CORRESPONDENCE

Histocompatibility antigens in a population based silicosis series

Sir,—Kreiss *et al* (1989;46:364–9) investigated the problem of genetic predisposition to silicosis by studying the association between the presence of particular HLA antigens and the development of the disease. This report is far from being the first on the topic. About 20 publications by different authors have considered the prevalence of certain HLA antigens in groups of patients with various forms of pneumoconiosis (silicosis, asbestosis, coal miners' pneumoconiosis) and in control groups. The results of these investigations, however, seem to be controversial and not very convincing, as they claim to prove that 15 different HLA antigens indicate a predisposition to pneumoconiosis, but no two works have similar results. The paper by Kreiss *et al* only adds to this controversy as the authors consider two more HLA antigens—B44 and A29—to indicate such a predisposition, as well as the B27 antigen, which has been incriminated by other investigators. We think that such variability in the results is due to at least two principal methodological deficiencies.

Firstly, the groups to be compared were usually matched by sex and age but not by other factors that may also confer significant risks for contracting the disease. In the paper under discussion this problem is not touched upon. If one takes into account that small samples of the working population almost inevitably differ in their prevalence to such risk factors, then disregarding them makes the role of the genotype virtually unproved.

The data of Kreiss *et al* may serve as an example of this. Indeed, according to their table 4, the average period from the beginning of exposure to dust to the establishment of silicosis was 22.6 years in the "B44 positive" group and 19.5 years in the "B44 negative" group; in "B27 positive" and "B27 negative" groups these periods were 25.8 and 20.3 years. Thus one is entitled to suggest that contracting or not contracting the disease was due, not to the presence or absence of one or both of those antigens, but simply to the differences in the duration of exposure to dust.

Secondly, there are sufficient

grounds to assume that it is not separate antigens but the phenotypical complex as a whole that may be responsible for susceptibility to a non-hereditary disease. Therefore we believe that analysis based on the comparison of the frequency of a separate HLA antigen in groups of patients *v* controls is inadequate. A method is needed to allow the estimation of all the complex of antigens characteristic of the individual—non-linear discriminant analysis, for example.

An investigation taking into account both of these points has been carried out and has produced promising results.¹

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1 Polzik EV, Kochneva MJu, Kasantsev VS, Khodyrev VN, Khalfina ME. HLA antigens and silicosis. *Gig Tr Prof Zabol* 1988;8:28–31. (In Russian.)

The authors reply:

Publications regarding associations of HLA antigens with pneumoconiosis is confusing. Our findings, however, extended and refined published data by identifying two antigens that are subsets of antigens previously reported to occur in excess in silicotic patients.

We concur that exposure to silica dust is the most important risk factor for the development of silicosis. Unfortunately, Katsnelson and Polzik misinterpreted our data on latency (period from first exposure to diagnosis) as an index of dust exposure. A surrogate for cumulative dust exposure was given in our table 4 as years in mining. This exposure estimate differed by less than one year in silicotics with and without either B44 or A29 antigens. Neither exposure estimates nor latencies differed in a statistically significant way between

subgroups of silicotics, classified by antigen presence.

We have refined our estimates of exposure for those subjects using cumulative dust index based on dust measurements for a variety of job titles described elsewhere.¹ No statistically significant differences in cumulative dust exposure existed between subgroups of silicotic patients classified by A29, B44, or B27 antigen presence or absence (table). If antigen positive silicotic patients had lower cumulative dust exposure estimates than antigen negative silicotic patients, a greater susceptibility to silicosis would have been suggested. As this was not the case, we can only say that exposure to silica dust, estimated by years in mining or cumulative dust index derived from tenure in specific job titles, was equivalent in the two groups. We have shown, in further analysis of a larger study, that latency requirements appeared to be met and silicosis rates among individuals exposed to dust did not increase with latencies over 20 years.

The suggestion that phenotype may be important is an interesting one. We were not able to confirm a previous suggestion² that the Aw19, B18 phenotype is increased in silicosis, although A29 is a component of Aw19. Unfortunately, our silicotic population was too small to proceed to phenotypic analyses of combinations of antigens in relation to silicosis.

We look forward to obtaining translation of their work.

- 1 Kreiss K, Greenberg LM, Kogut SJH, Lezotte DC, Irvin CG, Cherniack RM. Hard-rock mining exposure affect smokers and nonsmokers differently. *Am Rev Respir Dis* 1989;139:1487–93.
- 2 Koskinen H, Tiilikainen A, Nordman H. Increased prevalence of HLA-Aw19 and of the phenogroup Aw19-B18 in advanced silicosis. *Chest* 1983;83:848–52.

Cumulative dust exposure of Leadville cases of silicosis by HLA antigen presence

Cumulative dust exposure	B44 positive (n = 22)	B44 negative (n = 27)	A29 positive (n = 10)	A29 negative (n = 39)	B27 positive (n = 8)	B27 negative (n = 41)
Mean (mg-months/m ³)	228	197	239	204	224	209
Standard deviation	87	82	96	81	71	87