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

References

1. WHO Expert Committee on Diabetes Mellitus (1980) Second Report. Technical Report Series 646. World Health Organisation, Geneva

2. Jarrett RJ (1981) Reflections on gestational diabetes mellitus. Lancet II: 12–20
3. National Diabetes Data Group (1979) Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 28: 1039–1057
4. O'Sullivan JM, Mahan CM (1964) Criteria for the oral glucose tolerance test in pregnancy. Diabetes 13: 278–285

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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-
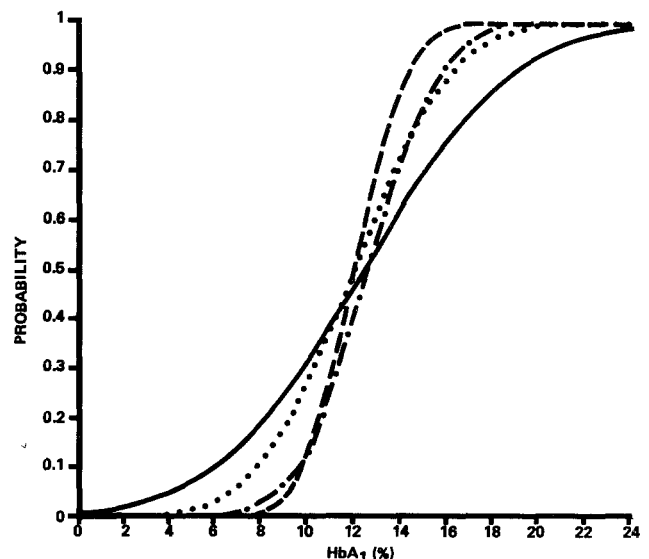

Fig. 1. Probability that a HbA$_1$ percentage represents a mean plasma glucose of > 11.0 mmol/l. Key: —— Type 1 diabetes; · · · · · Type 2 diabetes on insulin; —·—·—· Type 2 diabetes on tablets; – – – – Type 2 diabetes on diet or no treatment

Table 1. Regression equations of plasma glucose on HbA$_1$ percentages

Group		Coefficient of correlation (r)	Fitted line	Estimate of variance about fitted line
All patients	(n = 996)	0.60	log$_e$ glucose = 0.71 + 0.14 HbA$_1$	0.16
Type 1 diabetic patients	(n = 157)	0.42	log$_e$ glucose = 0.94 + 0.12 HbA$_1$	0.35
Type 2 diabetic patients:				
on insulin	(n = 244)	0.49	log$_e$ glucose = 0.82 + 0.13 HbA$_1$	0.18
on tablets	(n = 431)	0.65	log$_e$ glucose = 0.73 + 0.13 HbA$_1$	0.10
on diet	(n = 152)	0.71	log$_e$ glucose = 0.39 + 0.17 HbA$_1$	0.08

Table 2. Estimated mean plasma glucose concentrations and confidence intervals

HbA$_1$ (%)	Estimated mean plasma glucose (mmol/l)	Range of plasma glucose values (±1SD)	Range of plasma glucose values (±2SD)
7.0	5.4	3.6– 8.1	2.4–12.1
8.0	6.2	4.2– 9.3	2.8–13.9
9.0	7.2	4.8–10.7	3.2–16.0
10.0	8.3	5.5–12.3	3.7–18.4
11.0	9.5	6.4–14.2	4.3–21.1
12.0	10.9	7.3–16.3	4.9–24.3
13.0	12.6	8.4–18.7	5.6–27.9
14.0	14.4	9.7–21.5	6.5–32.1
15.0	16.6	11.1–24.8	7.5–37.0
16.0	19.1	12.8–28.5	8.6–42.5
17.0	22.0	14.7–32.8	9.9–48.9
18.0	25.3	17.0–37.7	11.4–56.3

ma glucose about the fitted lines increased with increasing HbA$_1$, thus the variance of plasma glucose increased with the mean. A logarithmic transformation (base e) of plasma glucose overcomes this problem and enables a statistical comparison of the fitted lines. Log$_e$ plasma glucose was regressed on HbA$_1$ for all diabetic patients, and for sub-groups that included Type 1 (insulin-dependent) diabetic patients and the treatment categories of Type 2 (non-insulin-dependent) diabetes. The results are given in Table 1.

The regression lines for Type 1 and the classes of Type 2 diabetes are mostly similar and the statistical test for inequality of the four lines is only marginally significant (p = 0.05). It is clear from the coefficients of correlation and the estimates of variance that for a given HbA$_1$ value, the scatter of plasma glucose values is greatest for Type 1 and least for Type 2 diabetic patients on diet.

Table 2 shows the estimated mean glucose values for any given HbA$_1$ for the entire group over the range of 7–18%, plus the 67% confidence limits (± 1 SD) and the 95% confidence limits (± 2 SD). Such an analysis enables the clinician to interpret HbA$_1$ in terms of the observed *mean* plasma glucose, with some accuracy. Similar tables can be constructed for each group using the regression equations and variances quoted above. Note that the confidence limits are narrower for Type 2 diabetic patients on diet (95% confidence limits for plasma glucose at HbA$_1$ of 11% are 5.4–16.9 mmol/l) and wider for Type 2 diabetic patients (95% confidence limits for plasma glucose at HbA$_1$ of 11% are 2.9–31.3 mmol/l).

Another way of using such correlations is to compute the *probability* that HbA$_1$ represents a given plasma glucose value. For example, if it is considered desirable to ascertain mean plasma glucose levels > 11.0 mmol/l (thus identifying risk of retinopathy [3, 4]), the probability that a HbA$_1$ reflects this value can be calculated. Figure 1 shows the probability that the mean plasma glucose exceeds 11.0 mmol/l for a given HbA$_1$ value. An HbA$_1$ of 11% gives probabilities of 0.39, 0.38, 0.26 and 0.27 for Type 1 patients, Type 2 diabetic patients on insulin, on tablets and on diet, respectively, whereas for an HbA$_1$ of 8% the probabilities are 0.19, 0.11, 0.03 and 0.01.

Presenting regression data in the manner for HbA$_1$ and plasma glucose thus enables more meaningful interpretation of HbA$_1$ at a clinical level, indicating a mean plasma glucose level as well as illustrating the wide range of glucose values represented. Such data also provide a means of comparing results from different centres using different methods, providing that a suitably large number of paired samples for plasma glucose and HbA$_1$ are analysed. The marginally significant difference in regression lines between classes of diabetes is not likely to be of practical importance, but cognizance must be taken of the fact that Type 1 diabetes shows much more variability of plasma glucose than Type 2 diabetes for a given HbA$_1$.

Yours sincerely,
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References

1. Constable IJ, Welborn TA, Cooper RL, McCann VJ, Stanton KM, Greer DV, Stein G, Sebastian P (1980) Symposium on medical ophthalmology medical correlates and diabetic retinopathy screening. Trans Ophthal Soc UK 100: 78–82
2. Davis RE, Nicol DJ (1978) A rapid simplified method for routine measurement of glycosylated haemoglobin. Lancet II: 350–351
3. Jarrett RJ, Keen H (1976) Hyperglycaemia and diabetes mellitus. Lancet II: 1009–1012
4. Bennett PH, Rushforth NB, Miller M, Le Compte PM (1976) Epidemiologic studies of diabetes in the Pima Indians. Recent Prog Horm Res 32: 333–376

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