years earlier. The boy in the 3rd case has susceptibility genes and autoantibodies but still has normal β-cell function. If he remains antibody positive, he may very well develop diabetes. Thus, all 3 cases support the usefulness of immunogenetic markers of prediabetes.

The fact that the third patient developed psychiatric difficulties is probably a coincidence. In my experience (~2000 children tested and >12 found positive) and in the even greater experience of other investigators (2–6), to my knowledge, no such case has been found. In fact, a positive attitude of the tested families has been reported (7). Conclusions drawn from one case vis-a-vis such a large number of cases are misleading.

Bell et al. also express their concern about cyclosporin treatment in diabetic children. This concern is shared by many, including myself. Cyclosporin should only be used in carefully planned and conducted randomized trials. In fact, I question why patient 1 was treated with cyclosporin in what seems a rather casual context. However, cyclosporin is not the only type of treatment being studied for diabetes. There are other intervention protocols (e.g., nicotinimide) that seem to be generally free of toxicity and offer some promise of inducing remissions. These drugs are already being tested in prediabetic individuals.

Even if no intervention means were available, study of the autoimmune dysfunction in the prehyperglycemic stage of type I diabetes would still be of great interest to further characterize the autoimmune pathogenesis of this disorder. If Bell et al. meant that none of these activities are ready to be adopted by general practitioners, then I would wholeheartedly agree. However, the message I perceived was one of condemnation of these studies, which I think is inappropriate.

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REPLY

The intent of our letter to *Diabetes Care* was to emphasize the point to which Dr. Barbosa refers, namely that immunogenetic diagnosis of prediabetes has not yet advanced to the point that it is of use to the practitioner. In fact, unless such practices are a part of ongoing studies of the immunologic basis of type I (insulin-dependent) diabetes, they may cause undue confusion on the part of the practitioner and his or her patient. We strongly support the ongoing studies that are attempting to unravel the autoimmune basis of type I diabetes mellitus and to capitalize on this information to develop rational preventive and therapeutic strategies.

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DNA Polymorphism of the Insulin Gene, Diabetes, and Severe Obesity

Some reports have suggested that alleles with larger insertion in the 5′-flanking region of the insulin gene (type 3 allele) may be genetic markers of non-insulin-dependent (type II) diabetes (1–5). Aoyama et al. (5) have recently reported in this journal that frequency of larger 5′-flanking insertion is particularly high in non-overweight and <40 yr-of-age type II diabetic patients. In their study, type 3 allele has been found not related to the excess body fat. In our study, complementary to that by Aoyama, we aimed to evaluate the predictive value of type 3 allele on the worsening to type II diabetes of severely obese patients with previous impaired glucose tolerance (IGT).

Twenty-six (17 females and 9 males) severely obese

patients, already consecutively hospitalized in the metabolic unit of our hospital 5–13 yr before the present observation and having the diagnosis of IGT (7), were recruited.

At the first observation, body weight, height, and blood pressure were recorded; a fasting blood sample was also obtained for glucose, cholesterol, triglyceride, and uric acid determinations. At the second observation, diagnosis of diabetes was again made according to National Diabetes Data Group criteria (7). Furthermore, in all patients the 5′-flanking polymorphic region of the insulin gene was studied as described elsewhere (4), and alleles were classified according to Bell (6) as allele 1 and allele 3.

Statistical analysis was performed by one-way variance analysis, Student's t test for paired data, and χ^2-test where appropriate. Patients developing type II diabetes (13 of 26, 50%) had a mean age (38.8 ± 8.9 vs. 42.8 ± 11.2 yr, NS) and body mass index (BMI, 40.8 ± 6.3 vs. 51.0 ± 9.8 kg/m^2, $P < .05$) that was lower and a serum cholesterol level (255.0 ± 99.8 vs. 198.1 ± 41.1 mg/dl, $P < .01$) that was significantly higher than that of the group of obese subjects not developing diabetes.

Genotypes absent, heterozygote, and homozygote for 5′-flanking insertion [1/1, 1/3, 3/3 according to Bell's classification (6)] were found in 76.9, 15.4, and 7.7%, respectively, of those who developed diabetes and in 69.3, 23, and 7.7% of the other group. Therefore, the two groups did not differ in the frequency of these genotypes, and no difference was detectable versus the reference group (1/1, n = 33, 54.0%; 1/3, n = 22, 36%; 3/3, n = 6, 10%; 4).

No other anthropometric, biochemical, blood pressure, or familial parameters showed any relationship to the genotype. From our study it appears that severely obese patients with IGT are at very high risk (50%) to develop type II diabetes. We tried to evaluate predictive factors for such evolution, but except for higher values of serum cholesterol (8), lower excess body fat, and younger age, we were unable to detect any differences. In particular, the two subgroups did not differ in family history of diabetes or the occurrence of type 3 allele.

Note that the frequency of the type 3 allele was found lower in this group of severely obese patients than in the control group of our population. Type 3 allele appears to be associated with lower insulin production by β-cells (4), whereas insulin is essential for storing triglycerides in the adipose cells and excess body fat is linearly related to insulinemia. Severely obese patients might, therefore, constitute a selected group of individuals where insulin production must be high and, consequently, presence of type 3 allele uncommon. In conclusion, development of diabetes in severe obesity does not seem to be linked to the presence of type 3 allele.

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Is HbA_1 Measurement Superfluous in NIDDM?

Measurement of glycosylated hemoglobin (HbA_1), reflecting the integrated plasma glucose concentration over the preceding 6- to 8-wk period, has become a standard index of glycemic control in diabetes mellitus (1,2). Compared with measurement of plasma glucose, the cost of HbA_1 measurement is considerable in terms of assay reagents and labor. Nevertheless, many, if not most, centers use the test routinely as an accepted part of the management of both insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) diabetes mellitus. At our clinic, we first measured HbA_1 in selected patients in 1977, and since November 1980 it has become an integral part of our routine outpatient service, the aim being to have an HbA_1 measurement for every patient at every review appointment. In a previous report