The appearance of abnormal neurological signs in children with leukaemia in haematological remission may be due to the post-irradiation syndrome[9] or methotrexate toxicity[10] in the early months of treatment and meningeal leukaemia, haemorrhage, or infection of the central nervous system at any stage. The histological appearance of the brain in our case of measles encephalopathy resembled neither the appearances in acute measles encephalitis nor those in SSPE. There was a surprising absence of perivascular inflammatory cells, and the predominating features were focal neuronal loss, spongy changes, and gliosis, with many nuclear and cytoplasmic inclusion bodies in some areas and none in others. Similar appearances have been described previously.[1] Hence possibly some of the cases of encephalopathy that have been recorded in children with leukaemia may have resulted from measles infection without obvious inclusion bodies being seen in the brains of those who reached necropsy.[10 13] Lesions produced in the brains of monkeys by intracerebral and intranasal inoculation with different viruses can be modified by concurrent administration of cyclophosphamide[14]; animals given immunosuppressive therapy showed not only increased invasiveness of the viruses but also the replacement of the expected cerebral inflammatory changes by a degenerative process causing neuronal necrosis and spongy degeneration.

Conclusions and recommendations

In children on immunosuppressive treatment primary measles infection may present with very atypical clinical pictures. The incubation period may be prolonged, there may be no rash or a rash that lasts for weeks, and the illness may be mild or very severe. Commonly used doses of pooled immunoglobulin may fail to protect against measles infection and may further confuse the diagnosis by modifying the illness. Two doses of 1500 mg at an interval of 48 hours are recommended by the Public Health Laboratory Service for children over three years of age on immunosuppressive treatment.

In the giant-cell pneumonia resulting from measles infection the virus may persist in nasophrayngeal secretions for three weeks or more. In either giant-cell pneumonia or encephalpathy after measles infection antibody formation in the blood is unpredictable, and may be low or absent even when measles virus is present in profusion in the lungs or brain. Nevertheless, measles antibodies should be sought when leukaemia is first diagnosed and repeatedly in serum or cerebrospinal fluid in any unusual respiratory infection or encephalopathy during the course of cytotoxic treatment.

The histological picture resulting from invasion of the brain by measles virus resembles neither the acute inflammatory appearances seen in post-measles encephalitis nor those of SSPE. An appropriate term might be "immunosuppressive measles encephalopathy."

Repeated large doses of pooled immunoglobulin may have some beneficial effect in measles giant-cell pneumonia, but since no treatment is effective in measles encephalopathy every effort should be made to prevent measles infection. Non-immune siblings should be immunised and segregated from the patient for a fortnight.

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HLA-linked genes and islet-cell antibodies in diabetes mellitus

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Summary

In a random series of 139 insulin-dependent diabetics aged 30 or under at the onset of disease islet-cell antibody (ICA) was detected in 33 cases (24%). In 27 patients who had had diabetes for less than one year 16 (59%) had ICA. Only one out of 51 patients with maturity onset diabetes who were not dependent on insulin were positive for ICA. Four out of 19 patients with late onset insulin-dependent diabetes had ICA.

There was no association between the presence of ICA and any particular HLA phenotype. Within families containing two or more HLA haploidentical siblings with juvenile onset diabetes ICA was a variable finding both in its occurrence and in its relation to the duration of disease.

A possible mode of action for the HLA-linked gene may be to permit a rapid immunological destructive process, possibly associated with viral infection.

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Introduction

Recent studies have produced evidence that susceptibility to juvenile onset or insulin-dependent diabetes is associated with particular HLA phenotypes,[1-3] there being a twofold to three-

fold greater risk of developing this illness in people who are HLA-B8 or BW 15 positive. Viral infection may play an important part in causing this type of diabetes.[4] Antibodies reacting with islet cells have recently been shown[5,6] and seem to be associated particularly with recent onset juvenile diabetes.[7] Thus an inter-relationship between HLA-linked genes and viral agents which may trigger an immunological process that destroys islet cells is an attractive hypothesis.

Our aim was to investigate the prevalence of islet-cell antibodies (ICA) in a random series of patients with insulin-dependent and insulin-independent diabetes of variable duration and to assess whether there was any correlation with HLA phenotypes. Several families with HLA haploidentical affected siblings were also investigated.

Patients and methods

Random diabetic patients—Serum samples from 209 diabetic patients were tested for ICA and thyroid microsomal and gastric parietal cell antibodies. These patients, who had previously been HLA typed,[8] included: (*a*) 139 unrelated insulin-dependent diabetics with an age of onset of 30 years or less (juvenile onset); 27 had developed diabetes within the preceding 12 months and the duration of disease ranged up to 46 years; (*b*) 51 unrelated subjects with non-insulin-dependent diabetes with an age of onset between 33 and 79 years (maturity onset); in 12 diabetes had been diagnosed within one year of the study; and (*c*) 19 patients with an age of onset of diabetes ranging from 31 to 70 years, all of whom were insulin dependent.

Family studies—One hundred and one subjects from 25 families were investigated. In 23 families there were two or more siblings with juvenile onset diabetes, and in two families there was a parent and one offspring with this condition. Among the 101 subjects were two patients with maturity onset diabetes and 56 with juvenile onset diabetes, 18 of whom were included in the random juvenile onset series. The 23 families included 15 in which the affected siblings had both HLA chromosomes identical, and eight in which affected siblings possessed one HLA chromosome in common.

Immunofluorescent methods—ICA and thyroid and gastric antibodies were detected as described.[9] The titres of positive sera were measured in doubling dilutions starting at 1/5. Sheep polyvalent antihuman immunoglobulin (Wellcome Laboratories) was the second layer in all tests, which were performed using coded sera.

Results

ISLET-CELL ANTIBODIES

The prevalence of ICA in relation to the duration of diabetes for the three categories of diabetic subjects is shown in table I. Overall ICA occurred in 38 out of 209 patients (18%). Thirty-three of these were among the 139 insulin-dependent patients with juvenile onset diabetes (24%). In this latter group were 27 patients who had had diabetes for less than one year, 16 of whom were ICA positive (59%). In the second year of duration seven out of 13 (54%) were positive, and by the third year only two out of 11 (18%) were positive. ICA occurred in three patients who had had diabetes for 29, 33, and 37 years; all had thyroid microsomal antibodies, although none had clinical evidence of thyroid disease. Only one of the 51 patients with maturity onset diabetes had ICA, in low titre. Four of the late onset insulin-dependent group were ICA positive.

The results in the 139 diabetics with juvenile onset disease were analysed in relation to HLA types (table II). ICA occurred in 24 out of 86 patients who were HLA-B8 or BW 15 positive compared with nine out of 53 patients of other HLA types. These differences were not significant ($\chi^2 = 1{\cdot}6$; $P > 0{\cdot}1$). Similarly, in patients who had had diabetes for less than one year, 12 out of 18 patients positive for HLA-B8 or BW 15, or both, had ICA compared with four out of nine patients without HLA-B8 or BW 15.

TABLE II—*Prevalence of ICA in 139 patients with juvenile onset diabetes showing relation with HLA phenotypes*

HLA	ICA		Total
	Present	Not detected	
B8	16 (26%)	46	62
BW 15	6 (35%)	11	17
B8 and BW 15	2 (29%)	5	7
Non B8 or BW 15	9 (17%)	44	53

Among the 23 families containing two or more diabetic siblings the presence of ICA was variable in relation to the duration of diabetes. In four families only the sibling with the more recent onset of diabetes was ICA positive, but in four other families only the sibling with the longer duration of illness had ICA (table III). In a further pair of siblings in whom diabetes developed simultaneously two years before testing one had ICA while the other did not. All the affected siblings were ICA positive in two other families, but in one of these there was a considerable difference in the ICA titres between two siblings who developed diabetes simultaneously one week before testing (see figure). Sibling 2 in this family had abnormal glucose tolerance but no detectable ICA. In 12 other families affected siblings had no ICA. In two families with an ICA-positive diabetic parent the single diabetic siblings with shorter durations of diabetes had no ICA. In the 25 families 43 non-diabetic parents or siblings of diabetics were tested; none had ICA.

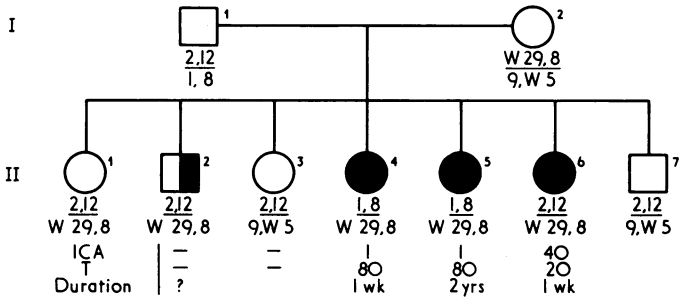
TABLE III—*Duration of diabetes, HLA genotypes, and ICA titres in eight pairs of siblings with at least one identical HLA chromosome. ICA was detected in the sibling with a shorter duration of diabetes in four families (group A) and in the sibling with a longer duration of diabetes in four other families (group B)*

Pair No	Duration of diabetes (years)		HLA genotypes		ICA titres
	ICA-positive sibling	ICA-negative sibling	ICA-positive sibling	ICA-negative sibling	
			Group A		
1	2 months	2	9, 5 / 2, W 15	9, 5 / 2, W 15	20
2	1	11	28, 22 / 9, W 18	28, 22 / 9, W 18	5
3	1	31	W 29, 12 / 1, 8	2, W 15 / 1, 8	40
4	2	14	2, 12 / 2, 12	2, 12 / 2, 12	1
			Group B		
5	7 months	4 months	3, 8 / 1, 8	3, 8 / 1, 8	5
6	10	3	9, 14 / 2, 7	9, 14 / 2, 7	5
7	24	3	28, 18 / –, W 10	28, 18 / –, W 10	40
8	25	4	1, 17 / 3, 7	1, 17 / 1, 8	1

TABLE I—*Prevalence of ICA in relation to duration of diabetes in 139 patients with juvenile onset diabetes (JOD), 51 with maturity onset diabetes (MOD), and 19 with late onset insulin-dependent diabetes (MOD-ID)**

Duration (years):	<1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	37	40	46
No of patients with JOD	27	13	11	5	5	5	2	5	3	2	5	7	1	2	5	6	3	2	1		2	1	2	2		3			2	1		1		1	1	1	1	1
No with ICA	16	7	2					2	1						2															1				1		1			
No of patients with MOD	12	1	1	3	3	1	1	1	1	1	2	1	2		3	3						1																
No with ICA															1																								
No of patients with MOD-ID	2	1		1	1	2		1	1		2	1	1	1	2	1					1												1					
No with ICA				1				1	1						1																								

*The duration of diabetes was uncertain in 10 patients with JOD and 14 with MOD.



HLA genotypes, ICA titres, and thyroid microsomal antibody titres (T) in family containing siblings with juvenile onset diabetes.
● = Female siblings with diabetes. ◨ = Male sibling with abnormal glucose tolerance test result.

THYROID AND GASTRIC ANTIBODIES

Thyroid microsomal or gastric parietal cell antibodies, or both, were detected in 45 of the 139 patients with juvenile onset diabetes (32%); these antibodies occurred in 17 of the 33 ICA-positive individuals in this group. Thyroid or gastric antibodies, or both, occurred in 15 of the 51 patients with maturity onset diabetes (29%) and in seven of the 19 insulin-dependent subjects with diabetes of late onset (37%).

When the three groups of diabetic patients were considered together, thyrogastric antibodies occurred in 43 out of 119 patients who had HLA-B8 or BW 15, or both, compared with 24 out of 90 subjects with other HLA types. These differences were not significant ($\chi^2 = 1{\cdot}7$; $P > 0{\cdot}1$). There was no association between the presence of thyroid and gastric antibodies and any other particular HLA phenotype.

Discussion

The high prevalence of ICA in recently diagnosed insulin-dependent diabetics is again confirmed by the present study. ICA probably appears in most patients during the initial stages of development of this type of diabetes but decreases thereafter. In a few cases, however, antibodies may be detected as long as 37 years after the onset of symptoms.

No data have been reported concerning ICA in a random series of patients not dependent on insulin. In our 51 such cases, which included several recently diagnosed, only one positive low-titre result was found, and it therefore seems unlikely that humoral autoimmunity to islet cells plays any part in the pathogenesis of maturity onset diabetes.

A major factor determining susceptibility to juvenile diabetes is the presence of a diabetogenic gene or genes at a locus closely linked to the HLA loci.[8] Data on the diabetic population suggest that this gene occurs about twice as often on HLA chromosomes with alleles for HLA-B8 and BW 15 as on other homologous chromosomes (linkage disequilibrium). The mode of action of such genes remains speculative, but interactions with receptors for viruses and other pathogens and association with immune response genes have been suggested.[10] Possibly the effect of the gene or genes is mediated by ICA. If there is only one such gene then all juvenile diabetics would be expected to have ICA, and no association with a particular HLA phenotype would be found. Conceivably at an early stage of their disease process most, if not all, insulin-dependent diabetics do have circulating ICA. Similarly, if ICA is the usual consequence of islet-cell damage of any cause no association between ICA and any particular HLA phenotype would occur. We found no such association, which is consistent with either hypothesis. The possibility that a gene associated with a particular HLA allele might be responsible for the prolonged persistence of ICA in a subgroup of diabetics is unlikely since there was no significant correlation between demonstrable ICA and HLA phenotypes in either recent or long-standing cases.

With regard to the family studies it has been shown that when there are two siblings with juvenile onset diabetes in a family the development of diabetes is dependent on inheritance of at least one identical HLA chromosome.[8] If the mechanism of action of the diabetogenic gene on this chromosome implicates ICA production the affected siblings would be expected to show similar ICA results. Our study shows little evidence of such uniformity. In four of the families, however, ICA may have disappeared in the siblings with the longer duration of diabetes, and the observed variation in ICA in siblings may simply reflect differing rates of disease activity and antibody disappearance.

It remains speculative whether the genetic susceptibility to juvenile onset diabetes depends on immunological mechanisms including ICA production. But a possible mode of action for the HLA-linked gene may be to permit a rapid immunological destructive process, by analogy with lymphocytic choriomeningitis virus encephalitis in mice, in which the disease probably depends on the development of an immune response to the virus and is determined by a gene in the histocompatibility (H2) region.[11] Further studies of the possible cytotoxic role of ICA and of cellular immune mechanisms that may cause islet-cell damage may throw light on this important problem.

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