Letters to the Editor

HLA and Maturity Onset Diabetes of the Young

Dear Sir,
HLA factors have been demonstrated in Type 1 (insulin-dependent) diabetic patients [1]. Also, HLA has been involved in Type 2 (non-insulin-dependent) diabetic inheritance [2], especially in patients with recorded anti-islet cell antibodies [3]. A weak linkage has also been described between a putative diabetes gene causing maturity-onset diabetes of the young (MODY) to HLA [4]. Two MODY families were studied (Table 1). All family members were subjected to a glucose tolerance test as described by the National Diabetes Data Group [5]. Patients were typed for HLA-A,B,C,Bw4,Bw6 antigens using our routine 120 sera and a standard microlymphocytotoxicity technique [6]. Figure 1 shows that in family 1, siblings 3 and 4 are HLA identical, but MODY only has one phenotype. Siblings 5 and 6 show a similar situation. In family 2, the three siblings are HLA identical and only siblings 3 and 5 are affected by MODY.

It is clear that MODY does not segregate with HLA haplotypes in our two families. Our results contrast with those found by others [4] and may be due to clinical and genetic heterogeneity in MODY, but are concordant with those reported by Nelson [7].

Table 1. Plasma glucose and insulin levels (fasting and at 2 h after a glucose tolerance test) in the two families studied

	Age (years)	Fasting plasma glucose (mmol/l)	Plasma glucose after 2 h (mmol/l)	Fasting plasma insulin (mU/l)	Plasma insulin after 2 h (mU/l)
Family 1: members					
1	50	7.0	9.1	45	62
2	48	6.3	7.2	37	188
3	15	7.2	7.8	25	109
4	20	4.8	6.0	17	71
5	22	6.7	7.8	17	68
6	24	4.8	4.9	21.5	84
Family 2: members					
1	46	5.5	6.8	30	58
2	40	5.8	11.3	19	60
3	22	5.1	6.8	23	59
4	18	5.8	7.7	26	72
5	9	5.5	10.6	23	112

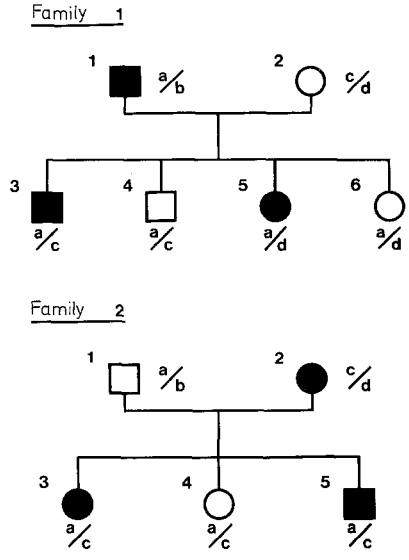

Fig. 1. HLA haplotypes in family 1: *a*=A11, Bw35, Cw4, Bw6. *b*=A3, B8, Bw6. *c*=A1, B17, Bw4. *d*=A3, B7, Bw6. HLA haplotypes in family 2: *a*=Aw30, Bw35, Cw4, Bw6. *b*=A1, B14, Bw6. *c*=Aw23, Bw35, Cw4, Bw6. *d*=Aw23, Bw39, Bw6

Yours sincerely,
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Glucose Intolerance in Pregnancy

Dear Sir,
Beard and Hoet in their review article 'Is Gestational Diabetes a Clinical Entity?' (*Diabetologia* (1982) 23: 307–313) express concern that the World Health Authority Expert Authority (sic; presumably the World Health Organisation Expert Committee on Diabetes Mellitus, 2nd Report [1]) recommends "that diagnostic criteria for diabetes should be the same in all adults, pregnant or not" and that it appears "to reject all the evidence" of possible adverse effects upon the fetus of "even a minor disturbance of carbohydrate tolerance". Leaving aside the dubious nature of that evidence, they would, I hope, have discovered their concern unfounded had they read the document in question with a little more care than they quoted its provenance. What the 2nd Report actually recommended was that a standard procedure be adopted for the conduct of the oral glucose tolerance test and for

the classification of its results. In brief, it suggested restricting the diagnosis diabetes mellitus to degrees of glucose intolerance clearly associated with increased risk of later development of the specific complications of diabetes. For lesser degrees of glucose intolerance, previously called diabetes by some and normal by others, it proposed the new class of 'impaired glucose tolerance'. This 'at-risk' category called for case-by-case decisions on action, rather than unjustifiably including it as unequivocal diabetes or ignoring it as normal. The Expert Committee recommended, in terms, that one of the situations in which impaired glucose tolerance has special significance is pregnancy and the "during pregnancy, the treatment for impaired glucose tolerance should be the same as for diabetes" (p 12), hardly the sort of neglect that Beard and Hoet imply.

It is indicative of the present uncertainties about implications, and confusions about treatment, of lesser degrees of glucose intolerance in pregnancy that the recommendations of the Expert Committee should have been applauded by Jarrett [2] for applying the new diagnostic criteria in the pregnant state and attacked by Beard and Hoet for the same reason. Both partially misrepresent the Committee's views on glycaemic criteria in pregnancy which emerged after some debate, not least because the US National Diabetes Data Group [3] with which most of its other views were in close harmony, had decided to retain the O'Sullivan definition of 'gestational diabetes' [4]. This is based upon an initial screening blood glucose 1 h after 50 g glucose by mouth and then meeting certain glycaemic criteria in an oral glucose tolerance test followed for 3 h, after a 100 g oral glucose load in those screening positive. So defined, 'gestational diabetes' runs from comparatively trivial, probably totally benign, degrees of glucose intolerance into unequivocally diabetic hyperglycaemia. While there is perhaps some strength in the argument that since this method has been recommended in the past it should be used in the future, in practical fact most centres (including many in the US) do little or no systematic glycaemic screening in pregnancy. When a glucose tolerance test is done in pregnancy it is usually the local procedure interpreted as 'normal' or 'abnormal' on the basis of local, often unstandardised, criteria. The new WHO recommendations for the conduct and interpretation of the oral glucose tolerance test have met with wide acceptance and have been introduced into routine clinical use in many centres. Their use in the pregnant state would bring the "measure of agreement" that Beard and Hoet advocate, would include as 'gestational impaired glucose tolerance' all those women with lesser degrees of glucose intolerance for whom they express concern and would facilitate a more systematic and rational analysis of the extent to which that concern is truly justified.

The adverse effect of degrees of glycaemic abnormality qualifying for the WHO designation of diabetes mellitus upon fetal development and neonatal survival is not questioned. The evidence that lesser degrees of glucose intolerance per se, *independent of maternal obesity, advanced maternal age, history of obstetric difficulties or fetal loss,* represent a threat to the fetus is much less compelling.

It is not established that the cost of diagnosing the lesser degrees of glucose intolerance in the pregnant woman in anxiety, physical distress, dietetic disruption and risks of treatment, and to the medical services in use of resources is justified by any reduction in fetal morbidity or mortality. The whole question is, understandably, charged with emotion and it is difficult to see the truth for the prejudices. Another cool look at the problem with a lot more carefully collected data is required. If the WHO recommendations (however misunderstood) have brought that nearer and suggested an agreed framework within which new enquiry could be built then they have served some purpose.

Yours faithfully,
H. Keen

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Applying the Correlation Between Glycosylated Haemoglobin and Plasma Glucose Levels

Dear Sir,
The great practical value of glycosylated haemoglobin (HbA_1) measurement, as an indicator of the integrated plasma glucose values of the preceding 4–6 weeks, is reflected in its widespread use in diabetic clinics. Problems exist, however, in the interpretation of HbA_1. In clinical and laboratory practice, the definition of levels implying 'good control' versus 'poor control' is often arbitrary. On a wider scale the use of HbA_1 as an index of control in clinical and epidemiological studies is made difficult by the variety of methods used, the differing normal and abnormal ranges, together with lack of any convenient quality control samples to use as reference material.

The correlations observed between casual plasma glucose and HbA_1 levels provide useful interpretive data. Samples ($n=996$) obtained from diabetic patients in the course of rural screening programmes for retinopathy in Western Australia [1] between 09.00 and 17.00 h have been analysed (enzymatic method for glucose; total HbA_1 components measured by the micro-column method of Davis and Nicol [2]).

We performed regressions of plasma glucose concentrations on HbA_1 percentages. Residual plots revealed that the variability of plas-

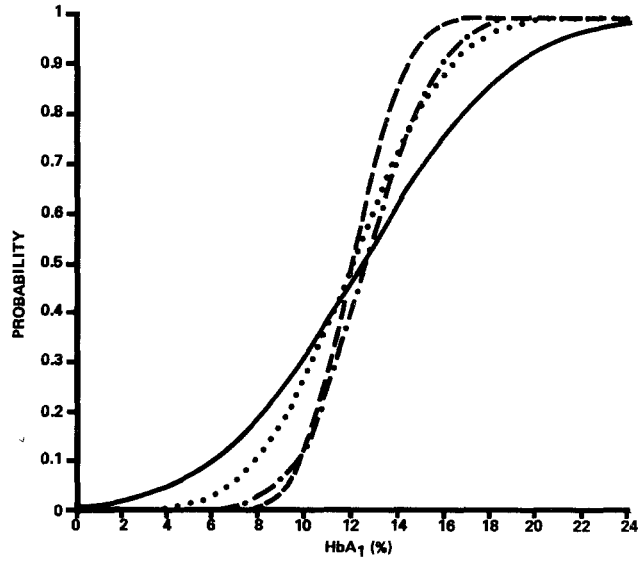

Fig. 1. Probability that a HbA_1 percentage represents a mean plasma glucose of >11.0 mmol/l. Key: —— Type 1 diabetes; ····· Type 2 diabetes on insulin; -·-·-· Type 2 diabetes on tablets; – – – – Type 2 diabetes on diet or no treatment