1.75 ± 0.68	0.72 ± 0.39*	0.26 ± 0.25*

S.D. = standard deviation.

* Differs significantly from healthy heterosexuals, $p < 0.01$.

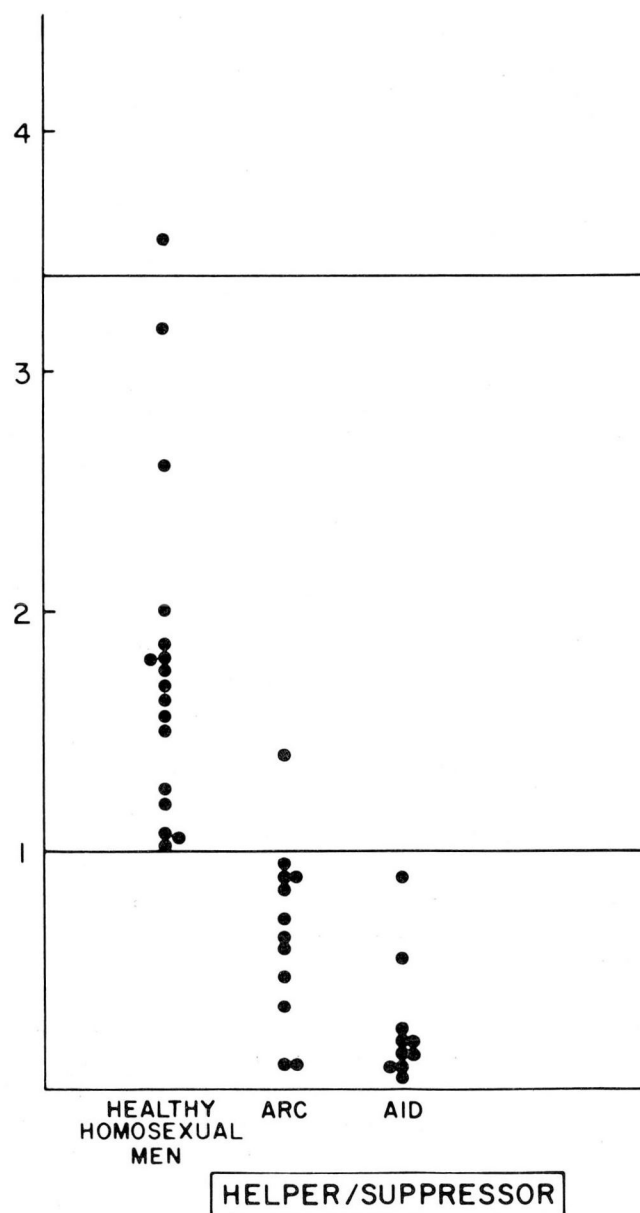† Differs significantly from Group I, $p < 0.01$.

Fig. 1. A plot of the helper/suppressor ratios (OKT-4/OKT-8) for healthy homosexuals and patients with ARC and AIDS. The lines indicate the normal range for 20 heterosexual controls.

Immunologic data

Analysis of T cell subsets (*Table 2*) revealed that Group III (AIDS) had the lowest helper/suppressor ratio (0.26) with profound depletion of all cell lines (OKT-3, OKT-4, OKT-8, $p <$ .003 vs healthy heterosexuals). Group II (ARC) had a helper/suppressor ratio of 0.72 and had a significant depression of absolute numbers of T-4 helper cells ($p <$ .0001 vs healthy heterosex-

uals). Group I (healthy homosexuals) had a helper/suppressor ratio of 1.75; when compared with controls this failed to attain the preselected p value of <.01 when multiple comparisons were taken into account. There were no significant differences between absolute numbers of T-4 or T-8 cells in this group, although six patients had T-8 cell values greater than two standard deviations from the mean of the healthy heterosexual controls. Furthermore, a scattergram of the lymphocyte subpopulations (*Fig. 1*) demonstrated that no Group I patient had a helper/suppressor ratio below the normal range, as determined by the mean plus or minus two standard deviations of our 20 healthy heterosexual controls.

Evaluation of serum immunoglobulins revealed significant mean elevations of IgG for Group II and elevations of IgG and IgA for Group III when compared with the healthy homosexual controls in Group I (*Table 3*). The mean values of IgG, IgA, and IgM for Group I patients did not differ significantly from established laboratory control values. Furthermore, of the 18 Group I patients only one patient had elevation of a single isotype (IgG); the remainder were entirely within the established normal range.

Group III patients demonstrated statistically significant reductions in total white cell count when compared with Group I. Serum beta-2 microglobulin was significantly elevated in all three groups when compared with laboratory control values. The mean values for Groups II and III were significantly elevated over that of Group I.

Mitogen stimulation with PHA, PWM, and Con-A revealed that Group II and Group III had depressed response to PWM in comparison with Group I and controls, but there was no significant difference for PHA or Con-A (data not shown).

Serum interferon determinations (*Fig. 2*) revealed that levels greater than 16 U/ml were found exclusively in the AIDS group. The single patient in Group II whose interferon level was elevated to this range was the only patient who progressed clinically from Group II to Group III. *Pneumocystis carinii* pneumonia developed in this patient four months after the determination of serum interferon, at which time he had had only lymphadenopathy and fatigue.

Interferons detected in these patients were characterized for specific type and acid lability; all specimens were typed as alpha and were found to be at least partially acid-labile.

Table 3. Serum immunoglobulins, β_2 microglobulin, and HTLV-III Ab

	Healthy homosexuals (Group I)	ARC (Group II)	AIDS (Group III)
IgG (mg/100 ml, ± S.D.)	1030 ± 285	1828 ± 595*	1650 ± 469*
IgA (mg/100 ml, ± S.D.)	221 ± 75	265 ± 232	542 ± 371*
IgM (mg/100 ml, ± S.D.)	161 ± 87	148 ± 48	130 ± 50
β_2M (μg/100 ml, ± S.D.)	2.32 ± 62*	3.61 ± 1.41	4.92 ± 1.26*
HTLV-III Ab	3/17	14/15	9/9

S.D. = standard deviation.

Normal range mean ± 2 S.D.: IgG 662–1373 mg/100 ml; IgA 54–418 mg/100 ml; IgM 46–311 mg/100 ml; β_2M 0.8–2.2 μg/100 ml.

* Differs significantly from healthy hospital employees ($p < .05$).

The result of HTLV-III antibody testing revealed that among the healthy homosexuals (Group I) three of 17 were positive while in the ARC patients (Group II) 14 of 15 were positive. All AIDS patients (Group III) had positive tests for HTLV-III antibody (*Table 3*).

Test characteristics

Sensitivity, specificity, and predictive values for interferon, absolute numbers of T-4 cells, helper/suppressor ratio, beta-2 microglobulin, and HTLV-III Ab are displayed in *Table 4*, when used as variables for separating Group III (AIDS) from Groups I and II. Lastly, interferon, absolute numbers of T-4 helper cells, and the helper/suppressor ratio are displayed according to their receiver operator characteristics (*Fig. 3*) in an attempt to find the most efficient test for separating AIDS patients from ARC patients and healthy homosexuals.

Discussion

As of early 1984 the Northeastern Ohio area had been spared the dramatically increased incidence of AIDS now being observed in a number of large inland urban areas. The reasons for this phenomenon are not readily apparent. The local homosexual community, while not highly organized, is believed to be sizable and there are numerous gay clubs and several bath houses within the city. Regardless of the reason for the current low incidence it has afforded an excellent opportunity for epidemiologic/immunologic investigation in the very early phases of the AIDS epidemic. A natural drawback of such a study is the difficulty in accruing large numbers of patients with clinical disease, for by the very nature of a low-incidence area, the numbers are limited. Even with these reservations we have been able to draw several conclusions from our data.
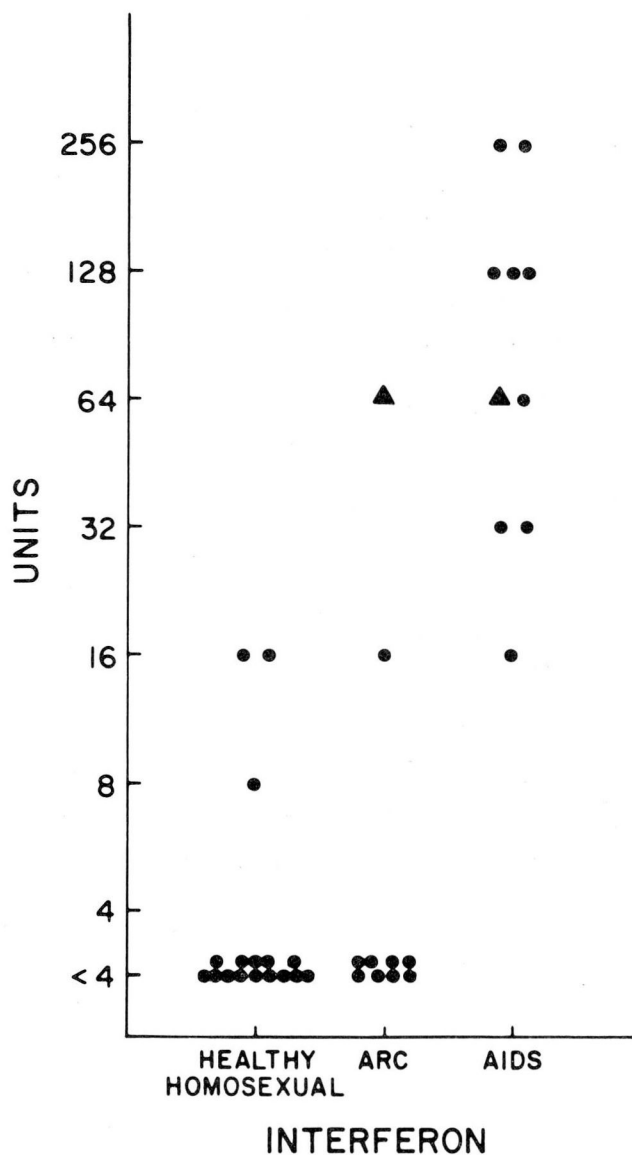

Fig. 2. A plot of serum interferon in various groups. The triangle indicates the sole non-AIDS patient with a serum interferon level greater than 16 U/ml, in whom *Pneumocystis carinii* pneumonia developed 16 weeks later.

Table 4. Test characteristics for differentiating AIDS from ARC and healthy homosexuals

	Healthy homosexuals (Group I)	ARC (Group II)	AIDS (Group III)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Test efficiency (%)
Depressed OKT-4*	0/17	4/11	10/10	100	86	71	100	89
Depressed OKT-4/OKT-8†	0/17	9/11	10/10	100	68	53	100	76
Elevated β_2M‡	5/17	9/14	10/10	100	52	40	100	68
Elevated IFN§	0/17	0/11	9/10	90	100	100	97	97
HTLV-III (Ab)**	3/17	13/14	10/10	100	48	38	100	61

AIDS subsequently developed in one of the Group II patients with elevated interferon levels, who is considered in the AIDS group for statistical purposes.
All calculations are based on 10 AIDS patients, which includes the sole Group II patient in whom AIDS developed during the study period.
* Less than 280 cells/mm^3.
† Less than 1/1.
‡ Greater than 2.4 μg/ml.
§ Greater than 16 U/ml.
** Ratio of test to negative control > 2.

Laboratory investigation of our study groups revealed that, consistent with previous reports from high-incidence areas,[4-6] our Group III (AIDS) patients were the most profoundly affected, and demonstrated the lowest helper/suppressor ratios and the most depleted absolute numbers of lymphocytes, especially those of the OKT-4 (helper-inducer) subset. Group II (ARC) patients were the next most severely affected;

Fig. 3. A plot of the receiver operator characteristics for four tests. This relationship allows comparison of different types of tests for the same clinical purpose.

they too had significantly depressed helper/suppressor ratios and OKT-4-cell absolute numbers when compared with both healthy homosexuals and heterosexuals.

In contrast to reports from high-incidence areas, the healthy homosexuals from Northeastern Ohio (Group I) differed little immunologically from healthy heterosexuals. There were no significant differences in the helper/suppressor ratio or in absolute numbers of OKT-3, OKT-4, or OKT-8 cells. A scattergram of these data revealed no Group I patient with a helper/suppressor ratio outside of the normal range (ie <1) (*Fig. 1*). This is in sharp contrast to immunologic studies from New York published relatively early in the epidemic, in August[4] and September[5] 1982, that showed marked perturbation of the T cell subsets in healthy homosexuals with mean helper/suppressor ratios of 1.2 and 1.1, respectively. In a recent study by Zolla-Pazner et al,[6] 13 of 40 healthy homosexuals in the New York City area had helper/suppressor ratios less than 1. Testing of our patients' lymphocyte function by stimulation with the mitogens PWM, Con-A, and PHA revealed no significant differences between Group I and controls. Serum immunoglobulin determinations showed only one Group I patient to have a single isotype (IgG) elevated above the normal range; in contrast, similar studies in New York City showed elevation of at least one isotype in over 50% of healthy homosexuals.[5] The immunologic marker significantly elevated in all groups when compared with nonhomosexual controls was beta-2 microglobulin. This is surprising in light of the recent report of Zolla-
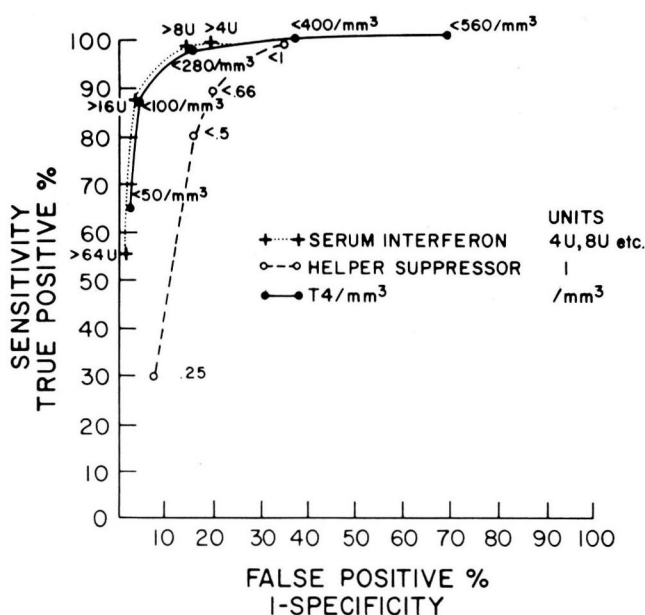
Pazner et al[6] showing relatively normal levels in healthy homosexuals in New York City. We have no ready explanation for this observation, such as the presence of active viral infection, renal insufficiency, or B cell neoplasms. These data suggest that subclinical immunodeficiency is not a de novo marker for the homosexual life style; in such abnormalities as described, in high-incidence areas it may indeed reflect exposure to the presumed etiologic agent.

Comparison of epidemiologic factors among our study groups was limited to Groups I and II, since only two eligible Group III (AIDS) patients were able to respond to our questionnaire. Such comparisons may still be informative in light of our current knowledge about men with generalized lymphadenopathy or ARC. The observation that 43% of a series of patients with Kaposi's carcinoma and 23% of patients with *Pneumocystis carinii* pneumonia had antecedent lymphadenopathy[13] has prompted many to term the disorder "pre-AIDS"; yet those series reflecting the most extensive experience with unexplained lymphadenopathy in homosexuals have not supported such clinical progression in the majority of cases.[14,15] It now appears that homosexual men with lymphadenopathy and depressed numbers of T helper cells have a high prevalence of antibodies to the HTLV-III virus.[3] Thus, ARC may, in fact, represent the appropriate adaptive response to the presumed etiologic agent, with only a minority of cases representing actual "pre-AIDS." As of this time we have observed clinical progression in six of our more than 40 Cleveland Clinic patients with this syndrome.

As expected, Group II demonstrated a statistically increased frequency of clinical symptoms including weight loss, fever, and lymphadenopathy, but no differences were detected for past history of a number of common infections (including a variety of sexually transmitted diseases) or for the use of drugs. There were no differences between our study groups for specific sexual practices, in particular passive (receptive) anal intercourse (*Table 1*). Travel histories revealed no significant differences in the frequency of travel, with subsequent sexual contacts, to high-incidence areas (New York, Los Angeles, and San Francisco) during the three years preceding the study. If travel to an epidemic area is not the means by which the disease-causing agent is acquired, then an alternative mode of acquisition would be through sexual contact with a clinically well intermediate. This hypothesis is strengthened by the fact that a sizable proportion of healthy homosexuals from high-incidence areas now have serologic evidence of HTLV-III infection.[16]

An interesting finding in this phase of the study is that the clinically involved Group II subjects were less sexually active than those in Group I (see *Table 1*). We did not think this was a secondary phenomenon, ie, decreased sexual activity secondary to illness, because the data (*Table 1*) reflect the same trend for up to two years prior to the illness. Studies of AIDS patients from epidemic areas have emphasized a strong correlation between promiscuity and clinical disease.[13] This has been variably interpreted as suggesting sexual promiscuity per se is in itself a high risk factor and that limiting numbers of partners may be protective. The reasons our data are not consistent with these previous observations are not apparent, but several are possible. We do not believe that these data reflect a selection bias for unusual promiscuity in our controls since in comparison with healthy homosexuals in previous studies[4] the sexual activity of our group was modest; furthermore the age and racial distribution of our healthy and diseased groups were similar.

Another interpretation of our data is that promiscuity per se may be a true risk for AIDS but not for ARC. If ARC is truly a relatively benign end point, then perhaps increased sexual encounters found in AIDS victims may supply the necessary cofactor, such as repeated exposure to other sexually transmitted diseases or to Ia antigens, that ultimately causes irreversible immune dysfunction. This hypothesis is not supported by the infrequent observations made by us and others that patients with only a few apparently healthy partners, as well as hemophiliacs and other recipients of blood or blood products, occasionally do get and die of AIDS. Furthermore, the recent report of Abrams et al[15] has demonstrated that gay men with ARC in San Francisco, a high-risk area, appear to have a high frequency of sexual encounters. Lastly, it must be considered that in an area of low incidence, the risk of disease acquisition may be more a function of the nature of one's sexual encounters than the sheer numbers. Of particular importance is whether an individual routinely has contact with the "core population" or that subset of the community that at any given time has the

highest prevalence of sexually transmitted disease.[17] A recent sero-epidemiologic study of 320 sexually active individuals from the Northeastern Ohio area has failed to show any significant association between promiscuity and serologic status to HTLV-III. These observations, while not totally explainable at present, would appear extremely important for counseling gay and bisexual men regarding safe sexual practices.[18]

Finally, with the increasing availability of sophisticated and expensive immunologic testing, we think it is important that serious consideration be given to some of the basic principles of test selection that allow more rational and cost-effective use of the clinical lab. Many now view AIDS as the spectrum of disease caused in whole or in part by a retrovirus, i.e., HTLV-III, that in some individuals apparently has no clinical sequelae whereas in others causes an intermediate syndrome, with some individuals ultimately progressing to an irreversible state of immunologic dysfunction known as AIDS. The definition provided by the CDC for AIDS is a highly specific one and is an excellent epidemiologic tool, but it is not an ideal one for individual patient care from a public health perspective. The ability to identify those individuals who are likely to progress clinically or to transmit the etiologic agent would also allow identification of those who might benefit from attempts at immunomodulation before the apparently irreversible immunodeficiency of AIDS occurs.

The HTLV-III virus appears to be the etiologic agent, and preliminary data regarding the sensitivity of the test for serum antibody to this virus suggest that it will be an excellent marker for exposure and will have a strong negative predictive value for absence of disease potential. Thus, it should serve as an excellent marker for screening of blood and blood products. Alternatively, these same data suggest that the test does not discriminate between uncomplicated infection and the development of AIDS, since the majority of patients with ARC[3] and many asymptomatic gays have detectable antibody.[19] Long-term follow-up of these patients and screening of much larger numbers of individuals in well-defined populations will determine its ultimate clinical value. The recent expansion of the case definition for AIDS, however, which includes HTLV-III antibody testing for certain clinical subgroups, would appear to broaden the clinical use of this test for diagnostic purposes.[20]

Examination of serum interferon, absolute numbers of T helper cells, the helper/suppressor ratio, and serum beta-2 microglobulin as potential discriminators of patients with AIDS from those with ARC and healthy homosexuals reveals that a serum interferon level greater than 16 U/ml has the best test efficiency (97%). The interferon activity was neutralized by antiserum to interferon alpha and was at least partially acid-labile in all subjects tested. Not only was the detectable presence of interferon in our AIDS patients the most sensitive and specific marker for the disease; we now have found, in accordance with the observation of others,[9,18] that two of our ARC patients with interferon levels of this magnitude progressed to AIDS within twelve and sixteen weeks. From these observations it appears that the presence of sustained levels of acid-labile serum interferon alpha may be an early marker for irreversible immunologic dysfunction.

A comparison of three of these tests by their receiver operator curve characteristics shows that serum interferon and absolute T helper cell enumeration are essentially equally efficient tests. If the value of the T helper count is interpreted on the basis of traditional laboratory values (280 cells/mm^3 representing the mean less two standard deviations of our 20 heterosexual controls) it is more sensitive but less specific than interferon levels of greater than 16 U/ml. However, if the criterion is a T4 count less than 100 cells/mm^3 the test equals the sensitivity and specificity of interferon levels (i.e., greater than 16 U/ml). It is interesting to note that at these cut-off points there was one false-negative value for each variable, accounting for the fall in sensitivity, but no AIDS patient had both a T helper count <100 cells/mm^3 and an interferon level of 16 U/ml or less.

These observations do not necessarily suggest that any test or combination of tests will be equally predictive of a true "pre-AIDS" state when applied to larger study groups in other areas, but they do point out the necessity of examining the principles of test selection and interpretation in such studies. It may be possible to predict reliably those destined for most severe disease by detection of sustained levels of acid-labile interferon alpha and/or falling numbers of T helper cells. Alternatively, assessment of subsets of helper and/or suppressor cell populations or other functional immunologic assays may prove to be more informative when studied seri-

ally. Other serious considerations to be addressed by long-term longitudinal studies include the accuracy and reproducibility of these tests as well as how they are influenced by complications, such as intercurrent infections, before practical guidelines can be accepted.

Acknowledgements

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