Reply from the authors

Dear Professor Berger,

We endorse the conclusions of the above letter and are in agreement with the authors' suggestion that interlaboratory differences for associations of insulin autoantibodies (IAA) and islet cell antibodies (ICA) may well be attributable to assay detection limits. One other aspect should not be overlooked. Although the most significant correlations are apparent without recourse to statistical analysis, unfortunately ICA/IAA associations do not fall in this category. Within the bounds of a Rapid Communication we could not elaborate, but we clearly stated [1] that our conclusions, not our findings, were at variance with those of Wilkin et al. [2]. By application of the χ^2 test to such a small proportion of our relevant data (~10%), it is hardly surprising that Drs. Wilkin and Armitage find a lack of correlation between IAA and ICA of assumed low titre. However, to use χ^2 analysis on any data obtained by an enzyme linked immunosorbent assay removes the advantages inherent in such a sensitive assay system. The bonus of the Mann Whitney U rank test is that it utilises all the available numerical data without introducing latent errors for values which lie in the ponderable zone of positivity/negativity.

Although complement-fixing (CF) – ICA titres invariably are lower than corresponding ICA-IgG titres, we would dispute that the system is less sensitive. The greater specificity of the CF-ICA test, as evidenced by the more ready discrimination of end-point titres, is precisely why we favour its continued use in conjunction with ICA-IgG for routine screening. We re-iterate here that our study group was selected after multiple sequential serum analysis for CF-ICA and ICA-IgG (approximately 12–20 samples from >600 individuals taken during 3–6 years follow-up). End-point titres have been determined for these antibodies in all samples available from the 30 ICA positive individuals studied for the presence of IAA [1]. Thus, we are able to categorise this group correctly in terms of high and low ICA-IgG titre. Fourteen of the group have titres constantly >8; the remaining 16 have values which lie ≤ 8 . Mann Whitney U analysis of this data now reveals a highly significant association of IAA with the high versus the low titre group ($p=0.003$), indeed proving that assay detection limits are of paramount importance.

The heterogeneity of ICA in terms of complement fixation and IgG subclass distribution is well established [3, 4], and our data for IgG and IgM class antibodies emphasises that the same concept is true for IAA. In addition, we believe our IAA measurements encompass a broad spectrum of cross reactivity with pro-insulin and other insulin species. Our preliminary report [5] of a high incidence of IgM IAA in the absence of ICA following common viral infections suggests that reactivity against the hormone can be triggered by several mechanisms with a distinct role of the class specificities for different disease states. The important message of IgG class specificity for significant associations of IAA with ICA, hopefully, should improve interlaboratory discrepancies.

Yours sincerely,

B. M. Dean, E. Gale and G. F. Bottazzo

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More about obesity and diabetes

Dear Sir,

Professor Jarrett's letter [1] concerning Dr. Modan and co-workers' article [2] suggests that obesity is not the determinant in the majority of patients with Type 2 (non-insulin-dependent) diabetes (in Great Britain). He concedes ignorance of previously published categorical data concerning the incidence of diabetes and Body Mass Index (BMI) among the Pima Indians [3].

As in the Israel study [4], the age-sex adjusted incidence of non-insulin-dependent diabetes among the Pima Indians increases significantly in the range of BMI below 30 kg/m² (BMI <20, 0.8 ± 0.8 cases/1000 person-years ($\pm$ SE); BMI 20–25, 10.9 ± 2.9 ; BMI 25–30, 17.3 ± 2.5), and is even higher in those who are more obese [3]. Furthermore, there is an important interaction between obesity and whether or not diabetes has occurred in parents. Pima Indians aged 25–44 years and BMI ≥ 30 had incidence rates of diabetes of 27.8, 45.2 and 84.0 cases/1000 person-years according to whether neither, one, or both parents had diabetes, whereas the corresponding rates in those with BMI <30 were 14.1, 16.4, and 25.1 cases/1000 person-years, respectively. These data indicate that parental diabetes is an equally important determinant. Interestingly, among the Pima aged 25–44 even the rate in those with a BMI <30 and neither parent diabetic (14.1/1000) was more than twice as high as the rate of 5.1 cases/1000 person-years (calculated from [4]) in the same relative weight, but older age group in Israel, a further reflection of differences in genetic or environmental determinants not accounted for by either BMI or parental diabetes.

Among the Pima there are also strong interactions between age, BMI and incidence of diabetes, with the more obese tending to show peak incidences at an earlier age and a lower incidence in the oldest age group, suggesting that, in susceptible individuals, obesity precipitates the disease at an earlier age than it would otherwise have occurred. As in the Israel study, the duration of obesity is also a stronger predictor of diabetes incidence in the Pima than the attained degree of obesity, with those who have attained and maintained a given degree of relative weight for longer having a higher incidence than those who have reached an equivalent weight more recently [5].

The Israel study illustrates another intriguing possibility. As among the Pima Indians [6], serum insulin levels for a given BMI are higher in the borderline and impaired glucose tolerance groups than in those with normal tolerance. Yet in the Israel study those whose BMI had increased showed greater variability of insulin response than those whose BMI fell or remained the same; this difference "resided completely in the glucose intolerant categories" [2]. Unfortu-

nately, as only summed 1- and 2-h serum insulin levels were reported, it is unclear if these differences are the result of variations in the fasting serum insulin levels, or differences in the actual *response* to the ingested glucose as suggested by the authors. Within the range of normal and impaired glucose tolerance, however, strong relationships exist between insulin resistance, as measured by the euglycaemic clamp technique, and fasting glucose, glucose tolerance, and fasting and post-load insulin levels [6, 7]. Insulin resistance appears to be uniformly present among non-insulin-dependent diabetic patients, and in those who do not already have diabetes it is predictive of its development and of worsening of glucose tolerance [8]. Furthermore, there is now clear evidence in populations with high prevalences of diabetes, such as the Pima [9, 10], and Mexican Americans [12], that serum insulin levels, both fasting and following a glucose challenge, among the *non-diabetic* individuals are higher than in Caucasians, even *after* correction for differences in glucose tolerance and obesity. Curiously, these same populations each have high rates of obesity.

Given these data it seems entirely possible that it is insulin resistance, and not primarily obesity, that leads to glucose intolerance and subsequently diabetes. Furthermore, Dr. Modan and her colleagues have presented evidence that hypertension is also independently associated with hyperinsulinaemia [13]. Insulin resistance, therefore, may be the key defect that *independently* leads to obesity, hypertension, and diabetes, and accounts for the well known associations among obesity, serum insulin levels and glucose intolerance. If so, insulin resistance, rather than obesity, may be the principal determinant of diabetes.

Sincerely yours,
Peter H. Bennett

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Errata

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Letter to the Editor by M. Modan, A. Karasik, H. Halkin

The Editor apologizes for the inadvertent mistake during the editing and production process of this letter. Instead of “in both Type 1 and Type 2 diabetes”, it should have been printed “in both diabetes categories” as originally submitted by Dr. Modan and her associates. The Editor deeply regrets this technical error.

Diabetologia (1986) 29: 417–420

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