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Letters to the Editor

Are HLA Types or Bf Alleles Markers for Diabetic Retinopathy?

Dear Sir,

The importance of HLA type as a risk factor for the development of diabetic retinopathy remains unclear because of the relatively small numbers of patients studied in each of the recent communications [1, 2, 3, 4]. We have HLA typed a larger series of patients with and without proliferative retinopathy than has hitherto been reported and present this data and the combined results of published reports. The alleles of properdin factor B (Bf) have also been determined in our patients. Previous reports have not considered Bf alleles in relation to retinopathy.

The patients were routinely attending the diabetic clinics at Dudley Road or the General Hospitals, Birmingham. All patients were European caucasians who had juvenile onset (< age 30 years), insulin dependent diabetes for at least 10 years. Two groups of patients were selected: group A – 26 patients who had no retinopathy or only minimal background retinopathy (Hammersmith grade A haemorrhages and exudates) intact vibration sense and ankle reflexes, less than 2 + proteinuria, non-ischaemic feet and no other major complications of diabetes. Group B – 22 patients who had active or treated proliferative retinopathy with or without other diabetic complications. All other patients were excluded. Groups A and B had similar mean ages (40 ± 13 years and 45 ± 7 years respectively) and durations of diabetes (23 ± 8 years and 25 ± 7 years respectively). The number of patients who were HLA B8, B15 and B18 were compared with a control group of 380 West Midland European caucasions (Table 1).

In agreement with previous studies [5, 6] there was a significant increase in the overall frequency of HLA B8 ($p = < 0.01$) and B15 ($p = < 0.05$) and a decreased frequency of B7 ($p = < 0.001$) compared with controls. In the present series there were no significant differences between the frequency of any HLA type in groups A and B. As with other reports, true differences may not be apparent because of the relatively small number of patients studied. The results have therefore been combined with the data from four other reports of HLA typing of patients selected on similar criteria (Table 1). Combining data from several centres in Western Europe has the disadvantage of obscuring local variations but would be expected to show up a strong widespread association between an HLA type and proliferative retinopathy if one existed. Overall the diabetics had an increased frequency of B8 ($p = < 0.001$) B15 ($p = < 0.001$) and B18 ($p = < 0.001$) and a decreased frequency of B7 ($p = < 0.001$) compared with the combined control population. Three out of four series reported a higher frequency of B8 in patients with severe retinopathy than in those who had minor complications. However, in the combined data no significant differences were detected between the 89 patients who had no retinipathy or minimal background retinopathy and the 128 who had proliferative changes. These results do not confirm the reports of an increased frequency of HLA B8 [1] and B15 [12] in patients with proliferative retinopathy.

In the present series the alleles of properdin factor B occurred with similar gene frequencies in the diabetics and the [200] controls (F1 = 0.03 and 0.03, F = 0.13 and 0.19, S = 0.80 and 0.77, S1 = 0.02 and 0.01 respectively). As would be expected BfF1 occurred in HLA B18 positive individuals. No significant differ-

Table 1

	Minimal complications					Proliferative retinopathy					Normal controls				
	n	B7	B8	B15	B18	n	B7	B8	B15	B18	n	B7	B8	B15	B18
Larkins et al. [1]	14		6			16		12			586		158		
Deckert et al. [2]	21	2	9	10	6	15	1	3	10	2	1967	527	466	352	140
Standl et al. [3]	28		8	9	7	12		5	2	1					
Jervell [4] et al.[a]							63	14	29	22	12	109		46	38
											1628	488	407	326	81
Cove et al. (present series)	26	2	10	8	3	22	3	14	5	0	380	125	114	41	20
Overall %		9	37	36	21		18	49	35	13		28	26	19	6

	B7	B8	B15	B18
All diabetics %	15	44	35	17

The numbers (n) of patients and controls studied and the number of subjects with HLA types B7, B8, B15 and B18 reported by each author

[a] All patients were insulin dependent diabetics with visual impairment and severe renal failure

ences were detected between groups A and B. Three previous reports describe an association between BfF1 and insulin dependent diabetes [7, 8, 9] but two others found no association [10, 11]. The discrepancies may be due to geographical variations or to differences in the selection of patients studied [9].

The available data provide no evidence that HLA type or Bf allele are genetic markers for proliferative retinopathy.

D. H. Cove and J. M. Walker
Dudley Road Hospital
Birmingham B18 7QH

P. Mackintosh
The Blood Transfusion Service
Vincent Drive
Birmingham 15

L. Wells
Department of Clinical Genetics
Birmingham Maternity Hospital
Birmingham B15 2TH

A. D. Wright
The General Hospital
Steelhouse Lane
Birmingham B4 6NH

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D. H. Cove
Senior Medical Registrar
Dudley Road Hospital
Dudley Road
Birmingham B18 7QH
England

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Rapid Fluctuations in Glycosylated Haemoglobin Concentration as Related to Acute Changes in Blood Glucose

Sir,

In a recent article [1] Dr. Bolli and co-workers reported that HbAI levels decreased significantly after only 3 days of treatment with the "artificial endocrine pancreas" (Biostator). This and other in vivo and in vitro observations [2–5] raise questions concerning the concept, based on previous clinical studies [6–8], that HbA_{Ic} degradation takes place slowly (on the order of weeks or months) and that HbA_{Ic} levels therefore are clinically useful to assess long-term blood glucose control.

It is of note that the original methods of HbA_{Ic} determination, on which this concept was based, included prolonged dialysis of the haemolysates, whereas many of the more recent modifications of this technique, including high pressure liquid chromatography, use nondialysed samples, and the microcolumn commercial methods, which include a haemolysing agent, use whole blood [9–11]. Although it is unclear whether all the clinical studies indicating rapid fluctuations in glycohaemoglobins utilized nondialysed samples for HbA_{Ic} analysis, it would appear that most did. It is well known that an unstable, dialysable, Schiffbase form of HbA_{Ic} may be formed as an intermediate for the stable ketoamine end-product [12]. It is therefore likely that the dialysis step is important to minimise the effect of acute changes in blood glucose on the level of glycohaemoglobin.

In order to evaluate this possibility, one of us (J. D.) determined blood glucose and HbA_{Ic} concentrations in a group of 24 ambulatory diabetic children, fasting and 6 hours postprandially, using three methods for HbAI determinations: the macrocolumn method of Schnek and Schroeder, as modified by Schwartz et al.