*Letters to the Editor***Of Genes and Proliferative Retinopathy**

Sir,

Cove et al. in a recent letter to DIABETOLOGIA [1] failed to find an association between HLA antigens and diabetic proliferative retinopathy in 22 patients. Our study of 200 insulin dependent diabetics with proliferative retinopathy and 100 without elicited an association of the antigen B15 with the severe form of eye disease [2]. Our findings apparently have been confirmed by two other groups [3, 4], who found DR4 (which is in linkage disequilibrium with B15) associated with proliferative retinopathy. This makes sampling bias as an explanation of our findings less likely, although it remains a possibility to be ruled out by more independent and large studies. Since the possibility of a genetic contribution to severe diabetic retinopathy is important, albeit currently unpopular, it is crucial that future population studies are carefully conducted. We would suggest that these studies should meet at least the following criteria:

1. Study of a large number (100 or more) of insulin-dependent diabetics patients with both with and without proliferative retinopathy carefully matched for duration of disease and possibly hypertension, the only two well established risk factors for proliferative retinopathy.
2. Preferably, the patients should come from an ethnically homogeneous population. Our diabetic population, for instance, is mostly of Scandinavian extraction.
3. Ascertainment should be carefully documented, e. g. Type 1 versus 2 diabetes, status of kidney function, etc.
4. All patients should have duration of disease of 20 years or longer, since shorter duration is compatible with later development of proliferative retinopathy in the control patients.
5. Absence or presence of proliferative retinopathy should be carefully investigated by an ophthalmologist under ideal conditions of examination.
6. The patients should be studied both as a group and stratified according to age at diagnosis; we found a significant association only for one of the patient subsets [2].

To our knowledge, none of the studies published so far on this subject, including Cove et al.'s report [1], have met all or even most these requirements with exception of our study.

Our 200 patients with proliferative retinopathy were originally chosen only if free of clinically significant nephropathy (normal serum creatinine) since they were being enrolled in the National Diabetes Retinopathy Study. Most of these patients (about 85%) remain free of progressive nephropathy after follow up of several years. More recently we have found that in a large group of insulin dependent diabetic patients with terminal diabetic nephropathy no association exists between HLA and renal disease [5]. This is in agreement with others [6]. Although sampling bias cannot yet be ruled out as an explanation for this surprising finding, it is possible that the HLA association reported by us for proliferative retinopathy [2] pertains only to those hitherto poorly studied insulin-dependent diabetic patients who have proliferative retinopathy but do not progress to terminal nephropathy [5].

These results illustrate the need to be as specific as possible about the patient ascertainment.

Finally, Cove et al. [1] state that we did not find an association between the rare BfF₁ allele and insulin-dependent diabetes. This is not true. In the report they quote [7], we found 4% of insulin-dependent diabetic patients typing for F₁ and more recently 7% (controls 1.9%). We have not searched for associations between the Bf system and proliferative retinopathy.

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