

## Original Contributions

### DECREASED HELPER T LYMPHOCYTES IN HOMOSEXUAL MEN

#### I. SEXUAL CONTACT IN HIGH-INCIDENCE AREAS FOR THE ACQUIRED IMMUNODEFICIENCY SYNDROME

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In June 1982, sexual and other behavioral patterns were examined in 245 homosexual men in relationship to T-lymphocyte phenotypes that are characteristic of the acquired immunodeficiency syndrome (AIDS). Mean helper T-cell counts in New York City ( $579 \pm 32$  cells/mm<sup>3</sup>) and Washington, DC, homosexual men with sexual contacts in areas at high risk (endemic) for AIDS ( $567 \pm 24$  cells/mm<sup>3</sup>) were significantly lower than in Washington, DC, residents without such contacts ( $672 \pm 36$  cells/mm<sup>3</sup>,  $p = 0.04$  by analysis of variance). Helper T-cell counts in the Washington men were inversely correlated with a greater number of endemic-area homosexual contacts ( $p = 0.005$ ), even after adjustment for multiple confounding variables ( $p = 0.02$ ). The 31 Washington men with more than 15 endemic-area partners had a mean helper T-cell count of  $517 \pm 44$  cells/mm<sup>3</sup>, and 12 of those 31 men had helper T-cell counts  $<400$  cells/mm<sup>3</sup>. AIDS patients are known to have a marked reduction in the number and function of helper T-lymphocytes. The data suggest that deficits of helper T lymphocytes can be acquired by homosexual contact with men in cities where AIDS is common. This supports the hypotheses that low helper T-cell counts may be caused by a sexually transmissible agent and that frequent homosexual exposure to residents of high-risk areas for AIDS may be an important means of spread of this agent.

**homosexuality; immunity, cellular; immunologic deficiency syndromes; regression analysis; retrovirus infections**

The acquired immunodeficiency syndrome (AIDS) is a complex of highly lethal

opportunistic infections and rare malignancies that first appeared in specific American

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populations in 1978 (1). More than 3,200 cases of AIDS have been reported to the Centers for Disease Control, Atlanta, Georgia, including instances of probable transmission between individuals by homosexual (2) or heterosexual (3) contact, by blood transfusions (4, 5), and perhaps by commercial plasma derivatives. Epidemiologic interview studies have found that homosexual men with AIDS report more homosexual partners than matched controls (6, 7), which is also consistent with the hypothesis that a transmissible agent causes AIDS.

Several studies have shown that many apparently healthy homosexual men have AIDS-type immunologic abnormalities, including anergy, poor proliferative responses to mitogens and antigens *in vitro*, and low helper:suppressor T-lymphocyte ratios (8-11). We have recently shown that Danish homosexual men apparently "acquire" low helper:suppressor ratios through homosexual contacts in the United States (12). The present study evaluates whether AIDS-type immunologic abnormalities are more common among American homosexual men who have frequent sexual contact in cities where AIDS is common.

#### METHODS

During May and June of 1982, all male patients who visited the private offices of two physicians in Washington, DC, were invited to participate in this study. These two physicians anticipated that greater than 90 per cent of these men would acknowledge homosexual or bisexual preference. To ensure absolute confidentiality, patients were identified by unique code numbers rather than by name. Signed permission forms to participate in the study, with the identification numbers, were retained in locked files by the private physicians. The results of all laboratory studies were made available to each patient through his physician. Patients who agreed to participate completed a self-administered questionnaire concerning medical conditions, drug use, and sexual practices,

and were physically examined by one of two physicians (J. J. G. or R. J. B.).

To relate these results to a comparable group of homosexual men in an area at high risk of AIDS, a parallel study was conducted simultaneously in the office of a New York City physician with a similar patient population, using the same enrollment procedures, survey instruments, and physical examination by the same physicians.

All subjects donated blood for white blood cell count and differential performed by a single commercial laboratory in each city. The procedure for obtaining, cryopreserving, and analyzing lymphocytes used the following established techniques (13-16). At the initial venipuncture, 30 ml of blood were collected in 1,500 units of preservative-free sodium heparin and immediately mixed with 30 ml of RPMI-1640 media. The blood was maintained at room temperature until separation. Within 24 hours, mononuclear cells were separated by Ficoll-Hypaque gradients and were cryopreserved in a controlled-rate freezer by a single laboratory (13-15). Cells were stored at or below  $-70^{\circ}\text{C}$  until testing. Analysis was performed on a fluorescence-activated cell sorter (FACS-II) in a single laboratory using single-lot reagent materials and identical methods (14-16). Coded samples of thawed and washed lymphocytes were labeled with OKT4, OKT8, and 9.6 monoclonal antibodies as measures of helper T-, suppressor T-, and total T-cell subsets, respectively. The helper and suppressor T-cell counts, shorthand terms indicating functional activities of the OKT4 and OKT8 subsets that are relevant to AIDS, were calculated as the total lymphocyte count times the proportion of helper or suppressor T cells, respectively.

For data analysis, the subjects were stratified by city of residence and, for the Washington, DC, men, by whether they reported homosexual contact in New York City, San Francisco, or Los Angeles (endemic-area partners) during the preceding 29 months

(January 1982). Heterosexual three group variance (1) respectively errors. Multiple testing for lymphocytopenia, and use, and partners, with relationship between the number of significant linear regression statistics. *P* values were c

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(January 1980 to the study date, June 1982). Heterogeneity and trends across the three groups were evaluated by analysis of variance (17) and linear regression (18), respectively, of mean values  $\pm$  standard errors. Multiple linear regression, controlling for lymphocyte count, age, race, presenting illness, frequency of nitrite inhalant use, and total number of homosexual partners, was used to evaluate the relationship between various T-cell phenotypes and the number of endemic-area partners. The significance of variables in least squares linear regression was assessed with *F* statistics. *P* values  $<0.05$  for partial *F* statistics were considered significant (18).

### RESULTS

Approximately 180 men presented at the offices of the two Washington, DC, clinicians during the enrollment period, of whom 163 (90 per cent) agreed to participate. Of these, three were excluded from analysis (one who refused to give blood and two who denied being homosexual), leaving 160 participants. Nineteen per cent of subjects had no clinical illness; an additional 27 per cent presented for follow-up of asymptomatic (hepatitis, hypertension) or treated (gonorrhea) conditions; the remaining 54 per cent had symptomatic outpatient conditions, predominately anal or genital discomfort related to gonorrhea, nongonorrheal venereal diseases, or sexually related abrasions (22 per cent). Approximately 100 men entered the office of the New York City practice, of whom 89 agreed to participate. Four were excluded because they had previously been diagnosed as AIDS cases, were suspected by the clinician to be AIDS cases, or denied being homosexual. This left 85 men enrolled in the comparison group. The presenting clinical conditions in the New York men were similar to those in the Washington men. Twenty-two per cent of the New York men had no clinical illness, 15 per cent had an asymptomatic or resolved condition, and 62 per cent had symptomatic conditions. Anal and genital con-

ditions were the most common sites of symptomatic illness (19 per cent) in the New York men.

The New York men were slightly older (mean age 36 years) than the Washington, DC, men (mean age 33 years) (table 1). Among the Washington subjects, 96 men (60 per cent) reported having at least one sexual contact between January 1980 and June 1982 with men in New York City, San Francisco, or Los Angeles, the three areas designated a priori as high-risk cities. These men are hereafter referred to as the "Washington-exposed" group and are compared with those Washington men who denied such exposure, i.e., the "Washington-unexposed" group.

The Washington-exposed group was intermediate between the unexposed Washington men and the New York men in sexual and drug use patterns (table 1). The unexposed Washington residents had an average of 26 sexual partners and 24 days of nitrite inhalant use in the prior year. The exposed Washington men averaged 42 partners and 42 days of nitrite use. The New York subjects averaged 78 partners and 59 days of nitrite use. The three groups were significantly different at  $p \leq 0.005$  for both partner number and nitrite use. The exposed Washington men had a median of 10 endemic-area homosexual partners, with a mean of  $22.7 \pm 4.9$  partners (range = 1-350).

Total lymphocyte counts were similar in the three groups. On T-cell phenotype analysis, the New York and the Washington-exposed groups had significantly fewer helper T-cells than did the Washington-unexposed group ( $p = 0.04$ ). Figure 1 shows the similarities in helper T-cell distributions between the New York and Washington-exposed groups. Helper T-cell counts were less than 400 cells/mm<sup>3</sup> in 29 per cent of the New York men, 28 per cent of the Washington-exposed men, but only 17 per cent of the Washington-unexposed men. The lower number of helper T-cells was reflected in the lower helper/suppressor ra-

TABLE 1  
Demographic, lifestyle, and immunologic variables in three groups of homosexual men, June 1982

	Study group			p values	
	New York	Washington-exposed	Washington-unexposed	Heterogeneity	Trend
No. of subjects	85	96	64		
Age (years)*	36 ± 0.8	33 ± 0.7	34 ± 0.9	0.006	0.03
White race	91%	80%	78%	0.08	0.04
Symptomatic at accrual	62%	52%	58%	0.51	0.38
No. of homosexual partners†	78 ± 15	42 ± 6	26 ± 6	0.001	0.0004
No. of days nitrite inhalants used†	59 ± 8	42 ± 6	24 ± 7	0.005	0.001
Lymphocyte count (cells/mm <sup>3</sup> )*	2,044 ± 67	1,944 ± 52	2,057 ± 72	0.36	0.98
Helper T-cell count (cells/mm <sup>3</sup> )*	579 ± 32	567 ± 24	672 ± 36	0.04	0.05
Suppressor T-cell count (cells/mm <sup>3</sup> )*	435 ± 28	390 ± 19	389 ± 25	0.29	0.17
Helper:suppressor ratio*	1.64 ± 0.12	1.72 ± 0.11	1.96 ± 0.12	0.16	0.07

\* Mean ± standard error.

† Mean ± standard error for 12 months preceding the study.

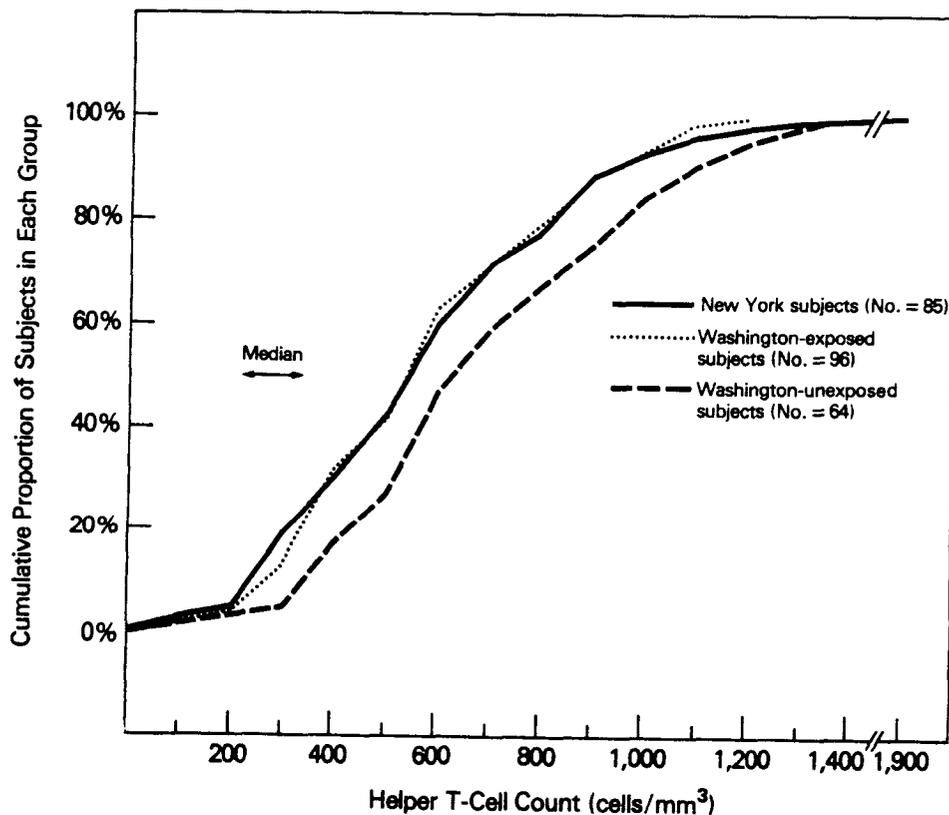


FIGURE 1. Cumulative frequency of helper T-cell counts in homosexual men consulting private physicians, by city of residence and by contact with homosexuals in AIDS-endemic areas. Washington-exposed subjects are distinguished from Washington-unexposed subjects by having had at least one homosexual partner in New York City, San Francisco, or Los Angeles between January 1980 and June 1982.

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TABLE 2

Decreasing helper T-cell counts in Washington, DC, men with frequent and recent endemic-area homosexual partners, June 1982

	No. of subjects	Mean ( $\pm$ standard error) helper T-cell count*	p values	
			Heterogeneity	Trend
No endemic-area partners	64	672 $\pm$ 36	0.05	0.006
1-4 endemic-area partners	32	594 $\pm$ 36		
5-15 endemic-area partners	33	587 $\pm$ 44		
>15 endemic-area partners	31	517 $\pm$ 44		
No endemic-area partners	64	672 $\pm$ 36	0.04	0.01
Endemic-area partners only during 1980-1981	46	579 $\pm$ 31		
Any endemic-area partners during 1982	50	555 $\pm$ 36		

\* Cells/mm<sup>3</sup>.

tios seen in the New York and exposed Washington-area men (table 1). Suppressor T-cell counts were similar in the three groups.

There was a consistent relationship between total number of endemic-area homosexual partners and lower helper T-cell counts. Washington men with no endemic-area partners had a mean helper T-cell count of 672  $\pm$  36 cells/mm<sup>3</sup> (table 2). With from one to four endemic-area partners, mean helper T-cell counts of Washington men decreased to 594  $\pm$  36 cells/mm<sup>3</sup> and further decreased to 517  $\pm$  44 cells/mm<sup>3</sup> with more than 15 endemic-area partners (significance of trend:  $p = 0.006$ ). Twelve of the 31 men (39 per cent) with >15 endemic-area partners had helper T-cell counts <400 cells/mm<sup>3</sup>.

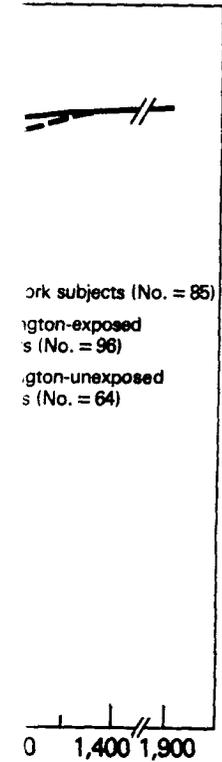
Endemic-area sexual contact that occurred in recent years was associated with decreased helper T-cell counts more closely than if this contact occurred in earlier years. In a comparison by year of contact, the strongest negative correlation between helper T-cell counts of the Washington men and their number of endemic-area homosexual partners was for contact during 1982 ( $R = -53.3$ ,  $p = 0.004$ ). This association was less marked for endemic-area contacts during 1981 ( $R = -31.2$ ,  $p = 0.06$ ) and nonsignificant for contacts during 1980 ( $R = -14.1$ ,  $p = 0.10$ ). Washington

men with endemic-area partners only in the 1980-1981 period had a mean helper T-cell count of 579  $\pm$  31 cells/mm<sup>3</sup> compared with a mean count of 555  $\pm$  36 cells/mm<sup>3</sup> in those who had endemic-area contact in the six months preceding the study (table 2, significance of trend:  $p = 0.01$ ). Seventeen of the 50 men with endemic-area partners during 1982 had helper T-cell counts <400 cells/mm<sup>3</sup>. Most of these men, however, also had many endemic-area partners during 1980-1981. Among the small number of men ( $n = 28$ ) who had endemic-area contacts only in 1980, only in 1981, or only in 1982, no trend could be demonstrated in mean helper T-cell counts (595  $\pm$  90, 579  $\pm$  56, and 588  $\pm$  143 cells/mm<sup>3</sup>, respectively). Thus, sustained endemic-area contact beginning in 1980 through 1982 was most strongly linked to decreased counts, although the interrelationship of year of contact and cumulative number of contacts could not be dissected entirely.

Since the total number of homosexual partners was different in the Washington-exposed and -unexposed groups, a multivariate analysis of the Washington data was done to characterize more precisely endemic-area contact as an independent determinant of low helper T-cell counts (table 3). Linear regressions controlled partner number as well as other variables which might have affected the observed

sexual men, June 1982

p values	
Heterogeneity	Trend
0.006	0.03
0.08	0.04
0.51	0.38
0.001	0.0004
0.005	0.001
0.36	0.98
0.04	0.05
0.29	0.17
0.16	0.07



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TABLE 3  
 Contribution of endemic-area homosexual partners to linear regressions of T-cell phenotypes in Washington, DC, men, June 1982

Dependent variable	Independent variables		R <sup>2</sup>	Statistics for added variable	
	Included	Added		F	p value
Helper T-cell count	Age, race, presenting illness, total homosexual partners,† frequency of nitrite inhalant use,† nonhelper lymphocyte count		0.23		
	Age, race, presenting illness, total homosexual partners,† frequency of nitrite inhalant use,† nonhelper lymphocyte count	Total endemic-area homosexual partners†	0.26	5.49	0.02*
Suppressor T-cell count	Age, race, presenting illness, total homosexual partners,† frequency of nitrite inhalant use,† nonsuppressor lymphocyte count		0.16		
	Age, race, presenting illness, total homosexual partners,† frequency of nitrite inhalant use,† nonsuppressor lymphocyte count	Total endemic-area homosexual partners†	0.16	0.42	0.52
Helper:suppressor ratio	Age, race, presenting illness, total homosexual partners,† frequency of nitrite inhalant use,† total lymphocyte count		0.16		
	Age, race, presenting illness, total homosexual partners,† frequency of nitrite inhalant use,† total lymphocyte count	Total endemic-area homosexual partners†	0.17	1.12	0.29

\*  $p < 0.05$ .

† During the 12 months preceding the study.

associations, including age, race, presenting illness, frequency of nitrite inhalant use, and lymphocyte count. After adjusting for these variables, the number of endemic-area partners significantly improved the fit of the regression with the helper T-cell count, with more endemic-area partners predictive of lower counts (partial  $F = 5.49$ ,  $p = 0.02$ ). When helper:suppressor ratios or suppressor T-cell counts were substituted for helper T-cell counts in the multivariate analysis, no significant association was ob-

served with numbers of endemic-area sexual partners (table 3). The negative relationship between endemic-area partners and helper T-cell counts persisted (partial  $F \geq 4.44$ ,  $p < 0.04$ ) after adjusting for the frequency of receptive anal intercourse and/or insertive fellatio (19), as well as the other variables in table 3.

#### DISCUSSION

In this study, helper T-cell counts were lower among Washington, DC, men having

ll phenotypes in

R <sup>2</sup>	Statistics for added variable	
	F	p value
0.23		
0.26	5.49	0.02*
0.16		
0.16	0.42	0.52
0.16		
0.17	1.12	0.29

homosexual contact in AIDS-endemic areas compared with Washington men without such sexual contact. Washington residents who had homosexual partners in areas at high risk for AIDS had mean helper T-cell counts similar to those observed in homosexual men resident in New York City. There was also a clear relationship between low helper T-cell counts and increasing numbers of endemic-area sexual partners, even after adjusting for the total number of homosexual partners and other potentially confounding variables. We intentionally permitted, if anything, excessive adjustment for variables that may have little relationship to the helper T-cell count, producing statistical analysis that is highly conservative.

Our earlier study showed that Danish homosexual men who had sexual contact with homosexual men in New York City and other high-risk cities of the United States had significantly lower helper: suppressor T-cell ratios than did a comparison group of homosexual men who had not visited the United States (12). This effect was most striking among visitors in the most recent year evaluated, 1981, and was not evident in those who visited the United States before 1980. A similar trend was observed in the current study, although it was clear that this pattern was most marked in persons with sustained endemic area contact over a period of years.

Since our Danish study, several reports have suggested that low helper T-cell counts rather than low helper:suppressor ratios might constitute the critical immunologic disturbance in AIDS patients (8, 20, 21). It was our a priori hypothesis that American homosexual men from an area at low risk of AIDS who had sexual contact with men from high-risk (endemic) areas would have lower helper T-cell counts than men without such exposure. The current findings confirm our earlier observation that homosexual exposure to men in AIDS-endemic areas is associated with an AIDS-type immunologic abnormality of T lymphocytes. It must be emphasized that, in

the two years since this study was performed, life-threatening clinical AIDS has become more frequent in areas previously considered as low-risk, including Washington, DC. There are currently few, if any, large American cities where promiscuous, anonymous homosexual activity can safely be considered free from a risk of AIDS.

It is possible that homosexual men with a low helper T-cell count have a subclinical form of AIDS or that this abnormality is an outcome of exposure to the putative AIDS agent. The risk factors for AIDS in homosexual men, especially those having significantly more homosexual partners than community-matched controls (6, 7), are similar to the risk factors in our study for low helper T-cell counts, suggesting that they may be part of the same clinical problem. It is also possible, however, that low helper T cells result from another cause and that this deficiency denotes a group of individuals who are especially susceptible to developing AIDS. In either case, low helper T-cell counts have not yet been shown to be clinically useful in identifying individuals who will eventually develop AIDS-related illnesses. It is possible that low helper T-cell counts are but one of several outcomes, including AIDS, of exposure to an immunoablative transmissible agent. Ongoing prospective studies of large cohorts of homosexual men should further define the relationship between T-cell phenotypes and AIDS. If a low helper T-cell count is either a subclinical marker of exposure to the AIDS agent or a predisposing factor, elucidating the determinants of T-cell phenotype abnormalities may help to clarify the pathogenesis of AIDS and to facilitate therapeutic intervention before the appearance of life-threatening manifestations of AIDS.

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