EBV. For other persons, a different degree of transformation, involving further cell-generic alterations, may be needed to induce neoplasia. Since such cell changes may be rare and may confer selective advantages in growth, the resulting tumors would be more likely to be monoclonal in origin. Admittedly, such tumors are made of cells that have a greater fundamental alteration than that imposed by the EBV genome in infectious mononucleosis, but as Nowell pointed out,1 there are different degrees of malignant change.

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HLA FACTORS IN NON-INSULIN-DEPENDENT DIABETES MELLITUS

To the Editor: It has been found that HLA-B15, B8, and B18 antigens are associated with a gene (or genes) for susceptibility to insulin-dependent diabetes mellitus (IDDM).1 This association is secondary to a stronger association with DR3 (or DRW8, in Japanese people) and DR4 (ref. 2). The BFI allele is appreciably increased in the Spanish population with IDDM, with a relative risk similar to that of DR3 (ref. 2 and unpublished data).

Non-insulin-dependent diabetes mellitus (NIDDM) has not been found to be associated with HLA factors, except perhaps in a report on the Japanese2 and also in a preliminary report suggesting that a special type of NIDDM (maturity-onset diabetes in the young) may be linked to HLA factors.3 We typed 90 patients, 36 with NIDDM and 62 with IDDM, for HLA-A, B, C, 4a, and 4b antigens using our routine 120 serums and a standard technique for microlymphocytotoxicity,4 and also for Bf alleles, using an electroneumunofixation technique.5 Our results are shown in Table 1, in which patients with IDDM and NIDDM are compared with the normal population. B18 is increased significantly in IDDM but not in NIDDM. The frequencies of the BFI allele and B18-BFI haplotype were both increased in IDDM (Rodriguez de Córdoba S, Boitello A, Arnaiz-Villena A. Unpublished data); these values were not increased in NIDDM. The value for the B8-Bnon-BFI haplotype was significantly increased in NIDDM, in contrast to the value in IDDM.

That the relatively rare BFI allele is more frequent in the Spanish population than in others (Rodriguez de Córdoba S, Boitello A, Arnaiz-Villena A. Unpublished data), and that it is in strong linkage disequilibrium with B18 may render our population a good model for studying this haplotype in relation to diabetes, and so overcome the relatively poor Bf polymorphism. In other populations a frequent and also diabetic (IDDM) haplotype is B8-BIS-DR3, BIS being a marker for many other HLA haplotypes; in the Spanish population B18-BFI-DR3 is the equivalent, as both a frequent and diabetic (IDDM) haplotype, and BFI is a marker for this particular haplotype almost exclusively (Rodriguez de Córdoba S, Boitello A, Arnaiz-Villena A. Unpublished data).

Our findings suggest that NIDDM factors linked to the HLA-B18-non-BFI haplotype may exist in our population. Several closely-linked diabetic factors (or genes) could exist within the HLA complex and all of them could be necessary for development of an IDDM form. On the other hand, absence of one or several HLA diabetic factors (for example, those linked to BFI) may lead to the development of an NIDDM form. Also, these results may strongly indicate a predominantly genetic character in NIDDM.6

More studies are necessary in our own population and others before firm conclusions can be established (our work was supported in part by Fundación Cultural de la Caja de Ahorros, Madrid).

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Table 1. Frequencies of B18 and BFI allele in Sample Groups from Normal and Diabetic Populations in Spain.

<table>
<thead>
<tr>
<th>Population (Sample Size)</th>
<th>Frequency (%) of HLA Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>B18</td>
<td>B18-BFI</td>
</tr>
<tr>
<td>Normal (360)</td>
<td>15.7</td>
</tr>
<tr>
<td>Diabetic</td>
<td>Insulin-Dependent (62)</td>
</tr>
<tr>
<td>Non-insulin-dependent (36)</td>
<td>25.0</td>
</tr>
</tbody>
</table>
| *P<0.001, in comparison with normal population.
| **P=0.05, in comparison with normal population.
| ***P=0.02, in comparison with normal population.

LEVAMISOLE IN INSULIN-DEPENDENT DIABETES MELLITUS

To the Editor: If the hypothesis that human insulin-dependent diabetes mellitus (IDDM) may, in some instances, be an autoimmune disorder is correct,2 it is reasonable to assume that suppression of the immune response should have a favorable effect on the course of the disorder in some patients.

To test this hypothesis we recently studied the effect of levamisole (an agent used successfully in other autoimmune disorders, including rheumatoid arthritis1) on T-cell function in three young adults with IDDM of three months' duration or less. Levamisole, at the doses used in this study, has been shown to be a stimulator of suppressor T cells;2 it was chosen over immunosuppressive agents such as glucocorticoids, cyclophosphamide, and azathioprine because of concern that the toxicity of these other agents could result in greater damage than the diabetes itself. The patients (one man 23 years of age and two women 23 and 34 years of age) were within 10 per cent of ideal body weight and had presented with ketocidosis or had rapid manifestations of ketoacidosis in the absence of insulin.

One patient also had autoimmune thyroid disease (goitrous hypothyroidism, anti-microsomal-antibody positive) but was euthyroid when taking replacement levothyroxine. Doses and duration of treatment were as follows: the man took 150 mg twice a week for two weeks; one woman took 100 mg once a week for 16 weeks; and the other woman took 100 mg once a week for eight weeks and then 150 mg weekly for 16 weeks. Glucose, glucagon, and C-peptide responses during standard 50-g oral glucose-tolerance tests were evaluated in each month of the trial. No noteworthy improvement in