

pression was made and appropriate therapy begun. He persisted in his delusions until a test for antibody to human T-lymphotropic virus type III yielded negative results. He then agreed that his symptoms could have been caused by depression. He recovered slowly.

This case and others illustrate how the fear of AIDS can cause symptoms paralleling those of the syndrome. Miller and Green² succinctly described how to counsel patients with fear of AIDS. As physicians we must keep up to date with the explosion of information about AIDS and be prepared to take the time to reassure our patients about their concerns and fears. In this way we may be able to allay the hysteria that has been fuelled by some media coverage of this phenomenon.

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Human T-lymphotropic virus: exposure and prognosis

The separation of risk factors for exposure from cofactors in prognosis is important at all levels of prevention. The recent *CMAJ* articles from the Vancouver Lymphadenopathy-AIDS Study group,¹⁻⁵ and in particular the last article, by Schechter and colleagues,⁵ contribute to our understanding of factors determining exposure

to the so-called human T-lymphotropic virus type III (HTLV-III) and prognosis.

Schechter and colleagues, however, draw conclusions from their data in the last article that in our opinion are not justified on the basis of the data they present. Specifically, in obtaining the initial results from their cohort the authors used a cross-sectional study design, postulating a hypothesis that could be tested only after adequate serial follow-up of their cohort, probably by way of a nested case-control design. The authors conclude that their "data do not support the hypothesis that further immunologic dysfunction arises from repeated exposure to the virus after seroconversion". We urge caution in this interpretation: although it may be correct, the cross-sectional perspective presented in their paper is not appropriate to addressing such a hypothesis.

We offer three explanations for the finding that the number of male sexual partners has no apparent effect on the absolute number of helper T cells when HTLV-III antibody status is taken into account.

- The data derive from an initial cross-sectional view of a study population. Given the very recent advent of a sexually transmissible (slow) viral agent in the Vancouver homosexual study population, prospective follow-up will be essential to validate this observation.

- Most of the lifetime sexual partners could have been encountered before the advent of the virus or could have been uninfected; the impact of infection on T-cell numbers must be observed prospectively.

- The reported lack of a statistically significant change in the mean number of helper T cells with an increase in the number of partners over the previous year may have been due more to a lack of statistical power than to a true lack of increase. However, the suggested trend toward an increase could have been due to any combination of several potential influences: the cut-offs selected for categorization

purposes, the implicit assumptions of a linear relation among the three categories, a temporary T-cell response to recent exposure, sexual practices that are unrelated to the risk of virus transmission, and differing age distributions among the categories (which also may be related to sexual practices). The data controlling such potential confounding variables should be reanalysed in an attempt to support the findings reported. This could be done on an enhanced sample with a logistic regression model so that continuous rather than categorized data could be used and so that a number of variables could be included simultaneously.

Inferences made throughout the last article about effects on persistent generalized lymphadenopathy and acquired immune deficiency syndrome (AIDS) would be more appropriate only after adequate follow-up of the cohort. Schechter and colleagues state that viral infection "may be a cofactor in accelerating immune dysfunction in HTLV-III-infected patients". This statement is supported by the data from both seronegative and seropositive men. However, any suggestion that AIDS-associated clinical manifestations are related to virus exposure cannot be substantiated from the data presented. The study was of cross-sectional design and showed the relation between seroconversion and T-cell counts; it showed no relation with more severe clinical or end-stage manifestations of HTLV-III infection.

Finally, reporting the results of only the first 219 HTLV-III antibody tests and T-cell counts may have introduced some classification bias. The authors do not explain the nature of the 219 subjects, especially relative to the subjects of the preceding reports in the series, whose numbers varied. The demand for testing by the only facility in Canada to have been conducting these tests is known to have been so great that delays of 8 months or more could have occurred. Could the testing of variously reactive sam-

ples (particularly the subset submitted for confirmation testing) have been delayed beyond the data analysis stage? Exclusion of such samples from the data set could have introduced a classification bias, particularly if the degree of reactivity is in any way related to T-cell dysfunction. Comparison of the 219 subjects of the last report with the sample complement for patient characteristics and proportional antibody reactivity would help to address such concerns.

We look forward to the prospective analyses from the Vancouver study.

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[Dr. Schechter and colleagues reply:]

We thank Dr. Soskolne and coworkers for their thoughtful comments on the articles from the Vancouver Lymphadenopathy-AIDS study. In many instances, the cautions they raise

are those that we stressed in our articles, and their correspondence can only help to reinforce these messages.

We confess some uncertainty as to how one goes about properly "addressing" a hypothesis. We are familiar, however, with how one might generate a hypothesis and how one might test it. We did say in our last article that our study was "clearly a hypothesis-generating investigation". Our colleagues know, as we do, that many tens of thousands of Canadians are already infected with HTLV-III, and many more are being infected every day. In hundreds, and perhaps thousands, of these people AIDS is in the process of developing by virtue of mechanisms we do not understand, and medical science has nothing to offer these people to alter this process. It is imperative to generate hypotheses about the pathogenesis of AIDS as expeditiously as possible; these hypotheses can then be tested epidemiologically and by using techniques of immunology and molecular biology. To ignore the extensive amount of data we have been fortunate enough to accumulate would be not only unjustifiable but also a disservice to the many thousands of infected people and to the public.

Hypotheses generated in this type of investigation must be interpreted with caution (as we urged), must be tested prospectively (as we pointed out) and must always be considered in the light of pre-existing evidence. The data we presented concerning viral cofactors, and our interpretation of these data, were entirely consistent with those from many other investigations reviewed in our discussion. Recently Laure and associates¹ have detected hepatitis B virus DNA integrated in the DNA of lymphocytes of AIDS patients, which provides corroborative evidence of a role for hepatitis B as a cofactor. As for our data on the role of repeated exposure, we concluded that they "do not support the hypothesis that further immunologic dysfunction arises

from repeated exposure to the virus after seroconversion". However, we pointed out that our data agree entirely with those of Goedert and collaborators,² the only other investigators to have carried out a similar analysis. In general, data either do or do not support a hypothesis. Since the former was not true, the latter must then hold. Surely this cannot be considered an overinterpretation.

Soskolne and coworkers have kindly supplied three explanations for our finding that the number of male sexual partners has no apparent effect on the absolute number of helper T cells when HTLV-III antibody status is taken into account. The first suggestion is that the AIDS virus has only recently appeared and is "slow"; we may have yet to see its results. However, our data in the second article, which showed significantly decreased helper T-cell counts in seropositive as compared with seronegative men, demonstrate that however recent and slow this virus is, its effects on our study population have already been pronounced.

The second explanation concerns changes in behaviour before and after the advent of the virus that are clearly dealt with in our discussion. We noted no effect on helper T-cell counts in seropositive men with an elevated number of sexual partners in the year preceding enrolment or with any other exposure factor. Moreover, the suggestion by Soskolne and coworkers that most of the lifetime sexual contacts could have occurred before the advent of the virus, or with uninfected people, is not consistent with our observation that an elevated lifetime number of sexual partners was a significant independent risk factor for seropositivity at the time of entry into our study.

As their third explanation Soskolne and coworkers suggest that the reported lack of a statistically significant increase in the mean number of helper T cells may have been due to a lack of statistical power rather than a lack of a true increase. There is, of course, always the possibility