OBSERVATIONS

Lack of Effect on LDL Oxidation and Antioxidant Status After Improvement of Metabolic Control in Type 2 Diabetes

Type 2 diabetes is associated with increased oxidative stress, which may contribute to microvascular and macrovascular complications (1). One of the consequences of increased oxidative stress may be increased lipid peroxidation. Improvement of metabolic control has a favorable effect on microvascular and possibly also on macrovascular complications (2). Whether reduction of lipid peroxidation plays a role in this respect is not known.

We investigated whether improvement of metabolic control by insulin therapy had a favorable effect on lipid peroxidation.

In this study, 21 patients with type 2 diabetes and insufficient metabolic control despite near-maximal doses of oral blood glucose–lowering agents participated (age 58 ± 12 years, diabetes duration 10 years [range 1–38], BMI 29.2 ± 7.1 kg/m^2, HbA_{1c} 10.6 ± 1.1%). Four of them smoked (10–40 cigarettes/day) and seven of them had clinically evident macrovascular disease. During the study, all patients maintained their diets according to international nutritional guidelines. Insulin treatment consisted of twice-daily injections of a mixture of short- and intermediate-acting insulin. The goal of therapy was to achieve fasting and postprandial blood glucose levels <7 and 10 mmol/l, respectively, and HbA_{1c} <8%. Checkups after 2 weeks and monthly thereafter consisted of taking measurements of body weight and HbA_{1c}. Insulin doses were adjusted weekly on the basis of self-monitoring of blood glucose levels.

Lipid peroxidation was assessed by *1*) thiobarbituric acid reactive substances (TBARS) (3), *2*) production of conjugated dienes after copper-induced LDL oxidation in vitro (4), and *3*) levels of IgG and IgM autoantibodies to oxidized LDL by enzyme-linked immunosorbent assay (5). Vitamin E was determined with high-performance liquid chromatography. A detailed description of the complete methodology was published previously (6). Differences between groups were analyzed with Student's *t* test for paired samples. When variables were not normally distributed, Wilcoxon's signed-rank test was used.

After 3–4 months of insulin therapy, HbA_{1c} decreased to 7.9 ± 0.6% ($P <$ 0.005). The daily insulin dose was 61 U (16–100), and the mean weight gain was 5.4 kg. Total cholesterol, LDL cholesterol, and HDL cholesterol did not change (6.0 ± 1.1, 3.7 ± 0.9, and 1.0 ± 0.3 mmol/l, respectively), neither did apolipoprotein B (apoB) and the LDL cholesterol/apoB ratio, the latter as a rough index of LDL size. Apolipoprotein A1 (apoA1) levels increased from 1.45 ± 0.28 to 1.63 ± 0.36 g/l, and triglycerides decreased from 2.44 (range 0.95–7.09) to 1.74 (0.87–5.67) mmol/l. Fasting insulin levels increased from 7.6 (2.0–35.5) to 12.4 (5.10–58.7) mU/l (P = 0.07). No decrease in TBARS was found (1.83 ± 0.79 vs. 1.50 ± 0.39 µmol/l), even when we excluded the three patients with triglycerides >4.5 mmol/l. Lag phase, as an index of the susceptibility of LDL to copper-induced oxidation, also remained unchanged (59 ± 6, resp. 62 ± 10 min), whereas the conjugated dienes production rate decreased from 17.8 ± 2.6 to 16.1 ± 3.0 nmol · l^{-1} · min^{-1}, $P <$ 0.005). Levels of autoantibodies to oxidized LDL did not change. Vitamin E levels, corrected for LDL cholesterol, remained unchanged.

Some, but not all, studies show evidence of increased LDL oxidation in type 2 diabetes (6,7). Increased LDL glycation and formation of advanced glycated end products may increase the susceptibility of LDL to oxidation. Hyperglycemia itself can stimulate free-radical production, and small dense LDL, more prevalent in type 2 diabetes, is prone to oxidation (7). Several factors contribute to LDL peroxidation, and this may explain why we, in contrast to our hypothesis, did not find convincing evidence of reduced LDL peroxidation. The achieved metabolic control may be of influence: one study found a reduction in lipid peroxidation only when HbA_{1c} dropped to <7% (8). In our patients who achieved an HbA_{1c} <7.5%, no change was found. Even when HbA_{1c} should have been <7%, the expected effect is small and therefore probably not clinically relevant. Seven patients had macrovascular disease, but there is no consensus in the literature on whether lipid peroxidation in these cases is increased; in a previous study, we did not find evidence for this (6). Maybe a favorable effect on LDL peroxidation is counteracted by factors that were also changed during the treatment period and that stimulate LDL oxidation; for insulin, in vitro pro-oxidant properties have been shown (9). Obesity is associated with increased LDL peroxidation (10), so weight gain may have influenced the results, although we think this effect is small. A change in antioxidant status seems unlikely; vitamin E levels remained unchanged and patients did not change their dietary habits during the study. Sulfonylureas may have an antioxidant effect, but this has been shown only for gliclazide in vitro (11). In our study, only four patients used gliclazide. Lipid peroxidation was tested 2 weeks after the oral agents were stopped, and no change in lipid peroxidation was observed. This makes it unlikely that cessation of these agents should have influenced the results. It is uncertain whether the decrease in the production rate of conjugated dienes that we found is important. Susceptibility of LDL to oxidation is explained mainly by the lag phase. However, the speed at which lipid peroxidation products are formed may be also of importance for its damaging effect. It is assumed that lipid peroxidation takes place mainly in the vessel wall, and, therefore, the question remains whether serum parameters and in vitro parameters are representative. Recently, in agreement with our earlier results, no association could be found between the prevalence of coronary heart disease and LDL susceptibility to oxidation in type 2 diabetic patients (12).

In conclusion, we found no convincing evidence of reduced LDL oxidation after improvement of metabolic control in type 2 diabetes. The importance of the reduced conjugated dienes production rate remains to be investigated further.

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Meal-Generated Oxidative Stress in Diabetes

The protective effect of red wine

Several epidemiological studies suggest that coronary heart disease mortality is lowered by moderate consumption of red wine (1,2). The cardiovascular benefits of moderate wine consumption have been thought to stem, at least partly, from antioxidant activities of red wine (3).

Recently, a preliminary report suggested the possibility that red wine, a polyphenol-rich beverage, increases the antioxidant power of plasma in humans (3). Since then, several authors have published results fully confirming that the consumption of moderate amounts of red wine elicits a prompt, though temporary, rise of plasma antioxidative defenses (4,5).

Consequently, it has been suggested that this property may provide a clue to the role of certain wines in the so-called "French paradox," according to which the consumption of moderate amounts of red wine by the French appears to afford some protection against cardiovascular disease, despite their consumption of a diet rich in saturated fat (2). Diabetes is characterized by a high incidence of cardiovascular disease (6), and oxidative stress has been recognized as a major pathophysiological link between cardiovascular disease and diabetes (7). In diabetic patients, the consumption of meals is accompanied by a significant decrease of antioxidant defenses due to the generation of oxidative stress (8). This observation is consistent with the recent report by Staprans et al. (9) showing increased postprandial oxidized lipid levels in poorly controlled diabetic patients. Therefore, meal consumption seems to play a crucial role in the generation of oxidative stress in diabetes.

Because red wine ingestion has been demonstrated to be accompanied by a significant increase of plasma antioxidant power (6,7), the aim of this study was to explore the possibility that red wine consumption may reduce oxidative stress produced in diabetic patients during meals.

Informed consent to participate in the present study was obtained from 10 male type 2 diabetic patients (age 55.1 ± 1.5 years, mean ± SEM, duration of diabetes 9.0 ± 1.2 years, BMI 25.6 ± 1.1 kg/m^2). In each subject, three different studies were performed in randomized order on different days: a standard meal test (8), fasting ingestion of 300 ml of red wine, and a meal plus 300 ml of red wine. The study protocol was approved by the Ethical Committee of the University of Udine.

Blood samples, obtained in the absence of venous stasis, were collected at baseline and 60, 120, and 180 min after the meals. In every sample, plasma glucose, insulin, triglycerides, and plasma total radical-trapping antioxidant parameter (TRAP) were measured. The assay of TRAP has been recently proposed to evaluate plasma antioxidant capacity, taking into consideration known and unknown antioxidants present in the plasma as well as their mutual cooperation: A higher TRAP number designates a higher antioxidant capacity (10). The antioxidant power of red wine (Merlot; Azienda Agricola Ermacora, Ipplis, Udine, Italy) was also tested in triplicate using the method described above and compared with the antioxidant power of a white wine (10).

By repeated-measures analysis of variance, plasma glucose (F = 48.0, P = 0.001), insulin (F = 42.4, P = 0.001), and triglycerides (F = 26.1, P = 0.001) significantly increased, whereas plasma TRAP (F = 27.8, P = 0.001) significantly decreased during the meal test. Fasting consumption of red wine significantly increased TRAP activity, whereas wine ingestion with a meal counterbalanced the decrease of TRAP (F = 8.2, P = 0.001). In vitro, red wine showed a TRAP activity of 6.1 ± 0.2 mmol/l, whereas the TRAP of white wine was 1.2 ± 0.3 mmol/l.

Our data show that red wine is able to preserve plasma from meal-induced oxidative stress in diabetes, suggesting that moderate consumption of red wine during meals may have a beneficial effect in decreasing the risk of cardiovascular disease in diabetic patients.

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Red Blood Cell Autoantibodies With a Shortened Erythrocyte Life Span as a Cause of Lack of Relation Between Glycosylated Hemoglobin and Mean Blood Glucose Levels in a Woman With Type 1 Diabetes

Glycosylated hemoglobin is the test most widely used to document the degree of glycemic control in patients with diabetes. The strong statistical relationship between mean blood glucose levels and glycosylated hemoglobin is well established (1); however, clinically significant differences in average blood glucose from individuals with identical glycosylated hemoglobin levels have been reported (2). Differences in erythrocyte life span among individuals are one of the proposed factors that may alter the relationship between a given glycosylated hemoglobin level and average blood glucose (1).

We report on a patient in whom lack of relation between glycosylated hemoglobin and mean blood glucose levels is explained by the presence of red blood cell autoantibodies.

A 30-year-old woman with type 1 diabetes of 11 years' duration was first seen at our clinic for preconception control. There was no family history of autoimmune diseases. She had no evidence of diabetes complications (normal dilated-eye examination and albumin excretion <20 μg/min) and was on three insulin injections per day. She took no other medications regularly. Physical examination was normal and she was asymptomatic. She reported habitual good glycemic control as assessed from glycosylated hemoglobin, though she rarely performed self-monitoring of blood glucose levels. Initial glycosylated hemoglobin (high-performance liquid chromatography; Bio-Rad, Richmond, CA) was 6.5%. On entering preconception care, she started daily capillary blood glucose self-monitoring (six to seven measurements/day). The glucose meter used (OneTouch Profile; LifeScan, Milpitas, CA), with storage capability, allows computer-assisted analyses of glucose readings. After 45 days, her mean blood glucose level was 11.3 mmol/l (252 readings) and her glycosylated hemoglobin was 5.8%. After another period of 45 days, her mean blood glucose level fell to 8.2 mmol/l (331 readings) and glycosylated hemoglobin to 4.9%. Both glycosylated hemoglobin values are by far lower than expected from each average blood glucose (3). Hemoglobin variants, which may lower results of glycosylated hemoglobin (4), were ruled out since the assay used is not affected by these. Ingestion of vitamin C or E, which has also been reported to lower glycohemoglobin values (5,6), was also excluded. Red blood cell life span, evaluated with chromium-labeled self-erythrocytes, showed a reduced half-life: 20 days (normal $t^{1/2}$: 28–30 days), with an increased erythropoietic activity index (2.4) and spleen participation in hemolysis. Her levels of lactate dehydrogenase, plasma hemoglobin, bilirubin, haptoglobin, and her reticulocyte count were normal. The Coombs' antiglobulin test showed the presence of IgG autoantibodies on the patient's red blood cell surface. Further evaluation of autoimmune disease showed a positive antinuclear antibody test, with positive anti-Ro/SSA, anti-La/SSB, and anticardiolipin autoantibodies. Anti-DNA, anti-Sm, and anti-RNP autoantibodies were negative.

Immunohemolytic anemia, in its mildest form with only positive antierythrocyte autoantibodies, seems to be responsible for the low glycohemoglobin values in this patient. Immunohemolytic anemia has been reported as a cause of decreased glycosylated hemoglobin in two patients with type 1 diabetes (7); however, in both cases, hemolysis, which was induced by drugs, was evident. This case suggests the possibility that the presence of red blood cell autoantibodies with shortened erythrocyte life span, but no clinical expression, might explain the lack of relation between glycosylated hemoglobin and mean blood glucose levels more often than has been suspected.

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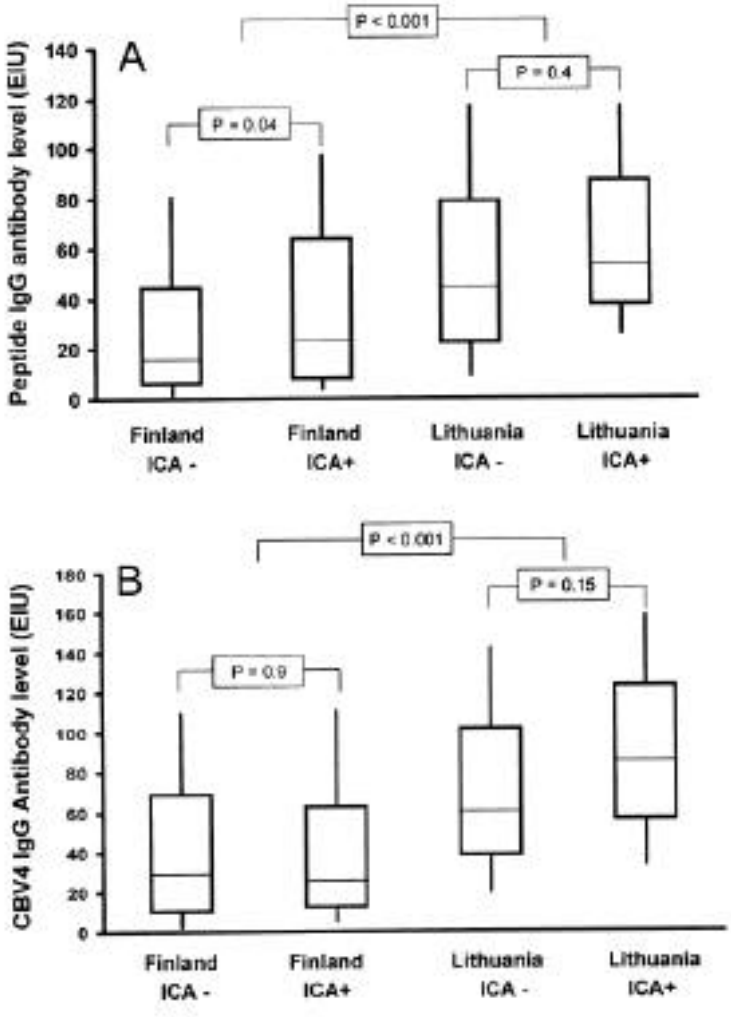

Figure 1—*IgG class antibody levels against enteroviral peptide antigen (A) and purified CBV4 (B) in healthy Finnish and Lithuanian schoolchildren with and without ICA. The boxes outline 25 and 75% percentiles, and the vertical lines mark 10 and 90% percentiles. The horizontal line in the box indi - cates median value. EIU, enzyme immunoassay unit.*

Enterovirus Antibodies in Relation to Islet Cell Antibodies in Two Populations With High and Low Incidence of Type 1 Diabetes

Enterovirus infections are among the most suspect environmental factors in the pathogenesis of type 1 diabetes (1–3). The present study was aimed at testing the hypothesis that the marked international variation in the incidence of type 1 diabetes may reflect differences in the epidemiology of enterovirus infections in various countries. We measured enterovirus antibody levels and islet cell antibody (ICA) prevalence in healthy schoolchildren in two geographically nearby countries, Finland and Lithuania, that differ in the incidence of type 1 diabetes. Finland has the highest incidence in the world, whereas in Lithuania, the incidence is substantially lower (averages of 35 per 100,000 and 7 per 100,000, respectively, in 0- to 14-year-old children during 1983–1992) (4).

Serum samples were collected during 1994 from 1,049 unaffected Lithuanian schoolchildren living within the region of Kaunas and from 3,651 unaffected Finnish schoolchildren living in northern Finland. We analyzed enterovirus antibodies from 200 age- and sex-matched pairs of Finnish and Lithuanian ICA^- children (38% male, mean age 10.8 years). ICA^+ serum samples were available from 102 Finnish children (50% male, mean age 11.8 years) and 23 Lithuanian children (48% male, mean age 11.6 years).

Group-specific IgG class enterovirus antibodies were analyzed against a synthetic peptide and purified Coxsackie B virus (CBV) 4 by enzyme-linked immunosorbent assay as previously described (1). Serotype specific antibodies against CBV4 and CBV5 serotypes, which have been connected to type 1 diabetes as well as poliovirus type 1, were analyzed using standard plaque neutralization test. Hepatitis A

virus antibodies were measured using the Enzygnost Anti HAV kit (Behringwerke AG, Marburg, Germany). ICA in the Finnish sera were analyzed as previously described (5). The detection limit of ICA was 2.5 Juvenile Diabetes Foundation units (JDF U). ICA in the Lithuanian sera were detected by indirect immunofluorescence method on 4-μm cryostat sections of blood group O frozen human pancreas (6). The $\log_2$ endpoint titers of test samples were converted to JDF U (7). The detection limit of ICA was 5 JDF U.

The Lithuanian ICA$^-$ children had significantly higher enterovirus antibody levels than the Finnish children (Fig. 1). This difference was seen in IgG levels against the enteroviral peptide antigen ($P < 0.001$) and purified CBV4 virions ($P < 0.001$), as well as in the frequency of neutralizing antibodies against CBV4 (75 vs. 63%, $P < 0.01$) and CBV5 (65 vs. 38%, $P < 0.001$). Seropositivity in the hepatitis virus A antibody assay was also more common in the Lithuanian than the Finnish children (20 vs. 1%, $P < 0.001$). However, the Finnish and Lithuanian children had similar titers of neutralizing antibodies against poliovirus type 1, indicating no difference in the efficacy of polio vaccination programs.

ICA prevalence was 2.8% among the Finnish children (8) and 2.2% among the Lithuanian children. The Finnish ICA$^+$ children had higher antibody levels against the enterovirus peptide antigen than the ICA$^-$ Finnish children ($P < 0.05$, Fig. 1). The Lithuanian ICA$^+$ children had higher antibody levels against CBV4 than the Lithuanian ICA$^-$ children, but the difference remained statistically nonsignificant ($P = 0.15$) (Fig. 1). Antibody levels against other enterovirus antigens, as well as against hepatitis A virus, were similar in the ICA$^-$ and ICA$^+$ children.

Higher enterovirus antibody levels in the Lithuanian children suggest a higher frequency of enterovirus infections in Lithuania. Higher enterovirus antibody levels in the ICA$^+$ children than in the ICA$^-$ children support the role of enterovirus infections in β-cell autoimmunity. Thus, the results are discrepant in an intriguing way: enterovirus infections seem to be associated with β-cell autoimmunity, which is in line with previous studies (1–3), and yet it looks as if these infections were more frequent in Lithuania, with a lower diabetes incidence, than in Finland.

In addition to enterovirus infections, hepatitis A virus infections were also shown to be less frequent in Finland than in Lithuania. The epidemiology of viruses with fecal-oral transmission, such as enteroviruses and hepatitis A virus, is highly dependent on climatic and socioeconomic factors. Accordingly, climatic differences between Finland and Lithuania (mean annual temperatures 2 vs. 6°C in the regions of serum collection), as well as higher socioeconomic status in Finland (gross national products $18,850 vs. $1,350 per capita at the time of the serum collection), may explain the lower frequency of these infections in Finland.

This is the first study evaluating the relationship between the incidence of type 1 diabetes and the frequency of enterovirus infections in different populations. The inverse relationship between the two suggests that the high diabetes incidence in Finland is not due to a generally high frequency of enterovirus infections in the Finnish population. However, it is still possible that diabetogenic enterovirus strains are more common in Finland than in Lithuania, which could partly explain the higher diabetes incidence in Finland. It is also possible that enterovirus infections occurring neonatally or in utero represent a greater risk in Finland and other countries with low frequency of enterovirus infections, because in these countries, maternal enterovirus antibody levels are low and give no protection to the child. Enterovirus infections during these early ages may be particularly important in the pathogenesis of type 1 diabetes, as suggested in recent prospective studies (1,2,9).

Taken together, the results show that at the population level, a high frequency of enterovirus infections does not necessarily lead to an increased incidence of type 1 diabetes. It remains to be determined in further studies whether the inverse relationship between the frequency of enterovirus infections and the incidence of type 1 diabetes within a population will be observed also in other countries.

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Troglitazone Efficacy in a Subject With Glucocorticoid-Induced Diabetes

Troglitazone is an oral antidiabetic agent that ameliorates insulin resistance in both peripheral tissues and liver (1). Troglitazone could be more effective in diabetic subjects with greater insulin resistance, estimated by homeostasis model insulin resistance index (HOMA-R) (2). Glucocorticoid administration, along with obesity, is one of the most common insulin-resistant conditions that we encounter in clinical settings. It is shown that troglitazone improved disturbed glucose homeostasis in glucocorticoid-treated rats (3). A preliminary study also reveals that glucocorticoid-induced insulin resistance could be reversed by troglitazone administration in human subjects with normal glucose tolerance (4). However, the efficacy of troglitazone has not been demonstrated in glucocorticoid-induced diabetes in humans.

We have studied a 66-year-old female in whom diabetes was induced by glucocorticoid. At age 58 years, she had been diagnosed with polymyositis. Prednisolone 20 mg/day was administered, and then the dosage was tapered and maintained at 7.5 mg/day. Before the glucocorticoid treatment, her fasting glucose level was normal, but she had a family history of diabetes in her elder brother. She experienced thirst and polyuria 4 years later (at age 62 years). She was diagnosed with diabetes, with fasting glucose 11.9 mmol/l and HbA_{1c} 11.6% (normal 4.3–5.8). A dosage of 5 mg glibenclamide/day decreased her HbA_{1c} levels, but the levels remained at ~8%. At age 66 years, she was referred to our division. Her BMI was as low as 21.3 kg/m^2. Her fasting glucose was 5.50 mmol/l, whereas the maximal postprandial glucose level in the daily profile was as high as 20.8 mmol/l. Serum insulin concentration was 55.8 pmol/l after fasting, but it increased to 282 pmol/l postprandially. Urinary excretion of C-peptide was also as high as 30.8 nmol/day (normal 5.3–39.7). HOMA-R was calculated to be 2.09, not increased to the level at which drastic effects of troglitazone would be expected (2). However, in consideration of the coexisting postprandial hyperglycemia and hyperinsulinemia, which suggests the presence of insulin resistance (5), we initially prescribed troglitazone 200 mg/day in addition to glibenclamide. At 1 month later, she complained of hypoglycemic symptoms, and the dosage of glibenclamide was tapered. Finally, 2 years later, 400 mg/day of troglitazone without sulfonylureas stabilized her HbA_{1c} levels at ~6%. Her BMI did not change throughout the observation period, but serum leptin concentration gradually decreased from 13.9 to 4.5 ng/ml. Plasma levels of the soluble fraction of tumor necrosis factor-α receptor 2, which was reported to be associated positively with body fat and negatively with insulin sensitivity index (6), were 2,320 pg/ml (normal 1,020–2,120) before the addition of troglitazone, and the levels remained unchanged during the observation period (data not shown).

Glucocorticoid-induced diabetes is often characterized by rather normal fasting glucose level and abnormally increased postprandial glucose excursion. In this context, we thought it adequate that the prediction of insulin resistance may depend on postprandial glucose and insulin levels rather than HOMA-R and made a trial of troglitazone administration. Consequently, the remarkable and sustained efficacy of troglitazone was demonstrated. In other words, her hyperglycemia might be attributable mainly to insulin resistance, but not to deficient insulin secretion. The underlying mechanisms of glucocorticoid-induced insulin resistance and its reversal by thiazolidinediones seem to be multifactorial. It seems possible that both glucocorticoid and thiazolidinediones can affect the postreceptor signaling cascade of insulin, although few studies have examined the interaction between these agents (7). The thiazolidinediones bind to peroxisome proliferator-activated receptor-γ mainly expressed in adipocytes and ameliorate the "bad" metabolism and signals that cause insulin resistance (8). The decrease in serum leptin concentrations by troglitazone in this subject may reflect the improvement in such alterations of adipocyte metabolism. Further analysis is necessary to confirm the beneficial effects of thiazolidinediones on glucocorticoid-induced insulin resistance.

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Safety of Human Insulin in Poor-Sighted Elderly Diabetic Patients

Preliminary reports and the opinion of patients did not completely eliminate the belief that human insulin may be dangerous, particularly during the transfer from animal insulin (1).

It is true that the efficacy of human insulin was not fully evaluated on a large scale or in long-term randomized controlled trials, nor were its adverse effects.

In one study (2), we assessed the glycemic control and tolerance during the transfer from animal to human insulin. We found that all of our 46 type 1 diabetic patients were efficiently and safely switched from animal to human insulin, without aggravating the incidence of hypoglycemia, in spite of two major risk factors, namely advanced age (the oldest patient was 92 years old) and long-standing diabetes of ~20 years' duration.

In the present study, we investigated the transfer to human insulin administered with a pen, as opposed to syringe for animal insulin, in 30 elderly diabetic patients (mean age 60.5 ± 15.1 years) who had a long diabetes duration of 25.7 ± 10.9 years and also had deteriorated vision. Diabetic retinopathy was detected in 69% of patients. Among these, it was nonproliferative in 60%, preproliferative in 10%, and proliferative in 30%. Of all patients, 62% had cataracts. Mean visual acuity in the left eye was 5.3/10 ± 3.5, Parinaud scale 3.0 ± 2.6, and in the right eye 5.8/10 ± 3.6, Parinaud scale 3.4 ± 3.3 (normal Parinaud value = 2).

The aim of the study in this particular population was evaluation after 2 months of glycemic control, hypoglycemic attacks, treatment satisfaction, and degree of autonomy. The Student's *t* test and the rank-sum test were used when appropriate.

At the end of study, the median dose of human insulin was 32 U/day (8–74), significantly lower ($P = 0.04$) than the initial dosage of animal insulin of 36 U/day (14–150). HbA_{1c} decreased from 8.6% (6.4–12.1) to 8.45% (7.0–10.7) ($P = 0.02$). Only one patient experienced a single severe hypoglycemic episode. Biological hypoglycemia (<60 mg/dl) was never observed in 67% of patients.

At inclusion, patients mildly satisfied with the previous treatment were rather autonomous: 77% were injecting insulin without assistance. General health condition was altered, anxiety was a predominant feeling, and 60% were depressed. At the end of the study, patients were significantly ($P = 0.009$) more satisfied with the new treatment and the autonomy rate increased: 85% were injecting insulin themselves. The subjects' general health condition improved significantly ($P = 0.003$). These benefits were remarkable in the vision-impaired patients: 83% proceeded to auto-injections in comparison with 71%, 83% considered the new treatment more practical, and 50% felt more autonomous.

Improvement in the subjects' quality of life and autonomy was probably related to the use of an insulin pen in poor-sighted elderly patients not frightened by changing habits. Amelioration of glucose homeostasis without increase of hypoglycemia reassures us about the safety of human insulin.

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Assessment of In Vivo Stability of a New Insulin Preparation for Implantable Insulin Pumps

A randomized multicenter prospective trial

Programmable implantable insulin pumps have proven to be safe and effective devices for achieving good metabolic control (1) and decreasing the risk of severe hypoglycemia (2). In 1993, changes in the insulin production process resulted in increased insulin precipitation in the pumps, worsening the clinical performances of the devices. Evaluation Dans le Diabète du Traitement par Implants Actifs (EVADIAC) proposed improved pump rinse procedures and a shortening of the interval between refills (3), and the MiniMed catheter was improved. Hoechst Marion Roussel (Frankfurt, Germany) produced a new insulin variant (21 PH ETP). EVADIAC designed a protocol study to examine the in vivo stability of 21 PH ETP using a multicentric, prospective randomized study with intervals of 3 months as compared with 45 days between refills.

A total of 176 patients were randomized into two groups, G_{45} (45 days) and G_{90} (90 days), between refills. The study criteria was the accuracy of insulin infusion with 21 PH ETP (human semisynthetic insulin, Genapol stabilized, 400 U/ml; Hoechst).

A total of 196 MiniMed MIP 2001 (MiniMed Technologies, Sylmar, CA) pumps were studied: 122 (pumps A)

without polyethylene-polypropylene glycol coating, previously used with other batches of insulin and washed with an alkaline procedure before the study, and 74 new pumps (pumps B) with polyethylene-polypropylene glycol coating on the inside.

The infusion accuracy (% error) was calculated as the ratio between theoretical and real volume infused difference over the theoretical volume infused.

The evolution of percent error, i.e., the delta of % (Δ%) error at 6, 9, and 12 months vs. 3 months, was compared between G_{45} and G_{90} and between pumps A and B, using nonpaired *t* tests. An analysis of variance was used to determine whether G_{45}, G_{90}, pumps A or B, and high percent error were related.

Results

A total of 88 pumps were randomized into G_{45} and 108 pumps into G_{90}. There was no difference between G_{45} and G_{90} in terms of Δ% error at 6, 9, and 12 months as compared with 3 months.

However, pumps B showed a greater Δ% error at 6 months ($P = 0.006$ for G_{45} and 0.024 for G_{90}). This higher increase in the percent error tended to attenuate during the following months. The analysis of variance showed that independently from groups G_{45} and G_{90}, pumps B presented a higher percent error than pumps A ($P = 0.0003$).

On the basis of the results of this study we may conclude that the stability of 21 PH ETP was comparable at 90 days to that at 45 days in implantable pumps in vivo. As this study was not designed to compare the two groups of pumps together, the difference observed between pumps A and pumps B must be interpreted with caution. This problem is currently under investigation.

We conclude that using 21 PH ETP, the clinical performances of implantable pumps are comparable in intervals of 45 and 90 days between refills and that an acceptable 3-month interval between refills may be proposed.

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In Diabetes Care, Moving From Compliance to Adherence Is Not Enough

Something entirely different is needed

We had two distinct reactions to the appearance of the recent article by Lutfey and Wishner (1) entitled "Beyond 'compliance' is 'adherence'." Our first reaction was that it was good to see an article, especially one coauthored by a prominent endocrinologist, that addressed several key issues related to patient-provider relationships. We concur with and applaud their discussions of the importance of patient-centered care, the shortcomings of traditional compliance approaches, and the need for a more psychosocial paradigm.

At the same time, we were disappointed that these authors had not referred to a large body of work that has addressed and gone beyond the adherence approach they recommend. Important work has been conducted over the past 15 years that bears directly on the issues raised. Investigators working in two areas began questioning the terms "compliance" and "adherence," and the implications of use of these terms, about 15 years ago.

Anderson (2) suggested that the use of the constructs "compliance" and "adherence" were counter-productive because they both construed the problem to be the patient's behavior—one of the main points in the article by Lutfey and Wishner. This was one of the earlier articles on their empowerment approach, which they have refined and evaluated over the years. Key contributions of this approach include explicitly contrasting the underlying assumptions and consequences of adopting a traditional compliance-based medical model approach with the patient-centered empowerment approach (3); the explicit identification of problems with the term "adherence" as an alternative to "compliance" (4); and the development and validation of both empowerment-based interventions for patients, and empowerment training programs for professionals (4,5).

The second early body of work questioning the usefulness of compliance and adherence terminology was based on empirical, logical, and methodological grounds. Both Johnson and colleagues (6,7) and Glasgow et al. (8) criticized these approaches based on their lack of utility; sending the wrong message to patients and to professionals; the multidimensional nature of adherence behaviors, rather than adherence being a single unitary construct; and the dynamic nature of the regimen, rather than being a static standard against which to compare patient behavior. These authors independently proposed the use of terms such as "self-care" or "self-management" to describe the cluster of daily behaviors that patients perform to manage their diabetes. This self-management terminology has been widely adopted by the American Diabetes Association and other diabetes organizations (9–11) as preferable to the terms "compliance" and "adherence."

The past 5 years have seen the emergence of two additional approaches and alternative terms that we believe are also preferable to adherence. The first is psychologically based and drawn from the work on self-determination theory by Deci et al. (12). The greatest amount of this research in the diabetes area has been by

Williams et al. (13). They prefer the term "autonomy motivation" to refer to the psychological process that drives patient behavior change and the term "autonomy support" to refer to actions by health care professionals that enhance patient autonomy motivation. Like empowerment (4) and self-efficacy (14), there is impressive and increasing literature supporting the utility of this approach.

Finally, from a health care delivery and medical systems perspective, Wagner (16) has promoted the concept "collaborative" or co-management of chronic illnesses such as diabetes. Like Etzwiler (15) and the authors cited above, Wagner proposes that chronic illness care be based on different principles and concepts than acute care. In particular, they emphasize the importance of collaborative goal setting and on-going self-management support as key elements of successful disease management systems (16,17).

Our second major point is that the recommendations for change proposed by Lutfey and Wishner did not go far enough. Appropriate diabetes care requires a new and fundamentally different set of roles for health care professionals and patients. Modification of the acute-care model will not work because its underlying assumptions are invalid for diabetes care. Diabetes care requires a truly collaborative approach, i.e., patients and health care professionals relating as equals, rather than the hierarchical approach embedded in the acute-care model. Unlike the treatment of acute illnesses, patients with diabetes are fully responsible for the self-management of their illness (18). This responsibility is non-negotiable and inescapable. Although that statement may sound like a very strong assertion, we believe it is an accurate description of the reality of diabetes self-management.

The complete responsibility that patients have for the self-management of diabetes rests on three characteristics of the disease. First, the most important choices affecting the health and well-being of a person with diabetes are made by that person, not by health professionals. Each day, patients make decisions about eating, physical activity, stress management, monitoring, etc., that are the major determinants of their diabetes control. Second, patients are in control. No matter what we as health professionals do or say, patients are in control of these important daily self-management decisions. When patients leave the clinic or office, they can and do veto recommendations a health professional makes (19), no matter how important or relevant the provider believes those recommendations to be. Third, the consequences of the choices patients make about their diabetes care accrue first and foremost to patients themselves. We cannot share in the risk of developing retinopathy, neuropathy, or cardiovascular disease nor can we share the cost to the patient's quality of life of making a commitment to rigorous blood glucose control. Diabetes, including its self-management, belongs to the person with the illness.

When we acknowledge that diabetes is a self-managed disease whose responsibility rests with the patient, we have begun laying the foundation for a collaborative diabetes care relationship. Collaboration requires us to give up trying to be responsible for our patients and instead become responsible to them.

Although we cannot relieve patients of their responsibility for the self-management of diabetes, we can provide expertise related to the self-management of diabetes, help them acquire the knowledge necessary to make informed decisions about self-management, teach self-care techniques, provide social and emotional support, offer suggestions for behavior change and coping strategies, and create opportunities for our patients to reflect on the choices they are making and the goals they hope to achieve.

Like Lutfey and Wishner, we believe that the words (and related world views) that we use to describe patient-provider relationships and diabetes self-management are important. They can either facilitate or inhibit patient empowerment, autonomy, decision-making, sense of responsibility, and quality of life. This is why we prefer terms like "collaborative diabetes management" or simply "self-management." We believe that such a collaborative relationship represents a true paradigm or world view shift, one in which the concepts of compliance or adherence have no place.

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Prevalence of Patients Reaching the Targets of Good Control in Normal Clinical Practice

A cohort-based study in type 2 diabetes

To prevent chronic complications, the control of diabetes must be extended from blood glucose to other cardiovascular risk factors (1–3). European guidelines for the target levels of glycated hemoglobin, blood pressure, lipids, and BMI identified three classes of control: good, borderline, and poor (4). According to the European Consensus (4), the targets for good control were as follows: <5.2 mmol/l (<200 mg/dl) for total cholesterol; <1.7 mmol/l (<150 mg/dl) for triglycerides; >1.1 mmol/l (>40 mg/dl) for HDL cholesterol; ≤25 kg/m^2 (men) and ≤24 kg/m^2 (women) for BMI; ≤140/90 for blood pressure; and within 3 SD above the mean value of the reference range (2.4–4.7% in our laboratory) for HbA_{1c}. Because the adherence to these targets in normal clinical practice is poorly known, we studied all 2,113 type 2 diabetic patients (1.6% of the reference population, i.e., ~80% of the diabetic patients of the area) referred to the diabetic clinic of Asti, Italy, from 1996 to 1997. The prevalence of patients in good control for a single target was higher for lipids and blood pressure (42.4, 60.9, 64.9, and 44.1% for total cholesterol, HDL cholesterol, triglycerides, and blood pressure, respectively), while the prevalence of patients in poor control was higher for HbA_{1c} (49.3%) and BMI (62.4%). The prevalence of patients without any target of good control (3.9%) and that of patients with all targets reached (0.8%) was low (Table 1). By increasing the number of targets reached, the prevalence of women became significantly lower ($P < 0.0001$ for four to six targets reached). In particular, for BMI only, 13.9% of women are within targets versus 72.8% with BMI >26 kg/m^2 ($P < 0.0001$). This is the first report, to our knowledge, on the prevalence of diabetic patients within targets of good control in normal clinical practice. These results indicate that an overall good control of diabetes, even if desirable (1–3), is difficult to obtain, particularly in women.

Table 1—*Prevalence of patients in good control for increasing number of targets in a cohort of 2,113 type 2 diabetic patients*

Number of targets of good control reached	Number and prevalence of patients
0	82 (3.9); (57.3/42.7)
1	310 (14.7); (59.0/41.0)
2	574 (27.2); (63.8/36.2)
3	626 (29.6); (55.6/44.4)
4	383 (18.1); (45.2/54.8)
5	121 (5.7); (39.7/60.3)
6	17 (0.8); (17.6/82.3)

Data are *n* (%); (female/male).

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Neonatal Anthropometric Measurements and Risk of Childhood-Onset Type 1 Diabetes

Evidence is accumulating from large studies that early life exposures, for which neonatal anthropometric measurements can be used as markers, are associated with several chronic diseases in adulthood. The relationship between neonatal size and chronic diseases with the onset in childhood is less apparent. There is evidence that the age at diagnosis of type 1 diabetes is getting progressively younger and more cases are diagnosed in patients younger than 1 year of age (1). This recognition has lead to the search for causal environmental factors operating very early in life and factors related to the neonatal period. A review of the literature shows that it is not clear whether high or low birth weight increases the risk of type 1 diabetes in childhood (2–4). The purpose of our study was to assess whether neonatal measurements, such as birth weight, birth length, and ponderal index of children who later developed type 1 diabetes, were different from those of nondiabetic children and from those of their nondiabetic same-sex siblings. The study was performed in a population-based manner in Finland where the incidence of the disease is the highest in the world (1).

Three groups of individuals were studied: individuals with childhood-onset type 1 diabetes, their nondiabetic siblings, and control subjects from the general population. All children with type 1 diabetes diagnosed at the age of 14 years or younger in Finland from September 1986 to April 1989 were invited to participate in the nationwide Childhood Diabetes in

Table 1—*Birth weight, birth length, and ponderal index in type 1 diabetic probands, nondiabetic siblings, and control children by sex*

	Siblings	Probands versus siblings	Type 1 diabetic probands	Probands versus control subjects	Control children
Boys					
Birth weight (g)	3,671 ± 482	0.751*	3,716 ± 461	0.035	3,639 ± 484
Birth length (cm)	50.9 ± 2.2	0.289	51.2 ± 1.9	0.007	50.8 ± 2.0
Ponderal index	27.5 ± 2.3	0.301	27.7 ± 2.5	0.354	27.6 ± 2.4
Girls					
Birth weight (g)	3,569 ± 488	0.132	3,564 ± 480	0.490	3,520 ± 460
Birth length (cm)	50.4 ± 2.0	0.980	50.4 ± 1.9	0.042	50.1 ± 1.8
Ponderal index	27.7 ± 2.6	0.181	27.7 ± 2.4	0.110	27.9 ± 2.4

Data are means ± SD or *P*. There were 129 pairs of boys and 103 pairs of girls for matched proband-sibling analysis and 335 pairs of boys and 282 pairs of girls for matched proband–control subject analysis. **P* value refers to the matched pair analysis.

Finland Study (DiMe). Of the 801 families invited, 782 participated. The present study included 373 boys and 289 girls with type 1 diabetes. Data were also collected for 773 siblings aged 3–19 years. Of those, 311 boys and 352 girls had their birth-size data available. The sibling control subjects were selected on the basis of being the oldest child of the same sex in the family of the proband. There were 54 siblings who had developed diabetes who were excluded from analyses. Birth date– and sex-matched nondiabetic control children, 363 boys and 313 girls, were randomly selected from the Finnish national population registry. In all three study groups, premature (≥2 weeks before term) children and children born to diabetic mothers or mothers with gestational diabetes were excluded from the analysis.

Means of birth weight (g), birth length (cm), and ponderal index {weight [kg]: [length (m)]^3} between groups were compared with the paired Student's *t* test.

The results are given in Table 1. Neither birth weight, birth length, nor ponderal index was significantly different between type 1 diabetic case subjects and their nondiabetic sibling control subjects in either sex ($P > 0.1$ in all instances). Boys with type 1 diabetes had a slightly, but not significantly, higher birth weight and birth length than their nondiabetic siblings and a significantly higher birth weight and birth length compared with the control boys ($P = 0.035$ and $P = 0.007$, respectively). The girls with type 1 diabetes were taller at birth than the control girls ($P = 0.042$). The correlation analysis revealed that neither birth weight, birth length, nor ponderal index was related to the age at diagnosis of type 1 diabetes ($r < 0.05$ in all instances).

It has been documented that children with type 1 diabetes are taller than their peers before or at the time of diagnosis (5). We may speculate that this observation is to some extent true already at birth. On the other hand, we were not able to document any differences in birth length within families of type 1 diabetic probands. The oldest siblings of the same sex of the proband did not differ in neonatal measurements in any respect from the proband. This could mean that both birth length and weight are genetically determined in families to a greater extent than type 1 diabetes is. On the other hand, the power to obtain statistically significant difference between the boys with type 1 diabetes and their siblings was not high. There are no previous studies where the anthropometric parameters at birth of type 1 diabetic children were compared with those of their nondiabetic siblings.

Birth weight was higher in boys with type 1 diabetes, but not in girls, compared with matched control subjects from the general population. In 1989, Rewers et al. (6) in Poland showed that newborns either >4,000 or <2,000 g were at an increased risk of type 1 diabetes. In 1992, Metcalfe and Baum (7) found the birth weight of British children who developed type 1 diabetes to be higher than that of the control subjects. Also, Dahlquist et al. (8) reported in 1996 that lower birth weight and intrauterine growth retardation were associated with a lower risk of type 1 diabetes in Sweden.

If there is an association between the birth weight and the risk of type 1 diabetes, it may be U-shaped instead of linear. At values in the physiological range and its vicinity, the effect of reduced weight and intrauterine growth might be in favor of reducing the risk of type 1 diabetes. In children with a severe weight deficit at birth, various disturbances of the developing organism might take the preponderance. The risk of type 1 diabetes due to lower birth weight might thus be modified by two different factors: *1*) by decreasing the demand of insulin at moderate birth weight deficit (and perhaps increasing it at higher birth weight values); and *2*) by predisposing to diabetes by a qualitatively different mechanism at more severe birth weight deficit and prematurity.

In conclusion, birth length influenced the risk of developing type 1 diabetes in childhood more than birth weight: Babies who developed type 1 diabetes in childhood were taller at birth than their nondiabetic peers. Basic neonatal anthropometric parameters of children with type 1 diabetes do not differ from those of their nondiabetic siblings of the same sex in the Finnish population.

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All Patients With Werner's Syndrome Are Insulin Resistant, But Only Those Who Also Have Impaired Insulin Secretion Develop Overt Diabetes

Abnormalities in insulin secretion, insulin action, or both contribute to the development of diabetes, but the relative contributions of these two factors are not fully elucidated. Insulin resistance is usually associated with glucose intolerance and diabetes, but insulin resistance may not necessarily result in glucose intolerance if hypersecretion of insulin can compensate for the insulin resistance. If this is the case, then only subjects with impaired insulin secretory capacity will develop diabetes in the presence of insulin resistance. One way to address this possibility is to study the relationship between glucose tolerance and insulin secretory capacity in syndromes with extreme insulin resistance, such as insulin receptor mutations and Werner's syndrome.

Werner's syndrome is a rare disorder with autosomal recessive inheritance, characterized by an aged appearance with various features, including glucose intolerance with marked insulin resistance (1,2). Despite the presence of insulin resistance in almost all patients with Werner's syndrome, glucose intolerance in patients with Werner's syndrome shows heterogeneity among patients (2). To investigate the reason for the heterogeneity, we studied insulin secretory responses in a family of consanguineous marriage in which two siblings shared the same mutation of the Werner helicase gene (3) but were discordant for diabetes. We performed oral glucose tolerance tests (OGTTs) and intravenous glucagon stimulation tests in the siblings, and intravenous glucose tolerance tests (IVGTTs) (4) in all members of the siblings' family (father, mother, two elder sisters, as well as the affected siblings).

Table 1—*Insulin responses to IVGTT in a family of a pair of siblings with Werner's syndrome and normal subjects*

	Glucose tolerance	Werner's helicase gene	IRI (pmol/l) response to IVGTT	
			Basal	Peak (3–5 min)
Case 1	Diabetes	M/M	85	127
Case 2	IGT	M/M	142	425
Father	Diabetes	N/M	60	79
Mother	Normal	N/M	95	452
Sister 1	Normal	N/N	79	480
Sister 2	Normal	N/M	61	252
Normal subjects (mean ± SD, n = 15)	—	—	79 ± 79	484 ± 217

Werner's helicase gene: M, mutant allele; N, normal allele. IRI, immunoreactive insulin.

The proband (case 1) was diagnosed with diabetes, whereas the other (case 2) was diagnosed with impaired glucose tolerance (IGT) on OGTT. Total insulin responses to OGTT and intravenous glucagon in the siblings were both increased, suggesting the presence of insulin resistance. The early-phase insulin response to IVGTT in case 1 was defective, whereas it was increased in case 2 (Table 1). A defect in the early-phase insulin response to IVGTT, similar to that in case 1, was observed only in their father with type 2 diabetes, but not in other members of this family (Table 1).

These data suggest that impaired insulin secretion with concomitant insulin resistance, which is characteristic of Werner's syndrome, contributed to the development of overt diabetes in case 1. In contrast, case 2, in whom increased insulin secretion compensated for the insulin resistance, did not develop diabetes, despite the same mutation in the Werner's helicase gene.

In summary, the present study implicated that impaired insulin secretion with concomitant insulin resistance is necessary for the development of overt diabetes even in syndromes with extreme insulin resistance, such as Werner's syndrome.

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Youth-Onset Type 2 Diabetes (Y2DM) Associated With *HNF1A S319* in Aboriginal Canadians

Table 1—*Clinical, biochemical, and genetic variables in Oji-Cree subjects aged ≤25 years*

	Diabetes	IGT	Normoglycemia
n (female)	16 (14)	15 (12)	286 (162)
Age (years)	19.6 ± 4.3	17.1 ± 4.7	17.0 ± 4.4
BMI (kg/m^2)	32.8 ± 5.1	28.1 ± 6.1	23.8 ± 5.5*
Blood glucose levels (mmol/l)			
Fasting	9.4 ± 4.4	5.8 ± 0.70	5.3 ± 0.46*
2-h p.c.	14.9 ± 7.5	8.7 ± 0.67	5.1 ± 1.3*
Fasting insulin (U/l)	409 ± 450	231 ± 171	104 ± 61*
C-peptide (U/l)	1.37 ± 1.11	0.73 ± 0.43	0.55 ± 0.35*
HNF1A genotypes			
S319/S319	2 (2)	0	0
S319/G319	7 (6)	5 (3)	49 (23)
G319/G319	7 (6)	10 (9)	237 (139)

Data are *n* (female) or means ± SD. *Significantly different from subjects with diabetes and IGT at $P < 0.001$. p.c., post challenge with 75-g oral glucose.

A form of diabetes, youth-onset type 2 diabetes (Y2DM), has emerged as a new, significant public health concern in several ethnic groups (1). Y2DM is actually more common in some Canadian aboriginal communities than type 1 diabetes is in the general pediatric population (2–6). Aboriginal Canadians with Y2DM are typically nonketotic obese female adolescents or young adults (2–6). This phenotype resembles typical type 2 diabetes that is associated with obesity and hyperinsulinemia. It is definitely distinct from maturity-onset diabetes of the young (MODY) (1–6). Most clinicians have assumed that the striking Y2DM phenotype has a component of genetic susceptibility (2–6). Recently, we identified a genetic marker, *HNF1A S319*, in adult Oji-Cree with type 2 diabetes (7). The *HNF1A S319* variant was private to Oji-Cree and altered a conserved glycine residue within the DNA binding domain of hepatocyte nuclear factor-1α. *HNF1A S319/S319* homozygotes and *S319/G319* heterozygotes had odds ratios for type 2 diabetes of 4.0 and 2.0, respectively, compared with *G319/G319* homozygotes (7).

To evaluate the relationship between *HNF1A S319* and Y2DM, we studied 317 Oji-Cree subjects aged 10–25 years from the Sandy Lake reserve in northern Ontario (7). We identified 16 subjects with type 2 diabetes (14 of whom were females), 15 subjects with impaired glucose tolerance (IGT) (12 of whom were females), and 286 subjects with normal glucose tolerance (162 of whom were females).

Table 1 shows the clinical, biochemical, and genetic features of Oji-Cree subjects with Y2DM, IGT, and normoglycemia. Compared with normoglycemic subjects, those with Y2DM had significantly increased BMI, glucose concentrations after fasting and 2 h after 75-g glucose challenge, and fasting plasma insulin and C-peptide concentrations (all $P < 0.001$). The values for all continuous traits in subjects with IGT were intermediate, with values between those for subjects with Y2DM and those for normoglycemic subjects.

All observed genotype frequencies followed the expectations of the Hardy-Weinberg law. The frequency of *HNF1A S319* was 0.343 and 0.086 in subjects with Y2DM and normoglycemic subjects, respectively ($P = 0.00005$). The frequency of *HNF1A S319* was 0.167 in subjects with IGT, which was not statistically different from that of subjects with Y2DM or normoglycemia. *HNF1A S319/S319* homozygotes and *S319/G319* heterozygotes had odds ratios for Y2DM of 119 (95% CI 6.1–2,320) and 2.9 (1.5–5.8), respectively, compared with subjects with the *HNF1A G319/G319* genotype. *HNF1A S319/G319* heterozygotes had an odds ratio for IGT of 1.9 (0.91–4.2). The Y2DM subjects who were homozygous for *HNF1A S319/S319* were not different from the *HNF1A* subjects for any clinical or biochemical phenotype (data not shown).

The cellular basis for the development of type 2 diabetes in Oji-Cree subjects with *HNF1A S319* is not yet established. Most mutations in *HNF1A* have been observed with MODY3, which typically occurs in lean younger adults and is associated with defective insulin secretion from pancreatic β-cells (8). In contrast, Y2DM in the Oji-Cree appears to be typical type 2 diabetes, associated with obesity and hyperinsulinemia (1–7). It is possible that adolescent obesity and insulin resistance in the Oji-Cree population may stress the capacity of *HNF1A S319* carriers to mount an adequate insulin response, but this would require confirmation with cellular and/or physiological studies. It is of interest that the adolescent subjects with Y2DM had a significantly higher mean fasting plasma insulin concentration than the other groups, suggesting that an insulin response is present, but is insufficient or ineffective in preventing the development of diabetes.

The emergence of Y2DM in Canadian aboriginal people has been attributed to recent population-wide increases in obesity and insulin resistance (2–6). These, in turn, have resulted from the decline in physical activity and the increased reliance on store-bought food (2–6). *HNF1A S319* appears to be a strong and significant contributor to the Y2DM phenotype. It might prove to be a useful marker for identifying young subjects at risk for developing diabetes. These subjects would be candidates for interventions, such as exercise and/or dietary modification. Similar associations with different genetic variants may exist in other ethnic minorities (1) for whom Y2DM is also an incipient public health dilemma.

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Two-Hour Post–Glucose Loading Plasma Glucose Is the Main Determinant for the Progression From Impaired Glucose Tolerance to Diabetes in Hong Kong Chinese

The category of impaired glucose tolerance (IGT) was created in 1979 by the World Health Organization and the National Diabetes Data Group to identify a group of subjects who were at higher risk for cardiovascular disease and subsequent development of type 2 diabetes (1,2). There have been few reports on the risk of progression to diabetes in Chinese people with IGT. We followed up 123 Chinese subjects with IGT with yearly oral glucose tolerance tests (OGTTs) and aimed to examine their risk of progression to diabetes and the risk factors for progression.

Between 1988 and 1995, 123 Chinese subjects with IGT were recruited for a yearly OGTT until they had progressed to diabetes or up to June 1997, which is when all of the data were analyzed. Glycated hemoglobin (HbA_{1c}) and fasting, 1-h, and 2-h plasma glucose (PG) levels were measured during the OGTT. Insulin assays of fasting, 1-h, and 2-h plasma samples were also performed, but they were available in 66 subjects only. Of these 123 subjects, 15 (12.2%) were men and 108 (87.8%) were women. The subjects were 22–66 years of age. After a mean follow-up period of 1.71 ± 1.35 years (range 0.92–7.64, median 1.06), 29 (23.6%) progressed to diabetes, 34 (27.6%) remained with IGT, and 60 (48.8%) reverted to normal OGTT. The 50% "survival time" (95% CI) from IGT to diabetes was 4.34 years (3.72–5.41) with the Kaplan-Meier analysis. With use of Cox regression analysis to predict the progression to diabetes with age, sex, BMI, blood pressure, HbA_{1c}, and fasting, 1-h, and 2-h PG as predictor variables, 2-h PG was the only significant independent parameter with $\beta = 0.616$, SEM = 0.203, $P = 0.002$, and relative risk (RR) (95% CI) = 1.85 (1.24–3.76). For those with 2-h PG ≥10.1 mmol/l (mean + 1 SD), the progression from IGT to diabetes was much higher, with the 50% "survival time" of 2.03 (1.53–2.53) years as compared with 6.16 (2.37–9.95) years for those with 2-h PG < 10.1 mmol/l (log-rank test: $P < 0.01$) (Fig. 1). Of the 66 subjects whose plasma insulin levels had been made available, there was no statistically significant difference in the insulin levels among subjects with diabetes, IGT, or normal OGTT. Through the use of Cox regression analysis with age; sex; BMI; blood pressure; HbA_{1c}; fasting, 1-h, and 2-h PG and insulin; insulinogenic indexes; and insulin resistance (calculated with a computer-solved homeostasis model assessment method) as predictor variables, 2-h PG was the only significant independent variable with $\beta = 0.837$, SEM = 0.326, $P = 0.010$, and RR (95% CI) = 2.31 (1.22–4.37).

The rate of progression from IGT to diabetes was reported to be 11.3% per year in the Da Qing IGT and Diabetes Study involving Chinese subjects in northern Mainland China (3). In the present study, 50% of our patients with IGT progressed to diabetes in 4.34 years. A crude rate of progression was hence calculated to be 11.5% per year in Chinese individuals in Hong Kong. Similar to most other studies (3–5), the most important risk factor predicting subsequent progression from IGT to diabetes is the baseline 2-h PG concentration. We found that subjects whose 2-h PG ≥10.1 mmol/l, in comparison with those whose 2-h PG <10.1, had a rate of progression three times higher. In addition, for every 1 mmol/l increase in the 2-h PG level, there is a 1.85-fold higher risk for progression from IGT to diabetes. Some other risk factors for progression from IGT to diabetes, such as age and obesity (4–6), have been reported. However, both of these disappeared as independent risk factors once plasma glucose (and/or insulin) had been introduced into the multivariate analysis.

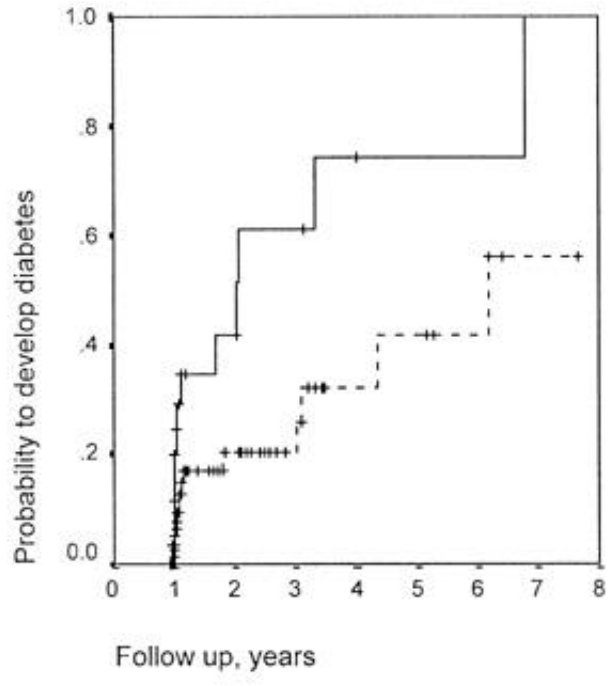

Figure 1—*Progression from IGT to diabetes in the subjects with 2-h plasma glucose above or below 10.1 mmol/l as determined by use of the Kaplan-Meier analysis. Log-rank test:* $P < 0.01$. ——, *Two-hour plasma glucose level* ≥*10.1 mmol/l;* – – –, *2-h plasma glucose level* <*10.1 mmol/l;* +, *data censored by the Kaplan-Meier analysis.*

In conclusion, in a typical cohort of Hong Kong Chinese subjects with risk factors for diabetes, 50% of these subjects with IGT progressed to develop diabetes within 4.34 years. The 2-h PG concentration was the key predictor for the progression. For those with baseline 2-h PG ≥10.1 mmol/l, the progression from IGT to diabetes was three times faster compared with that of those with 2-h PG <10.1 mmol/l.

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Total Plasma Homocysteine and Insulin Levels in Type 2 Diabetic Patients With Secondary Failure to Oral Agents

Homocysteine is a sulfur-containing amino acid formed in the metabolism of methionine, which is not a normal part of the diet (1). Hyperhomocysteinemia has been recently acknowledged as an independent risk factor for atherosclerosis (2,3). There is substantial evidence that high levels of homocysteine are associated with the increased risk for ischemic heart disease and cerebrovascular disease (2,4). It has been reported that hyperhomocysteinemia may contribute to nephropathy (5,6) and cardiovascular disease in diabetes (7). Because the studies performed in type 2 diabetic subjects have usually included subjects with good metabolic control (7), we aimed to assess the influence of chronic poor metabolic control of type 2 diabetes on plasma total homocysteine level.

Two study groups were formed with 44 type 2 diabetic outpatients without any overt cardiovascular damage. Group 1 consisted of 26 diabetic subjects treated with maximum doses of oral hypoglycemic agents (12 men, 14 women; mean age 66.8 ± 5.4 years, mean diabetes duration 11.9 ± 4.1 years, BMI 26.3 ± 3.3 kg/m^2, mean fasting plasma glucose 13.9 ± 4.6 mmol/l, HbA_{1c} 9.8 ± 1.6%) with poor metabolic control. Group 2 consisted of 18 well-matched well-controlled diabetic subjects, treated successfully with oral agents (10 men, 8 women; mean age 65.8 ± 4.7 years, mean diabetes duration 10.9 ± 4.2 years, BMI 25.7 ± 4.0 kg/m^2, mean fasting plasma glucose 7.3 ± 2.4 mmol/l, HbA_{1c} 6.6 ± 0.7%). There were 12 sex-, age-, and BMI-matched healthy people who served as control subjects. Total (free plus protein-bound) plasma homocysteine was measured during a fasting state by high-performance liquid chromatography with the Hewlett-Packard 1100 Series system

(Waldbronn, Germany). Insulin was measured under the same conditions by radioimmunologic assay (Bio-Rad, Swierk, Poland). HbA_{1c} was measured by commercially available chromatographic assay. Because normality of distribution was confirmed in each group of data, the Student's *t* test for unpaired data was used to analyze the differences between groups. To assess correlation between given parameters, the Pearson's correlation analysis was performed. Values for $P < 0.05$ were considered significant.

Mean ± SD fasting plasma total homocysteine concentrations were significantly higher in group 1 patients (17.1 ± 4.5 nmol/l, $P < 0.001$) than in group 2 patients (8.2 ± 3.9 nmol/l) and healthy control subjects (6.5 ± 4.9 nmol/l). HbA_{1c} values showed positive correlation with homocysteine concentration in group 1 ($r = 0.41$; $P < 0.05$). Inversely, insulin levels were significantly lower in group 1 (8.3 ± 5.2 μU/ml) than in group 2 (14.6 ± 5.2 μU/ml, $P < 0.001$), with no statistically significant difference between insulin levels in group 1 (8.3 ± 5.2 μU/ml) and healthy control subjects (9.3 ± 6.1 μU/ml). There was a negative correlation between homocysteine and insulin concentrations in the group 1 patients ($r = -0.32$; $P < 0.05$).

There are few studies analyzing the relation between plasma homocysteine and type 2 diabetes, especially in regard to metabolic control. Lanfredini et al. (6) and Hoogeveen et al. (7) recently confirmed the vascular-damaging impact of homocysteine in type 2 diabetic individuals. However, in the study by Hoogeveen et al., unlike in ours, the degree of metabolic control did not show any correlation with plasma homocysteine concentration. This discrepancy may be partly explained by the difference in the studies' designs. Mean HbA_{1c} level in the study by Hoogeveen et al. (7) was ~6.0%, whereas our group 1 patients showed considerably worse metabolic control as being in the long-term period of oral-agent failure. Our findings are in agreement with the observations of Munshi et al. (8), who described greater frequency of hyperhomocysteinemia in type 2 diabetes, and Passaro et al. (9), who also found correlation between high homocysteine levels and HbA_{1c} in type 2 diabetic people as well as duration of the disease. The latter was not confirmed in our study.

To our knowledge, there have been no reports so far on the relationship between plasma homocysteine and endogenous insulin level in patients with type 2 diabetes. We have demonstrated an apparent negative correlation between these two parameters in poorly controlled type 2 diabetic subjects. This observation seems to be in accordance with the reports about type 1 diabetes. Cronin et al. (10) and Robillon et al. (11) noted lower homocysteine levels in insulin-treated well-controlled type 1 diabetic subjects than in healthy control subjects. As shown by Hultberg et al. (12), deterioration of metabolic control in type 1 diabetes, typically caused by direct or indirect insulin deficiency, is accompanied by homocysteine plasma increase. We have found that high plasma homocysteine concentrations are associated with decreased insulin levels in type 2 diabetes. Fonseca et al. (13) noted that hyperinsulinemia decreases homocysteine levels in normal subjects, but not in insulin-resistant type 2 diabetic subjects. Animal studies published recently by Jacobs et al. (14) confirm that insulin is directly involved in the regulation of homocysteine metabolism. Therefore, it may be suggested that the compromised insulin action caused by the relative or absolute insulin deficiency is associated with plasma homocysteine level elevation. Insulin thus seems to play a significant, but yet unclear, role in the altered homocysteine metabolism found in diabetes.

In conclusion, we found that chronic poor metabolic control of type 2 diabetes was characterized by elevation of plasma homocysteine concentration and that the latter inversely correlated with endogenous insulin levels. Our results may add to the understanding of the increased frequency and mechanisms of vascular damage in diabetes.

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Benzodiazepine Interruption

Does it cause hypoglycemia?

We report on a patient who presented with a reduction in insulin requirements after discontinuing clonazepam. A 43-year-old diabetic man was admitted to the endocrinology ward for glycemic control after incomplete transcraneal adenomectomy of a pituitary growth hormone–secreting macroadenoma. After treatment with lanreotide was begun, his daily insulin dose decreased from >300 to 142 U and he was discharged on 104 insulin U/day, lanreotide 30 mg for 10 days, and replacement therapy with hydrocortisone and levothyroxine. One month after discharge, he was started on clonazepam 6 mg/day because of excruciating headaches that did not respond to other drugs. Three months later, clonazepam was discontinued. The following day (which was 3 days after a lanreotide injection), the patient was admitted to our day-care center because of hypoglycemic coma that was induced without changes in food intake, insulin dose, or physical activity. The dosage of insulin was progressively decreased to 30 U/day during the following week because of recurring episodes of hypoglycemia, and it stabilized at 58 U/day 6 months later. Because of schedule difficulties, the patient declined an acute test with clonazepam to assess his growth hormone/glucose response.

In rats, clonazepam has been reported to increase blood glucose (1) and growth hormone (2) levels in vivo, but not in a pituitary growth hormone–secreting cell line in vitro (3). In humans, diazepam had been proposed as a stimulation test for growth hormone secretion (4), but was later abandoned because of its inconsistency (5).

Our patient had stable secondary diabetes, but he presented with an abrupt reduction in insulin requirements. Had the recent administration of lanreotide been the cause, similar episodes would have occurred with previous doses; such episodes had not happened. It seems that only certain growth hormone–producing cell lines are sensitive to benzodiazepines, which would account for the irregular response observed with diazepam in acromegalics (5,6). Although definite proof is lacking, we propose that our patient's tumor was responsive to clonazepam, and the interruption of benzodiazepine treatment caused a decrease in growth hormone secretion and insulin requirements.

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American Orthopaedic Foot and Ankle Society Diabetic Shoe Survey

It is well accepted that the development of a foot ulcer in the diabetic individual is often the precursor of lower-extremity amputation. Once the ulcer develops, the patient's quality of life decreases appreciably (1). This increased morbidity utilizes a substantial proportion of health care resources (2–4). It is also well accepted that a comprehensive program of patient education, skin and nail care, protective shoes, and ongoing monitoring decreases that risk, thus decreasing patient morbidity and resource consumption (5–8; J.O. Krause, J.W. Brodsky, unpublished observations). This information led to the passage of the Medicare Therapeutic Shoe Bill, which provides these benefits to individuals with diabetes. In spite of this information, most experts feel that very few patients are provided with comprehensive prophylactic foot care or protective shoe gear.

Members of the Diabetes Committee of the American Orthopaedic Foot and Ankle Society randomly surveyed 402 diabetic individuals during visits to their endocrinologists. This venue was selected because it was felt to represent a "best practice" group of patients, i.e., those patients receiving the most comprehensive care for their diabetes. The demographics revealed that the patients were representative of a typical longstanding diabetic population, averaging 61.5 years of age and with a duration of diabetes of 27.3 years. To reinforce the premise of a "best practice" group, 93.5% had health-care benefits through Medicare and/or a private insurance carrier.

Only 73.4% had any form of patient education, which was usually provided by a nurse or podiatrist. The frequency of examination of their feet was variable, with only 59.9% having twice-yearly examinations and 8.5% never having an examination. Only 12.2% wore special shoes, and just 15.4% used any type of

custom foot orthosis. Only 7.7% of the shoes or foot orthoses were provided by the patients' health care providers (9).

This study highlights a substantial opportunity for improvement in the care of individuals with diabetes. The most common reason for hospitalization of the diabetic individual is foot infection. It is reasonable to assume that diabetic patients have their blood sugar levels tested periodically and that they meet with their dietitians and diabetes educators. In this light, it is reasonable to target 100% of diabetic patients to be educated about the care of their feet and methods to prevent infection or the development of an ulcer. It is also reasonable to target that 100% of diabetic individuals have their feet examined periodically. From available data, a reasonable target rate for prophylactic shoe gear is 25%.

Prophylactic foot care programs are less expensive and consume fewer resources than our current method of treatment. If we achieve these targets, we can improve the quality of health care for diabetic individuals, improve their quality of life, and actually decrease the overall cost of care. In the current cost-conscious environment, these reasonable goals can be attained without "up-front" high-tech capital expenditure. This study will be published in full in the November issue of *Foot and Ankle International*. This issue will be dedicated to the care of the diabetic foot.

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COMMENTS AND RESPONSES

Insulin-Sensitive and Insulin-Resistant Variants in Nonobese Japanese Type 2 Diabetic Patients

The role of triglycerides in insulin resistance

It is well known that two subtypes exist in Japanese nonobese type 2 diabetic patients: one with normal peripheral insulin sensitivity and the other with primary peripheral insulin resistance (1,2). In the present study, 70 untreated nonobese type 2 diabetic patients who visited our clinic participated. Type 2 diabetes was diagnosed based on the criteria of the World Health Organization (3). All subjects ingested at least 150 g of carbohydrate for the 3 days preceding the study. None of the subjects had significant renal, hepatic, or cardiovascular disease, nor did they take any medications known to affect lipid metabolism. The blood was drawn during the morning after a 12-h fast. Plasma glucose was measured with the glucose oxidase method and plasma insulin was measured with a radioimmunoassay kit. The total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and uric acid were also measured. The estimate of insulin resistance by homeostasis model assessment (HOMA-IR) was calculated with the following formula: fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5, as described by Matthews et al. (4). The HOMA-IR value of control subjects was 1.6 ± 0.9 (mean ± SD) and we defined any value >2.5 (mean ± SD of normal control subjects) as an insulin-resistant state and any value <2.5 as an insulin-sensitive state. The threshold value for insulin resistance in our study (i.e., 2.5) was similar to that (i.e., 2.77) reported in subjects with no metabolic disorders that was reported by Borona et al. (5). The clinical characteristics and clinical profiles of insulin-sensitive (n = 30) and insulin-resistant (n = 40) subtypes were compared. No significant difference was observed in age, sex, fasting plasma glucose, HbA_{1c}, and uric acid levels between the two groups. The patients with insulin resistance had higher BMI and higher total cholesterol and LDL cholesterol levels than those with normal insulin sensitivity, but the difference was not statistically significant. In contrast, the patients with insulin resistance had significantly higher levels of serum triglycerides than those with normal insulin sensitivity. (199.7 ± 20.0 vs. 94.2 ± 5.0 mg/dl, $P <$ 0.001). HDL cholesterol levels were significantly lower in type 2 diabetic subjects with insulin resistance (47 ± 2 mg/dl) compared with those with normal insulin sensitivity (60 ± 3 mg/dl, $P <$ 0.001). There was a positive correlation between HOMA-IR values and the levels of serum triglycerides in the patients studied (r = 0.857, $P <$ 0.0001). It is therefore suggested that hypertriglyceridemia, but not BMI, is associated with insulin resistance in our nonobese type 2 diabetic patients. This finding suggests that pharmacological agents that lower serum triglyceride levels might improve glucose tolerance in nonobese type 2 diabetic patients by reducing insulin resistance. In this regard, the study by Jones et al. (6) showing that treatment of patients with type 2 diabetes with bezafibrate improves not only glucose tolerance but also serum triglyceride

levels is very interesting. In summary, our present study demonstrated that nonobese Japanese type 2 diabetic patients are divided into two populations: one with normal insulin sensitivity and the other with insulin resistance. In addition, there is a possibility that hypertriglyceridemia per se is associated with insulin resistance in nonobese Japanese type 2 diabetic populations.

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Insulin Lispro, Pregnancy, and Retinopathy

We read with interest the letter titled "Insulin Lispro and the Development of Proliferative Diabetic Retinopathy During Pregnancy," by Kitzmiller et al. (1). We would like to share our experience in treating pregnant diabetic patients with insulin lispro.

Preston Acute Hospital NHS Trust is situated in the northwestern area of the U.K. and serves a population of 350,000. We have a combined diabetes and pregnancy clinic run by a consultant diabetologist and obstetrician with their respective registrars. Every attempt is made to see the patients before pregnancy to ensure good glycemic control before conception. Patients are thereafter seen at least every 2 weeks until the thirtieth week and then every week until they deliver. Our targets of blood glucose control are a fasting level between 4 and 5 mmol/l and a 2-h postprandial level between 4 and 7 mmol/l. Patients are admitted, if necessary, to ensure smooth glycemic control. Our routine diabetes care also includes annual retinal photography. We have analyzed our data on the possible effect of different types of insulin on the progression of retinopathy.

We analyzed the data of 30 patients with diabetes (3 with type 2 and the rest with type 1) going through 40 pregnancies. They were 24–36 years of age with duration of diabetes of 2–25 years (mean 15). There were 24 patients seen in the prepregnancy clinic, who went through 30 pregnancies; 16 pregnancies that were managed with insulin lispro; 21 that were managed with regular insulin; and 3 that were managed with pork Velosulin (they preferred to stay on animal insulin) as their short-acting insulin. When they were seen in the prepregnancy clinic, their HbA_{1c} was <7% (range 6.2–6.8). In all three patients with type 2 diabetes, insulin lispro was used (lispro was started before conception in two of these patients, and after confirmation in the other one, since she did not attend the prepregnancy clinic). The main indication for insulin lispro is patient convenience, since there is no gap required between injection and meal. On the whole, six patients with retinopathy went through nine pregnancies (five with background retinopathy and four with previously laser-treated retinopathy) and none worsened. None of the patients required ophthalmologic intervention during pregnancy or during the period immediately postpartum. In the rest of the patients, there was no retinopathy before, during, or after parturition. The prevalence of retinopathy was the same in the lispro and regular groups.

Worsening of retinopathy during pregnancy is well known, although the mechanisms are not completely clear. The factors implicated are preconception control, fluctuation of glycemic state, hypertension, different growth factors, and others (2–4). Kitzmiller et al. (1) found that three of their type 1 diabetic patients with no retinopathy who were managed with insulin lispro developed florid retinopathy, which required urgent treatment during pregnancy. It is important to note that in the second and third patient, the initial HbA_{1c} was 3.7 and 3.4% above the upper level of normal laboratory value (which was not mentioned), which was suggestive of poor glycemic control. Moreover, the mid-trimester decline of HbA_{1c} in all of the three patients was considerable (2.2–3.6%). In the Diabetes in Early Pregnancy Study, the two main important factors for deterioration or development of retinopathy were higher HbA_{1c} at entry and duration of diabetes >6 years (5). It has been clearly documented before that deterioration of retinopathy correlates with the plasma glucose at entry and the rate of improvement of glycemic control in the first 6–14 weeks after entry (6). These two factors might have been responsible for the deterioration or development of retinopathy in the above-cited cases rather than the type of insulin used.

It is well known that insulin enhances the action of IGF-I (7), but that is unlikely to be different with different types of insulin. Other than a slightly higher affinity for the placental membranes, no other difference in other cell lines using human insulin and insulin lispro was noticed (8). Anderson et al. (9) reported their experi-

ence in using insulin lispro in nonpregnant adults in whom no increase in incidence of retinopathy was observed. In summary, our experience with using insulin lispro in pregnant diabetic patients does not suggest any deterioration of retinopathy, in spite of their long duration (mean 15 years) of diabetes. We would, however, recommend careful pooling of data on the management of diabetes in pregnancy to obtain a large enough database for evaluation of the effect of different types of insulin on retinopathy during pregnancy.

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Response to Bhattacharyya and Vice

The interest of Bhattacharyya and Vice (1) in our observation of three cases with the development of proliferative diabetic retinopathy (PDR) during pregnancy in a group of 10 diabetic women with a baseline negative ophthalmologic examination (2) is appreciated. Since this observation is quite rare (2,3), we were concerned to note that the 10 pregnant type 1 or 2 diabetic women were treated with insulin lispro. Bhattacharyya and Vice (1) are correct to emphasize careful preparation for pregnancy in diabetic women (4), which unfortunately was not done in our three cases of rapidly developing PDR. They reported on 16 pregnancies in 15 women with type 1 or 2 diabetes treated with insulin lispro during pregnancy. Ten of these women with well-controlled diabetes had negative ophthalmologic examinations before, during, and after pregnancy, and three with background diabetic retinopathy and two with previous laser-treated retinopathy also showed no progression. To my knowledge, there has been only one previously reported case of the development of florid PDR during pregnancy from a baseline negative ophthalmologic examination (3). Although the title of that case report describes a gestational diabetes patient, the patient described was probably a woman with undiagnosed type 2 diabetes, since her initial HbA_{1c} was 16.2% (6%).

To date, there have been at least 314 diabetic women reported in the literature (1–3) with negative initial ophthalmologic examinations who were treated with standard insulin, and 1 case developed PDR during pregnancy. Now, 20 women with negative initial examinations who were treated with insulin lispro have been reported, and 3 developed PDR. To avoid the trap of anecdotal cases and uncontrolled observations seeming to infer a cause-effect relationship, as noted by Jovanovic (5) in her invited response to our observation, further studies are necessary to see if the association of our three cases of PDR with use of insulin lispro occured on the basis of chance. With use of the proportions noted above, a power calculation indicates that 110 diabetic women with initial negative ophthalmologic examinations would be required in each group to have an 80% power of finding a significant difference based on insulin therapy at the 0.05 level, one-tailed. I agree with Bhattacharyya and Vice (1) and Jovanovic (5) that the subgroup of diabetic women with poor glycemic control at the onset of pregnancy is at the highest risk of developing PDR, perhaps because they may already have undetected peripheral retinal ischemia. The feasibility of performing a randomized trial of continuing standard insulin therapy during pregnancy versus switching to insulin lispro or insulin aspart is good even in this subgroup with evidence of chronic hyperglycemia, since most diabetic women in North America still enter pregnancy without effective preconception care (4). They are then exposed to rapid intensification of glycemic control to prevent fetal damage, usually with days to weeks of wide glucose excursions (6).

In separate editorials, Merimee (7) and Chantelau and Kohner (8) discussed factors that might explain the temporary worsening of diabetic retinopathy in cases of chronic hyperglycemia exposed to intensified glycemic control. They discussed possible roles of IGF-1 and its binding proteins (IGFBPs), including increased circulating IGF-1 with intensification of insulin treatment (8). Attia et al. (9) observed acute reciprocal changes in free IGF-1 and IGFBP-1 levels with acute insulin withdrawal of up to 8 h (IGFBP-1 up, IGF-1 down), followed by insulin replacement for 2 h (IGFBP-1 down, IGF-1 up) in type 1 diabetic subjects. Merimee (7) stated that "increased intracellular transport of glucose initiated by levels of IGF-1 in local tissue beds can result in cellular hypertrophy and hyperplasia." Demonstrated effects of IGF-1 in the eye include promotion of chemotaxis of retinal endothelial cells, induction of vasodilation, microaneurysm formation, neovascularization (10), enhanced formation of collagenase, which can dissolve capillary basement membranes and the collagen

matrix of the retina (6,10), and stimulation of mitogenesis of human retinal endothelial cells (11). The latter effect was enhanced by basic fibroblast growth factor, which, in pregnant diabetic women, has been ascribed to placental production and associated with the development of PDR (12). Most authors emphasize local retinal production of IGF-1 and the IGFBPs, but Pfeiffer et al. (13) propose that a breakdown of the blood retina barrier with influx of serum proteins secondary to microvascular disturbances and hypoxia is responsible for the vitreous alterations of IGF-1 and IGFBPs found in PDR.

Insulin lispro was developed as an insulin with improved pharmacokinetics relative to human insulin through consideration of structural homology with IGF-1 (14).

Bhattacharyya and Vice state that "It is well known that insulin enhances the action of IGF-1, but that is unlikely to be different with different types of insulin" (1). One wonders about possible differential effects on the stimulation of IGFBP-3 synthesis by insulin in mixed liver cell cultures (15) and the increased IGFBP protease activity of pregnancy (16), since, in some situations, IGFBP-3 may enhance the cell growth promoting activity of IGF-1 (17). One wonders about possible differential insulin effects on inhibition of IGFBP-1 production by the liver while increasing IGF-1 production (18) and on stimulation of IGFBP-1 transport across the endothelial wall (19), and the fact that in pregnancy nonphosphorylated forms of IGFBP-1 have lower affinity for IGF-1 and more growth stimulatory activity (17). More research is needed on the possible effects of insulin analogs on the complex IGF/IGFBP systems, with and without pregnancy. Jovanovic (5) stated that "insulin lispro has the same affinity for the IGF-1 receptor as human insulin." Actually, the affinity of insulin lispro for the IGF-1 receptor was increased less than twofold relative to human insulin in studies at the Lilly Research Laboratories (14). More recently, Trüb et al. (20) found that the IGF-1 receptor affinity (HepG2 cells) of insulin lispro was 141.5% relative to human insulin and that the IGF-1 receptor affinity of insulin aspart (B28Asp) was 68.8% relative to human insulin. Nevertheless, the affinity of any type of insulin for the IGF-1 receptor is ~1,000-fold less than that of IGF-1, <1% of IGF-1 in circulating blood is in the free form (9), and free IGF-1 circulates in nanomolar concentrations, whereas free insulin circulates at picomolar concentrations (21).

Jovanovic (5) cites the work of Anderson et al. (22) as evidence that controlled trials of insulin lispro in nonpregnant diabetic subjects did not show significant differences in the frequency of retinopathy. However, in my reading of this article reporting the results of a 6-month randomized multinational clinical trial performed with an open-label crossover design comparing insulin lispro with regular human insulin conducted by the Lilly Research Laboratories in 1,008 type 1 diabetic subjects, I noticed that retinopathy was not mentioned as an outcome variable or an adverse event (22). It may be likely that the type of insulin used for intensified glycemic control has nothing to do with the rapid development of PDR in pregnant women with chronic hyperglycemia and the beginnings of peripheral retinal ischemia, but we will never know without properly designed controlled trials.

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Impaired Fasting Glucose Is Not a Risk Factor for Cardiovascular Mortality

In the June 1999 issue of *Diabetes Care*, Tominaga et al. (1) concluded that impaired glucose tolerance, but not impaired fasting glucose (IFG), is a risk factor for cardiovascular disease. This conclusion was based on the mortality of a cohort of Japanese people over a follow-up period of 4–6 years, with use of both the World Health Organization and the American Diabetes Association criteria for the diagnosis of glucose tolerance classes. The IFG group experienced three deaths per 832 person-years of observation. The odds ratio of this group compared with that of the normal glucose tolerance group was 1.32 with an extremely wide 95% CI (0.012–140.91), suggesting that the power to detect a significant association between IFG and mortality was very low (type II error).

The role of fasting glucose on cardiovascular mortality has been recently reported. Bjørnholt et al. (2) described the excess risk of cardiovascular deaths in nondiabetic men in the upper normal range of fasting blood glucose, and Balkau et al. (3) found a linear relationship between death from coronary heart disease and fasting blood glucose levels. If these observations were valid, namely, that the risk of cardiovascular death increases with increasing fasting blood glucose, one would expect that people in the IFG category would be at a higher risk than those in the normal fasting glucose category.

It is possible that the lack of association found by Tominaga et al. in the Funagata Diabetes Study is due to a relatively short follow-up period of the IFG group, combined with the low incidence of cardiac deaths, which is a well-known fact in the Japanese population.

Without challenging the value of the 2-h blood glucose levels as a predictor of cardiovascular mortality, it is premature to deny the role of IFG based on the presented data.

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A Drug Interaction Between Troglitazone and Simvastatin

Since its approval in 1997, troglitazone has been considered one of the more recent advances in the treatment of type 2 diabetes. Troglitazone is a member of the thiazolidinediones, a class separated from the other oral antidiabetic agents such as sulfonylureas, α-glucosidase inhibitors, and biguanides by its distinct pharmacology. Troglitazone decreases insulin resistance, which is thought to be the underlying pathophysiology of type 2 diabetes, by improving insulin sensitivity in peripheral tissues (1). It also inhibits hepatic gluconeogenesis, thus decreasing hepatic glucose production (2). In addition to its insulin-sensitizing ability, troglitazone appears to have lipid-lowering effects by inhibiting the synthesis and enhancing the clearance of triglycerides (3).

Limited studies are available to provide data on the drug interaction profile of troglitazone. Human in vivo drug interaction trials have indicated that troglitazone, at clinically relevant doses, behaves as an inducer of the CYP3A4 enzyme (4). This conclusion is further supported by the documented interaction of troglitazone with both oral contraceptives and terfenadine. Co-administration of troglitazone with oral contraceptives and terfenadine can decrease the plasma concentration of oral contraceptives and terfenadine by ~30 and 50–70%, respectively (4,5). To date, there are no published studies evaluating the significance of interaction between troglitazone and other drugs that are also metabolized by CYP3A4. The majority of HMG-CoA reductase inhibitors, including simvastatin, are metabolized by CYP3A4, whereas pravastatin is believed to be metabolized by isoenzymes other than CYP3A4 (6).

A retrospective analysis was conducted to evaluate a possible drug interaction between troglitazone and simvastatin. This was a subgroup analysis of the Pravastatin to Simvastatin Conversion-Lipid Optimization Program (PSCOP) that was in progress 2 years earlier (7). The program was designed with the goal of increasing the percentage of patients meeting their LDL cholesterol goal based on National Cholesterol Education Panel guidelines. Instead of initiating the simvastatin dosage according to the dose equivalency of two drugs, it was determined by the lipid profile and coronary artery disease risk factors of the individual patient.

The retrospective analysis identified 344 diabetic patients from 1,115 patients in the original PSCOP. These diabetic patients were further divided into two groups: the troglitazone group, which included 21 patients who were treated with troglitazone before and after the conversion; and the nontroglitazone group,

which included 323 patients who were not treated with troglitazone. Additionally, a two-to-one (two nontroglitazone patients to one troglitazone patient) matching process was performed in an effort to control for the effect of age and weight, which identified 42 patients. The matching criteria for age and weight were ± 3 years and ± 4.5 kg, respectively.

Pravastatin and simvastatin doses were not significantly different between the troglitazone and the nontroglitazone patient groups; the mean doses of pravastatin and simvastatin were 24–27 and 21–22 mg, respectively. There were significant percentage reductions in total and LDL cholesterol levels after antihyperlipidemic medications were changed from pravastatin to simvastatin in the nonmatched (−6.4 and −10.2%, respectively; $P < 0.001$) and matched nontroglitazone (−6.6 and −11.8%, respectively; $P < 0.05$) groups. However, no significant reductions in total (−2.7%; $P = 0.32$) and LDL (−1.3%; $P = 0.65$) cholesterol were observed in the patients receiving troglitazone. The percentage of patients meeting their LDL cholesterol goal increased in both nonmatched (48–65%; $P < 0.001$) and matched nontroglitazone (52–69%; $P = 0.13$) patient groups after converting to simvastatin; however, the increase was significant only in the nonmatched group. Nine (42%) of the patients treated with troglitazone met their LDL cholesterol goal while on pravastatin and only eight (38%) after the conversion to simvastatin ($P = 1.0$).

Our retrospective analysis compared lipid profiles before and after conversion from pravastatin to simvastatin in diabetic patients who were treated with and without troglitazone. Because the mean doses of pravastatin and simvastatin were similar, one would expect an additional percentage reduction (11%) in LDL cholesterol after changing pravastatin to simvastatin (8,9). However, this was evident only in the patients who were not treated with troglitazone. Moreover, after these patients were matched according to age and weight with the troglitazone patients, the reductions in total and LDL cholesterol were still significant. In addition, the percentage of patients meeting their LDL cholesterol goal after converting to simvastatin increased in both nontroglitazone groups. One potential explanation for the reduced lipid-lowering effect of simvastatin in the patients also taking troglitazone is enhanced enzyme-induced metabolism of simvastatin. This induction in metabolism by troglitazone is likely to be more pronounced with simvastatin than with pravastatin since CYP3A4 is the main metabolism isoenzyme for simvastatin, and troglitazone is known to induce CYP3A4 (4,6). Pravastatin has been shown to exhibit some affinity for CYP3A4 (10), even though CYP3A4 may not be the primary isoenzyme involved in its metabolism. Although retrospectively observed, this interaction between troglitazone and simvastatin is likely to be clinically relevant and has not been previously reported.

On the basis of the results from this retrospective analysis, we recommend additional monitoring of lipid profiles when troglitazone and simvastatin are used concomitantly. Higher simvastatin dosage may be required owing to the possibility that troglitazone may induce the metabolism of simvastatin, thus diminishing some lipid-lowering effects of simvastatin. To confirm this drug interaction and provide more definite information, a prospective trial is perhaps necessary.

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Response to Lin and Ito

Effect of troglitazone on atorvastatin pharmacokinetics and pharmacodynamics

The letter by Lin and Ito (1) raises the possibility of an interaction between troglitazone and simvastatin. We would like to add further information relevant to the discussion of interactions between HMG-CoA reductase inhibitors and troglitazone. In vitro studies have shown that various CYP isozymes, including CYP3A4, are involved in the metabolism of HMG-CoA reductase inhibitors (2–4). Currently available data indicate that troglitazone likely induces CYP3A4 activity (5,6). A prospective crossover study was conducted to evaluate the effect of troglitazone on the pharmacokinetics and pharmacodynamics of atorvastatin, which is a substrate of CYP3A4 (7). Although troglitazone moderately reduced the plasma area under the curve of atorvastatin by 33%, changes in lipids (triglyceride and total, LDL, and HDL cholesterol levels) were similar after administration of atorvastatin alone and after administration of atorvastatin with troglitazone (8). Therefore, we concur with Lin and Ito that a prospective clinical study might be helpful in clarifying the signifi-

cance of a possible troglitazone-simvastatin drug-drug interaction.

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C.-M.L. and A.J.S. hold stock in Warner-Lambert.

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