Letters to the Editor

The Development of Type 1 Diabetes in HLA Identical Siblings of Type 1 Diabetic Patients: Associations with Specific HLA Antigens

Dear Sir,

HLA-identical siblings of patients with Type 1 (insulin-dependent) diabetes mellitus are thought to be at greatly increased risk of developing the disease [1]. However, many of these 'high risk' children do not develop Type 1 diabetes. In order to examine in more detail which factors may relate to the development of Type 1 diabetes in HLA-identical siblings, we have determined the frequencies of HLA B7, B8 and B15 in members of nearly 200 families where there is at least one Type 1 diabetic child. All the full siblings in these families have been divided into four groups: (1) a group of Type 1 diabetic index cases, i.e. the diabetic child (the first diagnosed, if more than one has Type 1 diabetes); (2) HLA-identical (i.e. both HLA haplotypes are shared) siblings of the index case who also have Type 1 diabetes; (3) HLA-identical siblings of the index case who do not have Type 1 diabetes; and (4) non-HLA-identical siblings of the index case.

We then compared groups 2 and 3 in terms of age (at time of testing), sex and HLA types as shown in Table 1. The characteristics of the index cases are also shown as a point of reference.

Thus, although B7 is as frequent amongst our index cases (18%) and their HLA-identical non-diabetic siblings (25%) as in the general population (local frequency = 21%), it seems to be associated with protection for secondary cases amongst HLA-identical siblings (0 of 22

diabetic HLA-identical siblings of diabetic subjects possessed B7). Although some, but not all, previous studies have suggested a protective association with B7 [1], we believe this is the first demonstration that the protection is more common in secondary cases within families. This 'protection' is not a result of a fortuitous lack of sharing of other Type 1 diabetes associated antigens as the B7 was shared with B8 in seven of the 17 non-diabetic siblings positive for B7. Since our non-diabetic siblings were of similar age to the diabetic siblings, age differences are unlikely to have biased our results.

We also observed that the diabetic HLA-identical siblings more frequently have B8 or B15 than the HLA-identical non-diabetic siblings. This trend was stronger for girls (60% of the female diabetic siblings are B8+, 60% B15+) than boys (42% B8+, 33% B15+), although overall sex was not associated with secondary cases of Type 1 diabetes.

Therefore, this analysis suggests that any B7-associated protection from Type 1 diabetes may be more manifest in secondary cases, and further helps define the risk to siblings of Type 1 diabetic patients. Thus HLA B8 and B15 appear to be added markers for the development of the disease beyond HLA sharing status with the diabetic child, as it would appear, are autoantibodies to the islet cells which may be associated with a prolonged period of declining B cell function [2].

Yours sincerely,

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Table 1. Age, sex and HLA B7, B8, and B15 frequencies in HLA identical siblings of Type 1 diabetic patients by diabetic status and for index cases

HLA-identical siblings	Age (years)	Males (%)	B7 ^a (%)	B8 ^b (%)	B15 ^b (%)
Non-diabetic siblings (n=69)	16.4 ± 0.8	49	25	26	19
Diabetic siblings (n=22)	16.2 ± 1.5	54	0	50	46
Index cases (n=66)	15.1 ± 0.9	47	18	35	29

Age expressed as mean ± SEM. ^aNon-diabetic versus diabetic siblings, Chi-square ($p < 0.01$) (1 degree freedom); ^bNon-diabetic versus diabetic siblings, Chi-square ($p < 0.05$) (1 degree freedom). N.B. The above significance levels are not corrected for multiple comparisons, the results of which gives $p < 0.05$ for B7 and B15 (2 degrees freedom)

References

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- Gorsuch AN, Spencer KM, Lister J, McNally JM, Dean BM, Bottazzo GF, Cudworth AG (1981) Evidence for a long prediabetic period in Type 1 (insulin-dependent) diabetes mellitus. *Lancet* 2: 1363–1365

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Insulin Degradation

Dear Sir

I refer to a paper which appeared in *Diabetologia* (1981) 21: 464–469 by C. A. Taylor and P. T. Varandani, entitled Insulin degradation. XXVIII. Immunocytochemical localization of glutathione-insulin transhydrogenase in the pancreas, kidney and liver of lean and obese (ob/ob) mice.

The particular enzyme dealt with by the authors, namely, glutathione-insulin transhydrogenase has been shown by H. Jering and myself (*Endocrinology* (1979) 104: 1639) to be of negligible importance in insulin degradation in liver homogenates at physiologically meaningful concentrations. Taylor and Varandani have chosen not to cite that work stating in the Introduction: 'This reaction, i.e. the splitting of the hormone by glutathione-insulin transhydrogenase, is the first step in the sequential pathway of insulin degradation, both at physiol-

ogical and pharmacological concentrations of insulin'. They then cite only their earlier references on the subject without acknowledging our own later contribution showing that such claims are not in accord with definitive experimentation.

Yours sincerely

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