Letters to the editor

Infant nutrition and subsequent risk of Type 2 (non-insulin-dependent) diabetes mellitus

Dear Sir,

Hales and Barker [1] have pieced together a number of disparate observations to provide a fascinating and novel hypothesis on the aetiology of Type 2 (non-insulin-dependent) diabetes mellitus. Central to their hypothesis is the notion that beta-cell function is diminished as a result of under-nutrition at a critical point in the development of the islets of Langerhans during fetal and early infant life.

We are unable to reconcile this hypothesis to observations of increased insulin levels (in relation to Caucasian populations) in normal, glucose intolerant and diabetic individuals in developing populations, such as Pacific islanders [2], Australian Aborigines [3], American Indians [4] and Asian Indians [5]. According to Hales and Barker [1], these populations (or the individuals within them) are at increased risk of developing glucose intolerance with modernization, presumably because early under-nutrition resulting in beta-cell damage has left the pancreas unable to cope with the increased insulin requirements of the diet, obesity and reduced activity levels of a modern lifestyle.

However, the very populations with the greatest susceptibility to Type 2 diabetes, are those with the highest beta-cell function, based on their total immunoreactive insulin levels. Hales and colleagues [1, 6] claim that much of this "immunoreactive" insulin is biologically less active proinsulin and des 31,32-split proinsulin. This appeared to be the case in newly diagnosed Type 2 diabetic patients, particularly 30 min after an oral glucose load [6], but is not the case in mild non-insulin-dependent diabetes [7]. If a high proportion of insulin in susceptible populations could be shown to be composed of physiologically inactive proinsulin and its split products, then the Hales and Barker hypothesis of relative insulin deficiency might still hold. To date, there is no confirmation that population differences in total insulin levels can be explained by differences in concentrations of true insulin compared to proinsulins.

Within populations, the Hales and Barker hypothesis also runs into difficulties. In several populations it has been shown that increased (not decreased) insulin levels (fasting, 2-h, etc.), predict deterioration in glucose tolerance from normal to impaired or to Type 2 diabetes [8–11]. While admittedly these studies need to be repeated measuring true insulin, they suggest that the beta cells of *individuals* with deteriorating glucose tolerance tend to have *increased* (but possibly still "abnormal") rather than decreased function. If it is only first phase secretion [12] that needs to be diminished to provide the susceptibility (and this is not outside the bounds of possibility), it is not clear that the "thrifty phenotype" hypothesis relating infant nutrition to pancreatic development adequately explains such a specific lesion.

Furthermore, we should point out that Hales and Barker have misinterpreted our data showing a recent decline in the incidence of glucose intolerance in the high prevalence Nauruan population [13]. We certainly did not attribute the recently observed changes in prevalence and incidence to natural selection – the time-course is obviously too short. Rather, we hypothesised that the reduction was due to the intensity of the epidemic and the fact that most of the genetically susceptible individuals had already "caught" the disease, leaving a relatively resistant group of individuals with normal glucose tolerance at the time of the most recent follow-up survey. Moreover, the decline in incidence did not occur only in younger age groups, presumed to have better nutrition, as incorrectly asserted by Hales and Barker. The decline in the incidence of impaired glucose tolerance and Type 2 diabetes amongst subjects with normal glucose tolerance at baseline occurred right across the age range (the age-specific data were not shown in the original article). In addition, while we have recently shown that fasting and post-load insulin concentrations, after adjusting for body mass index, are higher in Nauruans aged 8–

19 years than in older age groups, these high levels also predict subsequent deterioration in glucose tolerance [14]. Therefore, if pancreatic function has "improved" in young Nauruans as a result of better nutrition, it would appear that the result will have been to increase rather than decrease susceptibility to Type 2 diabetes.

In conclusion, Hales and Barker [1] have presented a provocative hypothesis and reviewed some intriguing data. At present, however, there are some major inconsistencies which need to be explained before the hypothesis can be given greater credence.

Yours sincerely,

G. K. Dowse, P. Z. Zimmet and K. G. M. M. Alberti

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Dr. G. K. Dowse
International Diabetes Institute, 260 Kooyong Road
Caulfield Vic 3162, Australia

Response from the authors

Dear Sir,

We thank Drs. Dowse et al. for their comments on our "thrifty phenotype" hypothesis and the opportunity to address the questions which they pose.

There is now a large measure of agreement that the pathogenesis of Type 2 (non-insulin-dependent) diabetes mellitus involves a varying combination of defective insulin secretion and insulin resistance. Caucasians with Type 2 diabetes seem to be heterogeneous. Some exhibit only an insulin secretory defect while others, who often have abdominal obesity, show both defective insulin secretion and insulin resistance [1, 2]. In other populations insulin resistance may be dominant. There is, however, substantial evidence that a defect of insulin secretion often precedes the development of Type 2 diabetes [2–10].

Dowse et al. suggest that raised fasting and/or raised 2-h plasma insulin concentrations are evidence of good beta-cell function. We do not accept this. Small elevations of fasting "insulin" measured non-specifically may be due to elevated concentrations of proinsulin-like molecules. Also beta-cell dysfunction is associated with loss of the normal oscillatory pattern of insulin secretion in the fasting state [11] which may reduce the biological effectiveness of the secreted insulin and hence lead to raised fasting insulin concentrations. Raised 2-h plasma insulin concentrations are often secondary to a poor early insulin response to oral glucose [12]. They may therefore be a sign of beta-cell dysfunction rather than "high" beta-cell function.

Dowse et al. believe that our hypothesis cannot explain the "specific lesion" of loss of first phase insulin secretion. We find nothing particularly specific in this change since it is also seen prior to the onset of Type 1 (insulin-dependent) diabetes [13] and after partial pancreatectomy [14, 15].

We recently showed in our study of men from Hertfordshire that men with impaired glucose tolerance or Type 2 diabetes tended to have low birthweight and low weight during infancy [16]. We confirmed this finding in a second study of men and women living in another part of Britain [17]. This second study showed that the association with low birthweight depended on reduced fetal growth rather than premature birth. Our hypothesis is that both poor beta-cell function in adult life and insulin resistance are associated with retarded early growth. Animal studies provide strong evidence that poor fetal and infant nutrition can permanently impair insulin secretion. Evidence that retarded early growth is linked to insulin resistance comes from the association of low birthweight and infant weight with syndrome X [18], of which insulin resistance is an important component. A recent study using insulin tolerance tests showed that adults who were thin at birth were more insulin resistant as adults (D.I.W. Phillips, D.J.P. Barker and C.N. Hales, unpublished observation).

Though we misunderstood the explanation for the decline in Type 2 diabetes in Nauruans [19] our point still stands. Our hypothesis suggests that an improvement in nutrition in a previously malnourished population will lead, through improved growth of the fetus and infant, to a reduction in the incidence of Type 2 diabetes in later generations. Future studies should investigate such a possibility rather than seeking only genetic explanations of changes in incidence and prevalence.

We hope that these explanations and our continuing research will help to give the support for our hypothesis that Drs. Dowse, Zimmet and Alberti seek.

Yours sincerely,
C.N. Hales and D.J.P. Barker

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Prof. C.N. Hales
Department of Clinical Biochemistry
Addenbrooke's Hospital
Hills Road
Cambridge CB2 2 QR
UK