Letters to the Editor

Macrovascular disease in Caucasoid diabetic patients

Dear Sir,

The consideration one feels to be lacking from the analysis by Welborn *et al.* of factors associated with the clinical appearance of macrovascular disease in Caucasoid diabetic patients [1] is that of the plasma insulin levels. In Type II (maturity-type onset) diabetics there is a correlation between the plasma concentrations of glucose and insulin, and this may be why there is a weak correlation with glucose in the data presented, which one can hypothesise to have been much stronger with insulin.

Consideration of the plasma insulin level was also surprisingly little emphasised in the anguished analysis by Jarrett [2] of the increased amount of cardiac disease in diabetics; so many things are set out so clearly there, but the overall confusion could have been clarified by consideration of the plasma insulin levels, if the facts were available and are indeed as one suspects.

It seems reasonable to attempt such an assessment because of the association between raised insulin levels (even allowing for the degree of obesity) and the development of heart disease in three substantial prospective studies of general populations [3–5], as well as developing evidence that hyperinsulinaemia is related to cardiac deterioration in diabetics both in Finland and England [6, 7].

Yours faithfully,
T. D. R. Hockaday

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Reply from the authors

Dear Sir,

Most would agree with Dr. Hockaday's sentiment that studies of the possible association of hyperinsulinaemia with macrovascular disease are extremely relevant, especially since conventional treatments for diabetes apart from dietary regimes and exercise are likely to elevate serum insulin levels. In our recent cross-sectional study of diabetic subjects the effort and expense of measuring *free* insulin levels were not appropriate, bearing in mind the uncontrolled aspects of collecting "casual" blood samples without reference to the timing of meals or medications.

There is an enigma in this area in that the three *general* populations cited by Hockaday as showing an association between hyperinsulinaemia and subsequent coronary heart disease were all male. Our Busselton study gives the only information on a general population of females and there was no such association found. Recently we have re-worked the data from two separate Busselton cohorts (1966 and 1969) using survival analysis and we cannot find any trend whatsoever relating hyperinsulinaemia to cardiovascular disease end-points in females (unpublished). The Guy's Hospital team [1] have ventured an explanation for this sex difference. The situation may well be different in a population of *diabetic* females.

Perhaps a further prospective diet-heart study is required, along the lines of the Leiden Intervention Trial [2], with a quantitative assessment of coronary lesion progression in relation to prevailing free insulin levels in a comparatively small number of diabetic patients?

Yours faithfully
T. A. Welborn

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Glycosylated haemoglobins in normal pregnancy

Dear Sir,

We read with interest the report by Worth et al. on glycosylated haemoglobin in normal pregnancy [1]. However, when comparing our results [2] with their own, the authors missed a crucial point: in our longitudinal study, we did not report the levels of total glycosylated haemoglobin (Hb A₁), but those of the subfraction haemoglobin A_{1c} (Hb A_{1c}), which is, at least theoretically, a more reliable indicator of long-term glycaemia than Hb A₁ [3]. The cation exchange chromatographic macrocolumn method used in our study [2] also permitted measurement of the minor fast haemoglobin components. The values of Hb A₁ can be calculated as the sum of these fractions (Hb A_{1c} plus the minor fast haemoglobins). Because fetal haemoglobin (Hb F) co-elutes with Hb A_{1c} in this method, as it does with Hb A₁ in the cation exchange method employed by Worth et al. [1] (Bio-Rad Hemoglobin A₁ by column test, Bio-Rad Laboratories, Richmond, California, USA), we also reported the levels of Hb F [2] measured by the method of Betke et al. [4]. The changes of corrected levels of Hb A₁ (the apparent Hb A₁ levels minus Hb F) are shown in Figure 1, and were similar

Fig. 1. Haemoglobin A₁ (mean $\pm$ SEM) expressed as a percentage of total haemoglobin and corrected for haemoglobin F in 29 healthy women during pregnancy and 3 months after delivery. Figures in parentheses indicate the number of patients sampled. ☆ $p < 0.01$, ☆☆ $p < 0.001$; significant differences versus post-partum. Δ $p < 0.01$, ΔΔ $p < 0.001$; significant differences versus 38 weeks (Student's paired t-test). Haemoglobin A₁ values from 21 healthy non-pregnant women are also shown

to those reported by Worth et al. [1]. On the other hand, no significant changes of Hb A_{1c} during normal pregnancy and no difference between Hb A_{1c} in pregnant and non-pregnant healthy women were observed in our study [2]. In puerperium (3 months after delivery) Hb A_{1c} was significantly higher than during pregnancy ($p < 0.001$) and in non-pregnant controls ($p < 0.05$), respectively [2].

We agree with the conclusion of Worth et al., that the use of any measurement of glycosylated haemoglobins in pregnancy should take account of pregnancy-specific normal ranges, each laboratory having its own reference values. Moreover, the measurement of Hb A_{1c} in assessing long-term glycaemic control seems to be preferable to that of Hb A₁ especially during pregnancy [2, 5], and comparison between these two parameters should be made with caution. Recently, we have employed an improved method for measuring Hb A_{1c} by rapid fully automated high-performance liquid chromatography, which also determines Hb F, Hb A_{1a}, Hb A_{1b} and Hb A₂ [6]. Thus the method both detects a recent fetomaternal blood transfer, and eliminates the problem of erroneously high glycosylated haemoglobin values due to this phenomenon.

Yours sincerely,

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Intact glucose oxidation in human fetal pancreas

Dear Sir,

Harrison et al. have demonstrated for the first time on isolated human islets the sigmoidal nature of glucose-stimulated insulin release and its correlation with enhanced glucose oxidation [1]. Their work should be applauded because many studies of rodent islets may be applicable to man but this should never be assumed. Our own data has shown previously the marked discrepancies between the capacity of fetal mouse pancreas and human fetal pancreas to secrete insulin in response to a glucose stimulus [2, 3].

Subsequent to our finding that human fetal pancreas was unresponsive to glucose, and that a single defect in early glycolysis or deficiency of cyclic AMP was unlikely [3], a defect in glucose oxidation