OBSERVATIONS

Identification of the Source of Androgen Excess in Hyperandrogenic Type 1 Diabetic Patients

We recently reported that the prevalence of hyperandrogenic disorders is markedly increased in women with type 1 diabetes (1). The polycystic ovary syndrome (PCOS) defined by endocrine criteria was found in 18.8% of the type 1 diabetic women who followed-up in our hospital (1), as compared with the 6.5% prevalence in nondiabetic women from similar ethnic and genetic backgrounds (2). The prevalence of hirsutism in type 1 diabetic women was 30.6% (1), which is markedly higher than the 7.1% prevalence of hirsutism found in nondiabetic women (2).

In the present study, we evaluated the adrenal and ovarian steroidogenic profiles of hyperandrogenic and nonhyperandrogenic type 1 diabetic women and compared them with those of nondiabetic hyperandrogenic women and healthy control subjects.

A total of 24 women with type 1 diabetes were recruited for the study (1). Fourteen diabetic patients (age [mean ± SD] 20.6 ± 4.0 years, BMI 24.8 ± 2.9 kg/m^2) were considered to have hyperandrogenism. The other 10 women with type 1 diabetes (age 19.0 ± 3.0 years, BMI 23.3 ± 2.6 kg/m^2) had no evidence of clinical or biochemical hyperandrogenism and had regular menstrual cycles. Both groups of type 1 diabetic patients had similar HbA_{1c} levels (7.4 ± 1.2 vs 7.8 ± 1.2% in nonhyperandrogenic and hyperandrogenic diabetic patients, respectively, $F = 0.591$, $P = 0.450$), and there were no differences in the mean daily insulin dose used for their treatment (0.82 ± 0.27 vs. 0.66 ± 0.28 U · kg^{-1} body wt · day^{-1} in nonhyperandrogenic and hyperandrogenic diabetic patients, $F = 1.875$, $P = 0.185$).

A total of 86 nondiabetic women were included as control subjects. Nondiabetic women were matched for BMI and age with the diabetic patients to avoid any influence of age and obesity on the results. Thirteen regularly menstruating women (age 23.2 ± 3.2 years, BMI 24.6 ± 5.1 kg/m^2) without signs or symptoms of hyperandrogenism served as healthy control subjects; 73 untreated nondiabetic hyperandrogenic patients (age 20.6 ± 3.8 years, BMI 23.7 ± 3.2 kg/m^2) were included as hyperandrogenic control subjects.

Basal and adrenocorticotropic hormone (ACTH)-stimulated samples were obtained and assayed as previously described (1,3). The study was conducted according to the principles expressed in the Declaration of Helsinki.

The group of hyperandrogenic type 1 diabetic patients comprised seven women with PCOS and seven women with hirsutism and regular menstrual cycles. The percentage of patients with PCOS was not different among the groups of diabetic and nondiabetic hyperandrogenic patients (50.0 vs 38.4%, $\chi^2 = 0.662$, $P = 0.553$).

Both groups of hyperandrogenic patients had higher hirsutism scores compared with nonhyperandrogenic diabetic patients and healthy control subjects (Fig. 1), but the hirsutism score was higher in nondiabetic hyperandrogenic patients compared with hyperandrogenic type 1 diabetic women (Fig. 1).

Compared with healthy women, both hyperandrogenic type 1 diabetic patients and nondiabetic hyperandrogenic women had increased basal serum total and free testosterone concentrations, as well as basal Δ^4-androstenedione concentrations (Fig. 1). Nondiabetic hyperandrogenic patients had increased free testosterone levels and decreased sex hormone–binding globulin concentrations compared with all of the other groups (Fig. 1). No differences in sex hormone–binding globulin concentrations were found between the groups of diabetic women and healthy control subjects (Fig. 1).

Nonhyperandrogenic type 1 diabetic women had intermediate values of total testosterone, free testosterone, and Δ^4-androstenedione that were not significantly different than those of hyperandrogenic diabetic patients and healthy control subjects (Fig. 1). No differences were observed among the groups in the serum concentrations of dehydroepiandrosterone-sulfate, luteinizing hormone, follicle-stimulating hormone, and estradiol (Fig. 1).

Hyperandrogenic type 1 diabetic patients had higher ACTH-stimulated Δ^4-androstenedione levels than healthy control subjects, whereas ACTH-stimulated Δ^4-androstenedione and 17-hydroxyprogesterone levels were higher in nondiabetic hyperandrogenic patients than healthy control subjects and nonhyperandrogenic diabetic patients (Δ^4-androstenedione 12.3 ± 3.0, 15.7 ± 3.1, 12.4 ± 4.3, and 16.1 ± 4.4 nmol/l, $F = 4.84$, $P < 0.005$; 17-hydroxyprogesterone 6.1 ± 1.5, 9.2 ± 5.2, 6.7 ± 1.9, and 10.1 ± 5.4 nmol/l, $F = 3.30$, $P < 0.05$, in nonhyperandrogenic diabetic patients, hyperandrogenic diabetic patients, healthy control subjects, and nondiabetic hyperandrogenic patients, respectively).

However, the net increments in Δ^4-androstenedione and 17-hydroxyprogesterone after ACTH stimulation were not statistically different among the groups (Δ^4-androstenedione 1.4 ± 2.2, 3.3 ± 2.3, 3.1 ± 2.5, and 3.4 ± 2.6 nmol/l, $F = 1.904$, $P = 0.134$; 17-hydroxyprogesterone 3.5 ± 2. 1, 6.3 ± 4.3, 4.4 ± 2.2, and 6.2 ± 4.6 nmol/l, $F = 1.761$, $P = 0.159$ in nonhyperandrogenic diabetic patients, hyperandrogenic diabetic patients, healthy control subjects, and nondiabetic hyperandrogenic patients, respectively).

Basal and ACTH-stimulated cortisol and 11-deoxycortisol levels were not different among the groups (data not shown), whereas basal 17-hydroxyprogesterone concentrations showed a near-significant tendency ($P = 0.056$) to higher levels in nondiabetic hyperandrogenic patients.

Finally, because ovulation may normalize many reproductive variables, we used analysis of covariance to rule out a significant impact of the presence or absence of oligomenorrhea on the differences in hormone analyses described above. None of these differences were influenced by oligomenorrhea (data not shown).

Our present results demonstrate that hyperandrogenic type 1 diabetic women have increased serum levels of total and free testosterone and Δ^4-androstenedione comparable with those found in nondiabetic hyperandrogenic women. Considering that hyperandrogenic type 1 diabetic women had normal dehydroepiandrosterone-sulfate concentrations and that the increase in ACTH-stimulated Δ^4-androstenedione levels found in these patients possibly reflects a normal adre-

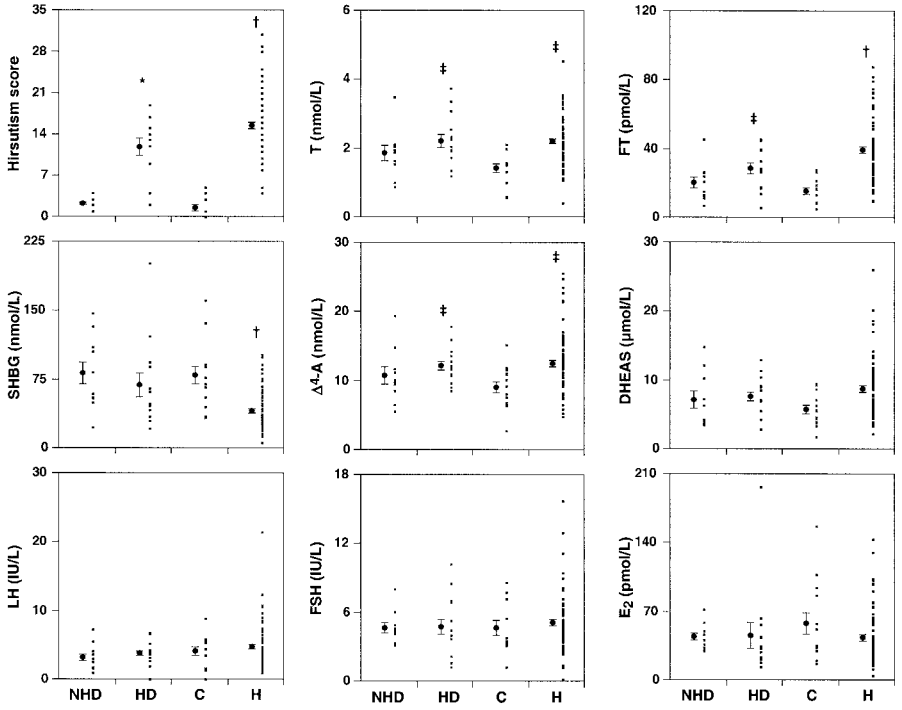

Figure 1—*Comparison of the serum androgen and gonadotropin levels among nonhyperandrogenic diabetic women (NHD,* n *= 10), hyperandrogenic type 1 diabetic patients (HD,* n *= 14), healthy control subjects (C,* n *= 13), and nondiabetic hyperandrogenic women (H,* n *= 73). Data are represented as means ± SEM, and the dot scattergram shows the individual data. The mean values of all groups were compared by one-way ANOVA followed by the least-significant difference test for multiple comparisons. Hirsutism score = modified Ferriman-Gallwey score; T = total testosterone; FT = calculated free testosterone; SHBG = sex hormone–binding globulin; Δ^4-A = basal Δ^4-androstenedione; DHEAS = dehydroepiandrosterone-sulfate; LH = luteinizing hormone; FSH = follicle-stimulating hormone;. E_2 = estradiol. *P < 0.05 vs. nonhyperandrogenic type 1 diabetic women and healthy control subjects; †P < 0.05 vs. hyperandrogenic and nonhyperandrogenic type 1 diabetic patients and healthy control subjects; ‡P < 0.05 vs. healthy control subjects.*

nocortical response taking place in addition to an increased basal secretion of this steroid (the net increment of Δ^4-androstenedione was not different compared with that of healthy control subjects), a significant contribution of the adrenal gland to the androgen excess of these patients is not supported by our present results. Nevertheless, because of the small sample size, we cannot exclude that lack of statistically significant differences in dehydroepiandrosterone-sulfate concentrations and in the net increment of Δ^4-androstenedione after ACTH-stimulation could reflect a type II error.

Virdis et al. (4) recently reported functional ovarian hyperandrogenism (defined by an exaggerated response of 17-hydroxyprogesterone to the gonadotropin-releasing hormone analog leuprolide) in five of nine type 1 diabetic adolescents with oligomenorrhea, which is in conceptual agreement with the main ovarian source for androgen excess in type 1 diabetic patients suggested by our present results.

Surprisingly, serum sex hormone–binding globulin levels were normal in hyperandrogenic type 1 diabetic patients. The regulation of serum sex hormone–binding globulin levels depends on the inhibitory influence of insulin and androgens and the stimulatory effect of estrogens (5). The hyperinsulinism resulting from insulin resistance together with increased androgen levels explains the decrease in sex hormone–binding globulin levels found in most nondiabetic hyperandrogenic patients (5). On the contrary, as stated above, sex hormone–binding globulin levels were normal in hyperandrogenic type 1 diabetic women.

Sex hormone–binding globulin concentrations are mainly regulated by portal vein insulin concentrations (6). However, in type 1 diabetes, insulin is administered subcutaneously instead of being released directly to the portal circulation, as in insulin-resistant patients.

This difference may help to explain the normal sex hormone–binding globulin levels in hyperandrogenic type 1 diabetic patients. In addition to ameliorating the increase in free testosterone levels, a normal sex hormone–binding globulin concentration may decrease the tissue availability of circulating testosterone. This mechanism might contribute to the lower hirsutism scores found in hyperandrogenic type 1 diabetic women compared with nondiabetic hyperandrogenic patients, despite similar serum total testosterone concentrations in both groups.

In summary, our present results suggest that the ovary is the main source of androgen excess in hyperandrogenic type 1 diabetic patients. The normal serum sex hormone–binding globulin levels found in hyperandrogenic type 1 diabetic patients might partially protect these patients against androgen excess by reducing the delivery of androgens to tissues.

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The Use of Continuous Insulin Delivery Systems in Severely Insulin-Resistant Patients

Obese type 2 diabetic patients with severe insulin resistance tend to develop chronic hyperglycemia, despite maximal treatment with diet, physical exercise, and oral hypoglycemic agents. Insulin therapy in these patients usually does not lead to satisfactory glucose control, even when the insulin dosage is very high. High doses of insulin also cause weight to increase, which aggravates insulin resistance and exacerbates other cardiovascular risk factors.

Continuous subcutaneous insulin infusion (CSII) provided by an insulin pump reduces the incidence of both postprandial hyperglycemia and severe hypoglycemia. To determine whether CSII has a beneficial effect on insulin resistance in obese type 2 diabetic patients with severe insulin resistance, a trial of CSII was initiated in this group.

A total of 10 severely obese (BMI $>$ 30 kg/m^2) type 2 diabetic patients with severe insulin resistance (insulin dose of $> 1\ \mathrm{U \cdot kg^{-1} \cdot day^{-1}}$) were recruited from a hospital-based practice. Subjects who qualified for the study had an HbA_{1c} $>$ 8.5%, despite strict diet and compliance with the insulin regimen. After receiving training, patients were started on an insulin pump (Minimed 507) . Blood glucose levels were monitored with a glucometer and patients were instructed to measure their blood glucose at least four times a day. Insulin dosage was optimalized by the study physician. Weight, insulin dose, and HbA_{1c} levels were measured at baseline and throughout the study.

The patients' age (mean ± SD) was 59 ± 10 years. The duration of the study was 40 weeks. All subjects in the study had a reduction in insulin requirements (in units per kilogram per day) from 1.46 ± 0.43 (mean ± SD) at week 0 to 1.19 ± 0.42 at week 40. Concomitantly, there was a slight decrease in weight (in kilograms), from 95.9 ± 13.2 at week 0 to 93.4 ± 12.7 at week 40. Most significantly, glycemic control improved, with a decrease in the percentage of HbA_{1c} levels from 12.34 ± 1.74 at week 0 to 9.56 ± 0.76 at week 40.

These findings suggest that CSII may be an effective therapy to reduce insulin resistance in obese type 2 diabetic patients without the deleterious side-effects associated with increasing insulin dosage. To further determine the effectiveness of CSII, the Israeli Diabetes Research Group is now conducting a randomized clinical trial with a cross-over design comparing CSII with intensive multiple-injection insulin treatment in this population.

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Postprandial Leptin Responses After an Oral Fat Tolerance Test

Differences in type 2 diabetes

The finding that circulating leptin concentrations exhibit a diurnal pattern (1,2), with peak nocturnal concentrations up to two times higher than nadir levels, raised the hypothesis that the evaluation of fasting leptin levels might have underestimated the effect of food secretagouges on postpradial leptin regulation and action. This variation in diurnal leptinemia is related to insulin excursions in response to meals (2), and shifting mealtime by 6.5 h without changing the light and sleep cycles will shift plasma-leptin rhythm by 5–7 h (3). In a recent study (4), it was reported that meals with high fat content result in the production of lower 24-h leptin concentrations compared with meals high in carbohydrates, a phenomenon attributed to lower insulin excursions after fatty meals. However, the impact of reduced insulin sensitivity on short-term leptin production in response to meals has not been investigated in subjects with similar degrees of obesity. We hypothesize that patients with type 2 diabetes (a well-established insulin-resitant state) show lower postprandial incremental leptin production in response to an oral fat tolerance test.

A total of 18 type 2 diabetic male patients and 14 control subjects were matched for age and anthropometric parameters. After a 14-h fast, a test meal of 700 kcal/m^2 (consisting of 4.75 g protein, 24 g carbohydrates, and 65 g fat) (5) was ingested. Blood samples were drawn at fasting and at 2-, 4-, 6-, and 8-h after the meal to determine the levels of glucose, total cholesterol, triglycerides, HDL-C, insulin, and leptin.

Triglycerides increased significantly from baseline only in diabetic patients ($P = 0.001$ vs. $P = 0.066$, respectively), with peak concentrations attained at 6-h. Postprandial total cholesterol, LDL cholesterol, and HDL cholesterol levels did not differ significantly between groups or from levels at fasting. Insulin levels increased postprandially in both groups ($P = 0.001$ and $P = 0.002$), with peak

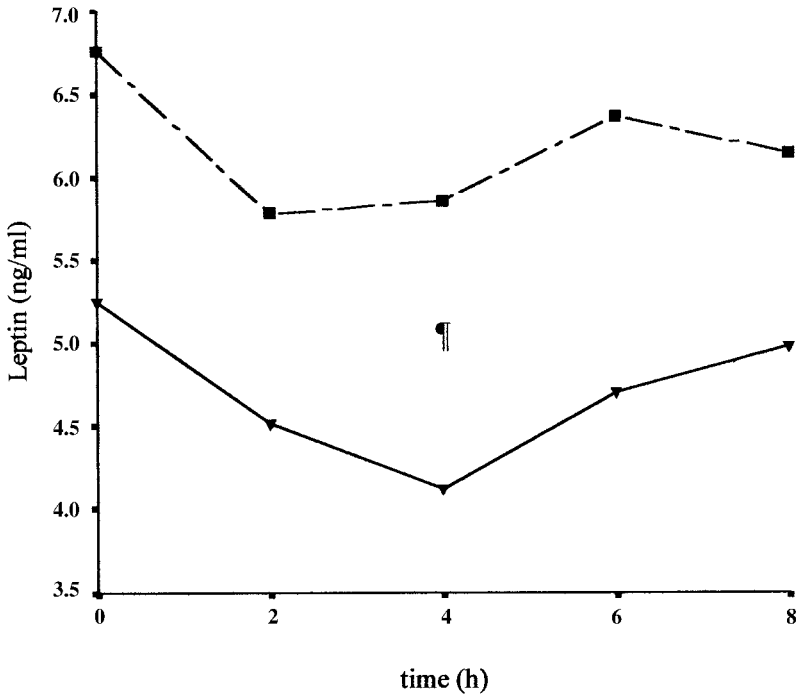

Figure 1—*Plasma leptin after ingestion of the test meal. — - —, control subjects* (P = *0.332); ——, type 2 diabetic patients* (P = *0.698); ¶*P = 0.015 for the comparison of leptin levels at 4 h between the two groups.*

values observed at 2 h. Compared with control subjects, diabetic patients displayed a prolonged insulin response, with 4-h values being significantly different from fasting insulin levels ($P = 0.008$). Although we could not legitimately evaluate the significance of differences at each time point ($P > 0.05$) (Fig. 1), leptin levels tended to decrease postprandially in both groups, with nadir levels observed at 4 h in diabetic patients and at 2 h in control subjects. Leptin levels at 4 h were significantly lower in diabetic patients compared with control subjects (4.12 ± 0.45 vs. 5.85 ± 0.47 ng/ml, $P = 0.015$).

Although we did not observe significant variations of leptin concentrations in the two groups, some points need particular consideration. The initial decrease in leptin concentration observed at 2 h was common in both groups. Interestingly, in type 2 diabetic patients, leptin continued to decline contrary to control subjects, with nadir levels observed at 4 h. Regardless of feeding, this early waning appears to be a continuation of decline from peak nocturnal levels. The same tendency was observed in another study (1), where the 24-h profiles of circulating leptin levels were studied using isocaloric diet. No such decrease was observed after lunch, supper, or evening snack.

Although there was no interaction between time and postprandial leptin performance, leptin concentrations continued to decline at 4 h in type 2 diabetic patients, reaching values significantly lower compared with those of control subjects, in whom leptin tended to increase after the initial drop. A similar time difference regarding leptin increase was observed during hyperinsulinemic clamp studies, where a significant increase in leptin concentration was observed after 6 and 8.5 h in control subjects and type 2 diabetic patients, respectively (6). It is reported that an insulin-mediated increase in leptin levels is dependent on glucose entry and metabolism in adipocytes (7). We hypothesize that the delayed response of leptin observed in diabetic patients might be related to impaired-insulin sensitivity at the level of adipose tissue. Indirect evidence of insulin resistance (8,9) in our study arises from the enhanced triglyceride response exhibited only by diabetic patients. Although we cannot exclude the contribution of relative insulin deficiency in impaired leptin response found in diabetic patients, the comparable insulin concentration in the two groups does not favor this hypothesis.

In conclusion, we found that a lipid load does not have a short-term effect on leptin levels in both type 2 diabetic patients and healthy control subjects. The tendency of a delayed postprandial leptin response in diabetic subjects might be related to impaired insulin sensitivity at the level of adipose tissue. Further studies are needed to confirm this observation and to address the corresponding metabolic significance.

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Use of Nicotinic Acid in the Management of Recurrent Hypoglycemic Episodes in Diabetes

Chronic administration of nicotinic acid (NA) has been shown to cause a deterioration in glycemic control in diabetic patients (1,2). Acute use of NA inhibits lipolysis in adipose tissue suppressing circulating nonesterfied fatty acid (NEFA) levels. Once the effect of NA abates, NEFA levels increase above baseline (3). According to the Randle cycle hypothesis, when NEFA availability increases, NEFA oxidation occurs at the expense of glucose oxidation with a resultant reduction in glucose uptake by skeletal muscle and an increase in blood glucose levels (4).

Some patients with type 1 diabetes have frequent and often unpredictable hypoglycemic episodes. We hypothesized that the addition of regular oral NA to deliberately induce insulin resistance and increase blood glucose levels would result in an increase in insulin requirements and reduce the propensity to severe hypoglycemia. We report the cases of two patients with long-standing poorly controlled diabetes in whom NA has been used to decrease the occurrence of hypoglycemic episodes. Both patients understood and agreed to the use of NA in an experimental fashion.

Case 1

A 49-year-old woman with a 30-year history of type 1 diabetes complicated by a painful peripheral neuropathy and autonomic neuropathy (gastroparesis and chronic constipation) reported a long-standing history of erratic blood glucose control and daily hypoglycemic episodes interspersed with marked hyperglycemia. Her insulin requirments were 30–35 U daily. Following an addition of 1.25 g NA daily, insulin requirments increased to 70–75 U daily. There was a more predictable pattern to her glucose levels; the patient felt better and reported a reduction in hypoglycemic episodes to less than once a week. After several months, the patient withdrew from use of NA because of recurrent nausea and vomiting. Blood glucose control again became erratic with more frequent hypoglycemic episodes. Insulin requirements returned to 30–35 U per day. The patient recommenced NA at 1.25 g daily with subsequent improvement in the rate of hypoglycemic episodes and an increase in her insulin requirements.

Case 2

A 46-year-old woman with secondary diabetes resulting from chronic pancreatitis also suffered from recurring major hypoglycemic episodes. In addition to having chronic low back pain and coronary artery disease, she had exocrine pancreatic insufficiency that required the use of pancreatic enzymes, and she used methadone for the management of chronic narcotic dependency. The introduction of NA at 1.5 g daily did not change her insulin requirements but did cause a reduction in the reported frequency of major and minor hypoglycemic episodes.

The problems encountered by these two patients occur in a small number of patients with long-standing diabetes. Other potential causes of severe recurrent hypoglycemia were excluded, such as hypothyroidism, adrenal insufficiency, and celiac disease. Attempts to regulate blood glucose control through strict control of diet, physical activity, and changes to insulin regimens (including the use of lispro insulin and a return to bovine insulin) all failed to provide relief from symptoms. Both patients benefited from a reduced rate of hypoglycemia, and in the first patient there was an increase in insulin requirements. The malabsorption syndrome in the second patient may have had an impact on her response to the treatment.

We feel that NA therapy as a preventative treatment of recurrent hypoglycemia warrants further investigation in a larger group of patients with a formal randomized controlled trial.

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Metabolic Control Matters: Why Is the Message Lost in the Translation?

The need for realistic goal-setting in diabetes care

The scientific evidence is clear: metabolic control matters. The question is, why doesn't this message persuade most patients? In this letter, we address one important consideration: goal-setting and its role in promoting behavioral change and improved glycemic control.

The conclusive evidence from the Diabetes Control and Complications Trial (DCCT) (1) and the U.K. Prospective Diabetes Study (UKPDS) (2) that established causality between glycemic control and the microvascular complications of diabetes has highlighted the importance of the glycohemoglobin level as a critical predictor of future health. Inevitably, the

focus of diabetes care and the interaction between the patient and clinician has increasingly become directed around self-monitoring of blood glucose (SMBG) records and glycosylated hemoglobin measurements (3). However, despite this evidence for the efficacy of tight glycemic control, as pointed out in a recent article in *Diabetes Care* by Narayan et al. (4), translation of these goals into clinical practice has generally been unsuccessful.

The Clinical Practice Recommendations of the American Diabetes Association (ADA) suggest a treatment HbA_{1c} standard of <7% and a blood glucose self-measurement target of 80–120 mg/dl before meals and of 100–140 mg/dl at bedtime in patients who do not have severe or unrecognized hypoglycemia (5). These targets are similar to those recommended by the American Association of Clinical Endocrinologists (6). For the patient in the earlier pathogenic stages of type 2 diabetes who has residual β-cell function and is focused on exercise and following a diet, these can be attainable and realistic goals (2). However, even the most conscientious type 1 diabetic patient using a complex regimen of multiple injections or the insulin pump can face a frustrating battle in trying to keep their daily blood glucose fluctuations in the prescribed "idealized" target ranges. For the vast majority of patients, especially those with type 1 diabetes, these "standards" are unattainable "goals." The median HbA_{1c} levels achieved by the intensive treatment cohort in the DCCT were higher than the currently recommended target goals. Furthermore, annual capillary blood glucose measurements drawn from this group also exceeded these targets: postbreakfast measurements were highest at 195 ± 50 mg/dl, and the calculated mean blood glucose level for this intensively treated group was 155 ± 30 mg/dl (7).

As evidence from clinical trials (such as the DCCT and the UKPDS) have clarified the impact of risk factors on the probability of developing long-term diabetes complications, recommended clinical standards, often inappropriately described as "treatment goals," have been specified. As a first step in discussing "goal- setting in diabetes care," we want to sharpen the distinction between standards and goals, terms often used interchangeably.

One of the first steps in clarifying the goal-setting process with our patients is differentiating and reconciling recommended clinical treatment standards and the patient's own personal goals. Why does the scientific evidence about the importance of metabolic control not persuade most patients? We propose that the current practice of imposing recommended standards, without first working with the patient to incorporate their personal goals, undermines patient motivation and engagement in treatment and thus sabotages "the message" that metabolic control matters. As the originators (8) of the "empowerment paradigm" have emphasized, mutual frustration frequently develops between patient and clinician when externally recommended standards are imposed on patients with diabetes.

In addition to distinguishing standards from goals, we want to clarify two fundamental assumptions about the use of insulin replacement therapy in type 1 diabetes and the more advanced pathogenic stages of type 2 diabetes with severely compromised β-cell function. First, from our perspective, despite tremendous recent technological innovations, the current tools for managing diabetes with exogenous insulin are imperfect. Second, blood glucose levels are not under the exclusive control of patient behaviors. Taken together, these two assumptions preclude the achievement of consistently ideal blood glucose control, even in the most motivated and conscientious patient with type 1 diabetes or the more advanced pathogenic stages of type 2 diabetes (9,10).

An exclusive focus on clinical treatment standards within diabetes creates a vulnerability to perfectionism in both patients and clinicians. We know from behavioral science research that perfectionism is frequently associated with severe behavior and mood disorders (11). Therefore, in the context of diabetes management, the price of perfectionism is dangerously high. Yet this does not mean promoting unhealthy glycemic goals. Rather, with respect to biological goals, it means we must encourage patients to monitor their own personal progress in terms of individual movement toward improved blood glucose levels, rather than in terms of ideal and often unrealistic clinical standards. Changing behavior does not necessarily result in a commensurate improvement in biological goals. However, behavior change is the only goal realistically in reach of the patient, and keeping this distinction between behavioral and biological goals in focus is a key element in fostering engagement of the patient in their self care. When concerted patient motivation and behavior change does not result in the expected biological (glycemic) change, clinicians need to help patients problem-solve the situation and encourage and reinforce them in their efforts in striving toward improvement.

Having standardized glycosylated hemoglobin treatment targets is important for disease management programs and serves a useful role as trigger points to prompt clinicians to action. As professionals, we must strive for the ideal, and in view of the compelling evidence of the DCCT and UKPDS, we must have in our minds the ideal HbA_{1c} level of <7% (or even lower). But translating this ideal into reality in the care of the individual with diabetes is complex. For the individual patient, SMBG and HbA_{1c} levels are more than just objective measures of glycemic control; they translate into a judgment of their performance, competence, and self-worth. By setting goals for the individual patient that are too ambitious and that overlook the complex difficulties of managing diabetes and the realities of life, we may end up tripping up our best intentions; too often the patient will try, fail, and then disengage.

The ultimate goal in diabetes care (as supported by the scientific evidence and outlined in the ADA guidelines) should be tight glycemic control. However, in translating these targets into clinical practice (4), it is important to recognize the critical role that goals can play in the complex process of promoting behavioral change in the patient, thus highlighting the need for incorporating the concept of individualized realistic goal setting into the accepted standards of diabetes care.

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High Incidence of Maternal Transmission of Diabetes in Obese Uruguayan Children

Metabolic experiences in utero, as reflected by a high amniotic fluid insulin concentration, may condition diabetes-associated risk factors such as high BMI (1).

As part of our survey (performed between June and September 2000) of overweight and obese Uruguayan children (age 9–12 years) and the contributing factors of their condition, we evaluated the incidence of maternal transmission of diabetes.

The cross-sectional survey comprised 886 children (452 boys and 434 girls), living in Montevideo, Uruguay, and other cities in Uruguay with >10,000 inhabitants, who were interviewed at home in the presence of at least one parent. The sample was stratified, aleatory, polyetapic, and systematic according to the last national survey (2) and represented an urban population (total 3,200,000: 91% living in urban zone, 88% Caucasian, 8% crossbred, and 4% black). The children were weighed and measured in light clothes and without shoes using equal balances and scales. BMI was calculated according to tables (3) for age and sex. Three subgroups were established: normal weight (NW) (BMI ≤ 85th percentile), overweight (OW) (BMI 85th to 94.9th percentiles), and obese (OB) (BMI ≥ 95th percentile). Incidence of antecedent diabetes was inquired and recorded for both the mother and father.

A total of 17% of the children were classified as OW and 9% as OB. No differences in BMI were found between sexes at the age interval studied. All of the mothers in the OB group had type 2 diabetes, 1% of the mothers in the NW and OW groups had type 1 diabetes, and no differences were found between diabetic and nondiabetic fathers. This maternal transmission of type 2 diabetes was addressed in a recent study (4).

These are the first data regarding Uruguayan children that emphasize the significance of intrauterine environment with respect to exceeding transmission obesity and insulin resistance (a prediabetic condition). Recent reports have suggested that early consequences of an adverse in utero environment do not seem to be attenuating with time (5). Considering the vertiginous increase in type 2 diabetes among adolescents (6) and the pivotal role that obesity plays in the disease (7), we feel these data are very important for the prevention of type 2 diabetes in our clinical practice.

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Risky Delay of Hypoglycemia Detection by Glucose Monitoring at the Arm

Several devices for self-monitoring of blood glucose (SMBG) (e.g., AtLast, Amira; OneTouch Ultra, LifeScan; FreeStyle, TheraSense, Alameda, CA; Glucometer-Elite XL+Microlet-Vaculance, Bayer; and Sof-Tact, Abbott) recently received Food and Drug Administration approval for alternative site monitoring of capillary blood glucose. These alternatives are marketed with considerable efforts under the assumption that capillary blood glucose measurements, e.g., those taken at the forearm, do not differ from the results obtained by classic finger pricking. Diabetic patients using different devices for SMBG reported

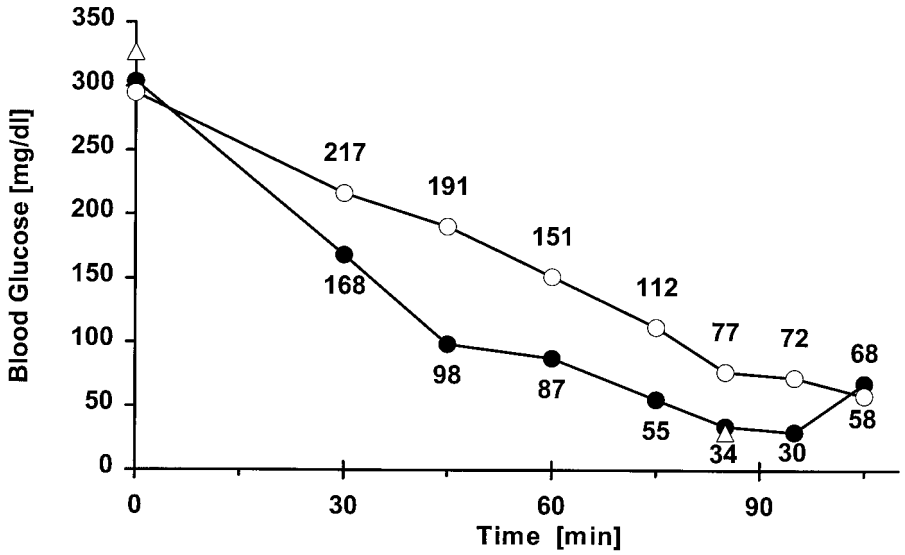

Figure 1—*Effect of a fast blood glucose decrease (3 mg · dl^{-1} · min) on capillary blood glucose values at the fingertip (●) and at the forearm (○) using the FreeStyle system in a type 1 diabetic patient. Control blood glucose values from the fingertip measured at the laboratory are indicated (△).*

discrepancies between clinical symptoms of hypoglycemia and normoglycemic SMBG values at the forearm. Neither standardized quality control assessments of technical performance of such SMBG devices (1,2) nor patient device handling resulted in any obvious explanation of the reported discrepancies. Because of this, we examined whether or not fast blood glucose changes over a larger range of blood glucose concentrations could result in clinically relevant blood glucose differences between forearm and fingertip.

Capillary blood glucose samples were taken from the fingertip and the forearm of six male type 1 diabetic patients on intensified insulin treatment (age 26–54 years, diabetes duration 0.1–25 years) using the FreeStyle system (TheraSense) because it required the smallest blood glucose amount: 0.3 μl/sample. To avoid any disturbance of the normal regional blood flow, the forearm skin was not rubbed before blood glucose sampling, as recommended by the manufacturer. The following protocol was applied: after an overnight fast the usual prebreakfast insulin was omitted and the breakfast was replaced by oral Dextro O.G.T. (Roche, Mannheim, Germany), equivalent to 75 g glucose, in order to achieve blood glucose values of 300–400 mg/dl. Then the patient's usual short-acting insulin was given intravenously at an individual dose (6–15 U/injection). The blood glucose decrease was followed every 5–15 min until either steady state or hypoglycemia (<60 mg/dl) was reached. Hypoglycemia was compensated by oral glucose. For control purposes, additional blood glucose samples from the fingertip were analyzed by the Gluco-quant method (Roche, Mannheim, Germany).

The capillary blood glucose decrease (mean ± SD) at the forearm (208 ± 38 mg/dl) was significantly smaller than at the fingertip (295 ± 16 mg/dl) (Student's paired *t* test: $P < 0.01$) within 111 ± 26 min for all patients. An example is shown in Fig. 1. For the two patients with hypoglycemic unawareness, the first asymptomatic hypoglycemic values at the fingertip (51 and 53 mg/dl) were accompanied by normoglycemic values at the forearm (142 and 159 mg/dl). Compared with the fingertip, it took an additional 27–34 min until the capillary blood glucose levels at the forearm reached hypoglycemic values.

Despite the preliminary state of our investigation, the consistency of clinically relevant delays of blood glucose changes at the forearm prompted us to draw attention to a potentially very dangerous situation. Our results raise the possibility that the delayed glucose concentration changes at the forearm occur physiologically. To our knowledge, this has not been fully recognized as a potential problem by the certifying administrations in the U.S. or Europe.

Even a few delays of hypoglycemia detection could unnecessarily endanger the life of diabetic patients. Because of this, we strongly recommend providing sufficient evidence that the suggested use of SMBG at the forearm and other alternative sites does not result in a risky delay of hypoglycemia detection. Meanwhile, SMBG at the forearm should only be used when ongoing fast blood glucose changes can be excluded.

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COMMENTS AND RESPONSES

Response to Jungheim and Koschinsky

Glucose monitoring at the arm

In this issue of *Diabetes* Care, we read with interest the letter of Jungheim and Koschinsky (1) comparing glucose measurements using blood extracted from the finger versus blood extracted from the forearm. The phenomenon they discuss is not a simple function of measurement technology, but a complex function of circulatory physiology. Our cognizance and study of the phenomenon resulted in the explicit instruction to the users of the TheraSense FreeStyle blood

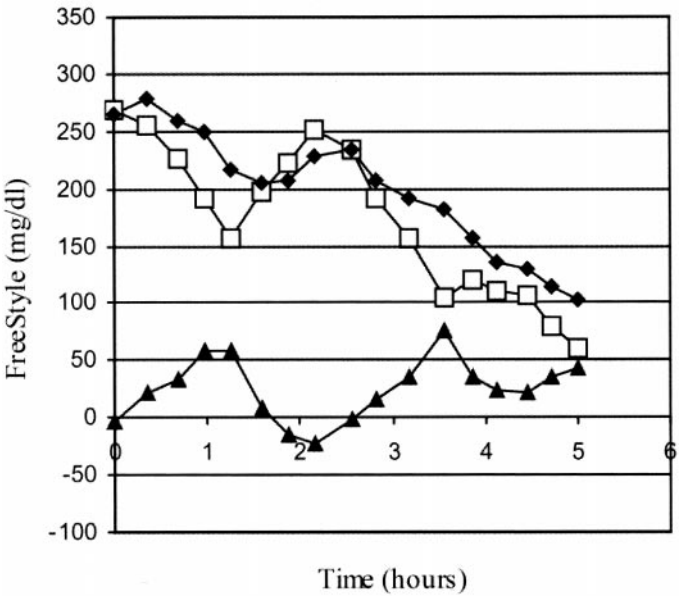

Figure 1—*Glucose profile of arm (no rubbing) and finger. —□—, average finger; —◆—, average arm; —▲—, difference. For average finger and average arm, the data points are the average of duplicate measurements.*

glucose monitoring system to rub the test site before drawing blood. The increased perfusion from rubbing significantly reduces the difference in fingertip and forearm blood glucose measurements (see discussion below). It is significant that Jungheim and Koschinsky did not rub the test site. In addition, their protocol, which involved a glucose tolerance test followed by intravenous insulin, created physiological extremes and influenced the observed differences in study subjects.

An initial TheraSense study involved 100 subjects with both type 1 and type 2 diabetes, in which blood glucose measurements from the arm versus the finger were taken at random times throughout the day. Blood from the forearm (obtained without rubbing) and blood from the fingertip was measured for glucose concentration with the FreeStyle meter. The elevated intercept and low slope were unexpected (Table 1). This was further examined in a study where finger and arm blood samples (obtained without rubbing) were measured over several hours in patients with type 1 diabetes. The study indicated that changes in blood glucose are first detected in finger blood and lag in forearm blood (Fig. 1). A similar study, which included blood from the forearm before and after rubbing, indicated that arm and finger differences are reduced by rubbing the test site (Fig. 2). This led to a final study of 120 subjects with type 1 and type 2 diabetes, in which blood obtained from the forearm (after rubbing) and blood obtained from the finger was measured for glucose concentration using the FreeStyle meter. The comparison yielded a correlation that was nearly ideal (Table 1). The final study also assessed the accuracy and clinical utility of the FreeStyle meter by comparing venous finger and arm (with rubbing) blood to YSI-plasma readings (Table 1).

The current state of our research indicates that there would be very little difference in therapeutic decisions when the arm (following rubbing) rather than the finger is used as the test site. However, when blood glucose concentration is falling rapidly, the lag in glucose change could cause a delay in the detection of hypoglycemia. Accordingly, when testing with the express purpose of detecting hypoglycemia (such as when symptoms of hypoglycemia are present or when a meal has been delayed after taking insulin), the finger may be the preferred test site. Our studies indicate that a delay in the detection of hypoglycemia is not a common occurrence in routine testing on the arm. However, this phenomenon must be seriously considered and thoroughly understood. TheraSense has undertaken additional studies under a variety of circumstances to better understand this complex question of circulatory physiology. These studies will be the subject of future publications.

We feel that the obvious benefits of new technologies should not be overshadowed by the manageable risks. The introduction of fingertip blood glucose testing enabled the aggressive management of glucose levels in people with diabetes, yet it also increased the frequency

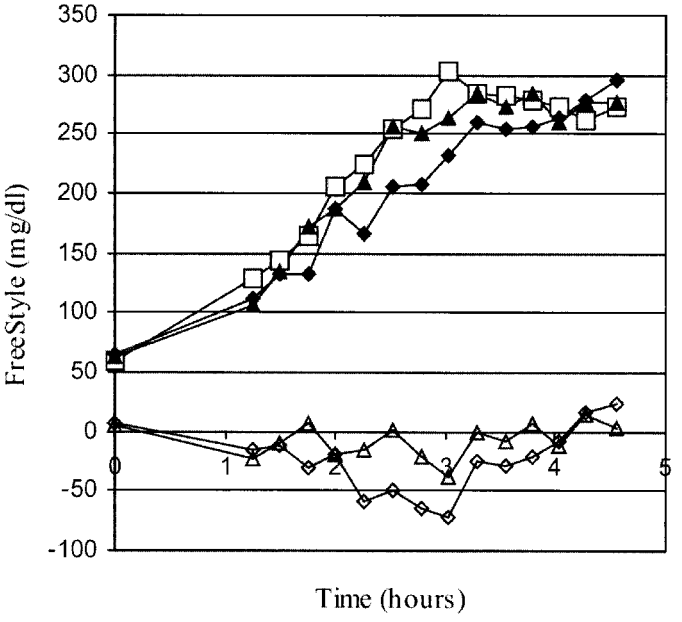

Figure 2—*Glucose profile of arm (no rubbing), arm (with rubbing), and finger. —□—, Average finger; —◆—, arm unrubbed; —▲—, arm rubbed; —◇—, difference unrubbed; —△—, difference rubbed. For average finger, the data points are the average of duplicate measurements.*

Table 1—*Linear regression statistics and Clarke Error Grid Analysis*

Comparison	Intercept (mg/dl)	Slope	*r*	Clarke Error Grid Zones (% of readings in the zone) A	B	C	D
Arm (no rubbing) vs. finger	19.4	0.913	0.956	NA	NA	NA	NA
Arm (rubbing) vs. finger	−0.5	1.027	0.971	NA	NA	NA	NA
Venous vs. venous YSI	7.1	0.923	0.992	99.6	0.4	0	0
Finger vs. finger YSI	6.6	0.934	0.982	98.3	1.7	0	0
Arm (rubbing) vs. finger YSI	9.0	0.945	0.967	87.7	11.4	0	0.8

NA, not applicable.

of hypoglycemic events. Clearly, the benefits of intensive insulin therapy outweighed the risks of hypoglycemia. Similarly, greatly reducing the pain associated with blood glucose testing by permitting testing on the forearm and other sites is likely to have a significant positive impact on compliance with monitoring regimens.

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How Cost–Effective Is the Treatment of Dyslipidemia in Patients With Diabetes but Without Cardiovascular Disease?

A response to Grover et al.

In the January 2001 issue of *Diabetes Care*, Grover et al. (1) reported on the cost-effectiveness of dyslipidemia treatment in patients with diabetes but without cardiovascular disease. Although the article was interesting and relevant, further review of the assumptions of the study's Markov model raise several questions.

First, in the cost-effectiveness model, the choice of years of life saved (YOLS) rather than quality-adjusted life years (QALYs) is debatable. Diabetes is known to have a significant effect on morbidity, mortality, and quality of life. In addition, other aspects of diabetes (including cardiovascular disease) are known to influence the quality of life of people with diabetes. Therefore, the use of YOLS as a measure of effectiveness may be simplistic and insufficient as an outcome measure because it usually counts as less than one full QALY (2). What effect would the use of QALYs have had on the study results and conclusions?

Second, the assumptions that lipid levels and the effectiveness of simvastatin therapy were similar to that observed in the Scandinavian Simvastatin Survival Study trial appear problematic in light of current evidence. The assumptions include LDL cholesterol of 188 mg/dl (4.87 mmol/l) and HDL cholesterol of 46 mg/dl (1.18 mmol/l). Expected effects of simvastatin therapy based on a decrease in LDL cholesterol of 35% and an increase in HDL cholesterol of 8% would be 122 mmol/dl (3.15 mmol/l) and 50 mmol/dl (1.29 mmol/l), respectively. However, these targets run contrary to the American Diabetes Association (ADA) practice guidelines for 2001 (3). The goals of lipid therapy include LDL cholesterol of ≤100 mmol/dl (≤2.60 mmol/l) and HDL cholesterol of 45 mg/dl (1.15 mmol/l) and 55 mg/dl (1.40 mmol/l) in men and women, respectively.

Very few patients were likely to meet current standards of lipid treatment based on the assumptions of the study. Therefore, to achieve ADA goals, higher doses of simvastatin or longer duration of lipid treatment may be required. The implication is that the cost calculations are likely to yield higher figures, which may alter the cost-effectiveness ratios. What effect would varying the cost calculations to achieve ADA end points have had on the study results?

These questions and comments should not undermine the importance of the work of Grover et al. Rather, they are important clinical questions that may need consideration in future studies on cost-effectiveness, particularly on primary prevention of cardiovascular disease in people with diabetes.

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Response to Egede

We thank Dr. Egede (1) for his letter in this issue of *Diabetes Care* and for taking the time to read our study (2) and provide us with his thoughtful comments. He raises several important points.

The first point concerns the choice of

years of life saved rather than quality-adjusted life years in the cost-effectiveness analysis. Dr. Egede's point that both diabetes and cardiovascular disease may have a significant impact on quality of life is well taken. We agree with him that it would be desirable to include quality-of-life issues in our analyses. We have recently completed a study evaluating the quality of life of individuals with and without cardiovascular disease, and we believe this study could provide utility measures suitable for part of the analysis.

Second, in our study, we compared the effects of simvastatin therapy for individuals with diabetes or cardiovascular disease based on the results of the Scandinavian Simvastatin Survival Study (4S) trial (3). Dr. Egede argues that the lipid targets currently recommended by the American Diabetes Association are lower than the mean LDL cholesterol levels obtained in the 4S study. We note that this is also true of the lipid targets recommended by the American Heart Association for individuals with cardiovascular disease. However, the focus of our analyses was on the benefits of lipid therapy among various groups of patients rather than on the benefits of following expert guidelines. As a first step, this approach allows for a level playing field so that the benefits of treatment and treatment alone are being compared. We also note that the currently recommended lipid targets represent levels that are not often achieved in current clinical practice. Finally, we are unaware of any data describing the costs of successfully treating groups of individuals to a specified target lipid level. Without such cost data, it is impossible to calculate the associated cost-effectiveness ratios. We chose the 4S study because it provided the necessary data on statin utilization and the largest reductions in LDL cholesterol associated with long-term clinical outcomes.

Third, the availability of results from the Heart Protection Study, which is expected later this year, should provide a wealth of additional information and finally help to resolve any remaining questions regarding the cost-effectiveness of lipid therapy in diabetic patients without coronary heart disease (4).

Dr. Egede has raised important research questions for future analyses. We believe that with the availability of results from ongoing studies, as well as the completion of additional research, the necessary pieces will eventually be available to adequately complete the puzzle.

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Pseudonormal Diastolic Filling Unmasked With Glyceryl Trinitrate in Patients With Type 2 Diabetes With Poor Metabolic Control

Poirier et al. (1) report very interesting data regarding pseudonormal diastolic filling in men who are free of clinical heart disease and have well-controlled diabetes. Specifically, 28% of their subjects had a pseudonormal filling pattern, which was detected using a Valsalva maneuver and/or pulmonary venous Doppler (PVD). We conducted a similar study in 34 high-risk type 2 diabetic patients (16 men, 18 women) who were middle-aged (mean age 55.8 years), obese (BMI 30.6 kg/m^2), and had poor metabolic control (HbA_{1c} 10.6%, fasting blood glucose 13.4 mmol/l). None of the patients had a history of heart failure or myocardial infarction, and we included patients with controlled hypertension. The patients underwent echocardiography methods similar to those used by Poirier et al. (1), although preload reduction was achieved with sublingual glyceryl trinitrate (GTN) (400 μg). PVD was suboptimal in one-third of the subjects and thus not included in the analysis.

Diastolic filling pattern was assessed at baseline, and 14 (41%) of the subjects had a normal filling pattern (*E*-to-*A* ratio 1.0–1.7, deceleration time 0.14–0.23 s); the remainder had an abnormal filling pattern. However, after administration of GTN, all of the patients had an abnormal relaxation pattern; 20 (58.8%) were classified as having abnormal relaxation and 14 (41%) as having pseudonormal relaxation.

A total of six subjects in the abnormal relaxation group had left ventricular (LV) dilatation (*M* mode: LV end-diastolic pressure >58 mm). In all but one of these subjects, LV size was normal when adjusted for body surface area (BSA) LV end-diastolic dimension [LVEDD]/BSA <32 mm/m^2). All patients had normal LV function as assessed by *M* mode fractional shortening (>25%) and subjective assessment of ejection fraction from the apical views. Compared with the abnormal relaxation group, the pseudonormal filling group was younger (52.6 vs. 58.1 years, $P = 0.03$) and had lower fasting blood glucose (12.1 vs. 14.3 mmol/l, $P = 0.03$). However, there were no differences in the levels of HbA_{1c} (10.3 vs. 10.8%, $P = 0.14$), duration of diabetes (6.8 vs. 7.9 years, $P = 0.48$), LV size (LVEDD: 50.4 vs. 54.1 mm, $P = 0.16$) or LV mass (143.9 vs. 156.6 g, $P = 0.38$).

Our group of patients had higher HbA_{1c} levels than those reported by Poirier et al. (1), none displayed a normal diastolic filling pattern, and 41% displayed a pseudonormal pattern in the absence of LV dilatation, hypertrophy, or systolic dysfunction. Our findings sup-

port the conclusions of Poirier et al. (1), highlighting the need for thorough echocardiographic evaluation in type 2 diabetes and, in particular, assessment of mitral filling under different loading conditions for thorough assessment of LV diastolic function.

In our study group, PVD was suboptimal in many subjects and thus may not be widely applicable in type 2 diabetic patients. Poirier et al. (1) found that while preload reduction always identified pseudonormal filling, PVD did not. Pseudonormal filling detected by preload reduction is related to LV diastolic pressure (2) and has been used to differentiate between true and pseudonormal filling patterns in both disease and healthy control subjects (3,4).

Traditionally, the focus of echocardiography has been to assess LV hypertrophy and systolic function. However, the presence of diastolic dysfunction in the setting of normal systolic function and no other structural heart disease may be important for long-term cardiovascular prognosis in diabetes. The pseudonormal group may represent a separate subgroup of patients who are at particular risk of developing a restrictive diabetic cardiomyopathy. A thorough evaluation using a longitudinal study is necessary to measure the natural time course of diastolic filling changes in diabetes, which would require the follow-up of a large cohort of patients.

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Response to Whalley et al.

We would like to thank Whalley et al. (1) for their letter in this issue of *Diabetes Care* and for their interest in our work (2). For the most part, the results they describe are in agreement with the conclusions of our article. However, the authors report a higher incidence of diastolic dysfunction, perhaps because their subjects constituted a higher risk group with poorly controlled type 2 diabetes. Interestingly, the group with a pseudonormal pattern of diastolic dysfunction was younger than the group with an abnormal diastolic function (on average, 4 years younger than our group).

These results further emphasize the importance of using preload reducing maneuvers, such as the Valsalva maneuver, to unmask left ventricular diastolic dysfunction in type 2 diabetic subjects. Clearly, erroneous conclusions about cardiac function may be drawn if such maneuvers are not used. This must be a consideration in the design of prospective future studies dealing with type 2 diabetic subjects. Finally, in our experience, the Valsalva maneuver is much easier, more rapid, and more sensitive than the use of glyceryl trinitrate, particularly when patients remain in the supine position.

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Erratum

Krampl E, Kametas NA, Nowotny P, Roden M, Nicolaides KH: Glucose metabolism in pregnancy at high altitude, *Diabetes Care* 24:817–822, 2001

The first sentence of the first full paragraph in the third column of page 818 should read, "Plasma proinsulin concentrations were below the lower limit of detection of 2 pmol/l in 26 pregnant subjects (28.0%) at high altitude and in 3 subjects (2.4%) at sea level."