OBSERVATIONS

Internal Carotid Artery Occlusion Detected With Nonmydriatic Fundus Photography

A case report

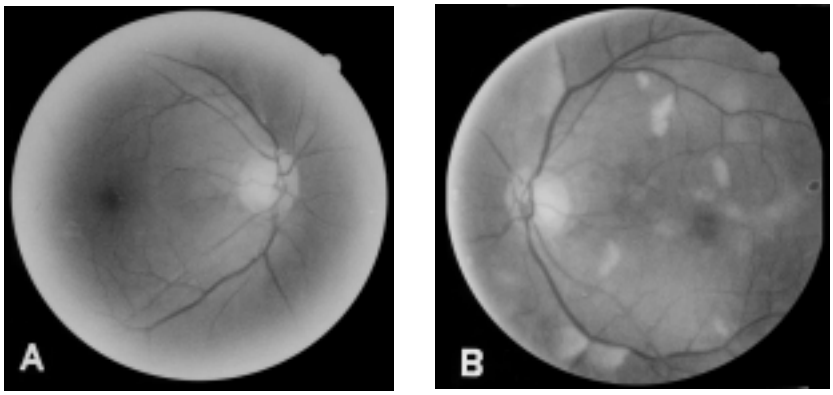

Figure 1—*Nonmydriatic fundus photograph showed asymmetric diabetic retinopathy, i.e., normal in the right eye, (*A*) and preproliferative retinopathy with cotton wools and hemorrhagic spots in the left eye fundus (*B*).*

Diabetic retinopathy is one of the major complications of diabetes, and it is the most common cause of blindness. Following the recommendation of the management guidelines for type 2 diabetes, we have established a routine screening for diabetic complications in our clinics (1). Although nonmydriatic fundus photography was widely used for screening of diabetic retinopathy, less attention has been directed toward the correlation between asymmetric retinopathy (i.e., more advanced retinopathy in one eye and no retinopathy in the other) and carotid artery disease. Here, we are reporting on a diabetic patient with asymptomatic internal carotid artery (ICA) occlusion who presented with significantly asymmetric retinopathy found by nonmydriatic fundus photography in our routine screening clinic.

A 59-year-old man with a known history of hypertension, type 2 diabetes, and dyslipidemia for ~10 years was regularly followed up in our hospital. Routine screening with nonmydriatic fundus photography found asymmetric retinopathy with hemorrhagic and cotton wool spots in the left eye and no retinopathy in the right eye ground.(Fig. 1). After noting this finding, we asked the patient about possible neurological symptoms. Only mild vision deterioration in the left eye was noted in the past 10 days. Because it did not hinder his daily life, he had not paid attention to the condition. He denied any other motor, sensory, or visual disturbances. There was no history of cigarette smoking, alcohol consumption, or previous surgical operation. On physical examination, his height and weight were 170 cm and 69 kg, respectively. His blood pressure was 138/90 mmHg, with a regular pulse and no carotid bruit or heart murmur. Examinations of the chest and abdomen produced normal results. No pitting edema was found in the extremities, the distal circulation was intact, and the bilateral ankle/brachial index was 1.06/1.06. No remaining evidence of any other neurological deficits was noted during normal sensory examinations and measurements of deep tendon reflexes and muscle power.

The laboratory studies revealed a hemoglobin level of 13.4 g/dl, a platelet count of 258 × 10^9/l, fasting plasma glucose level of 175 mg/dl, a postprandial plasma glucose level of 153 mg/dl, HbA_{1c} value of 6.9%, a creatinine level of 0.8 mg/dl, total cholesterol level of 275 mg/dl, triglyceride 690 mg/dl, and urinary albumin excretion count of 30–300 mg/g creatinine. We further performed a carotid ultrasound examination, and found total occlusion of the left ICA and mild plaque in the right ICA (Fig. 2). After weighing the risk of stroke during medical management versus the risks of surgery, the patient was prescribed aspirin 650 mg/day for antiplatelet

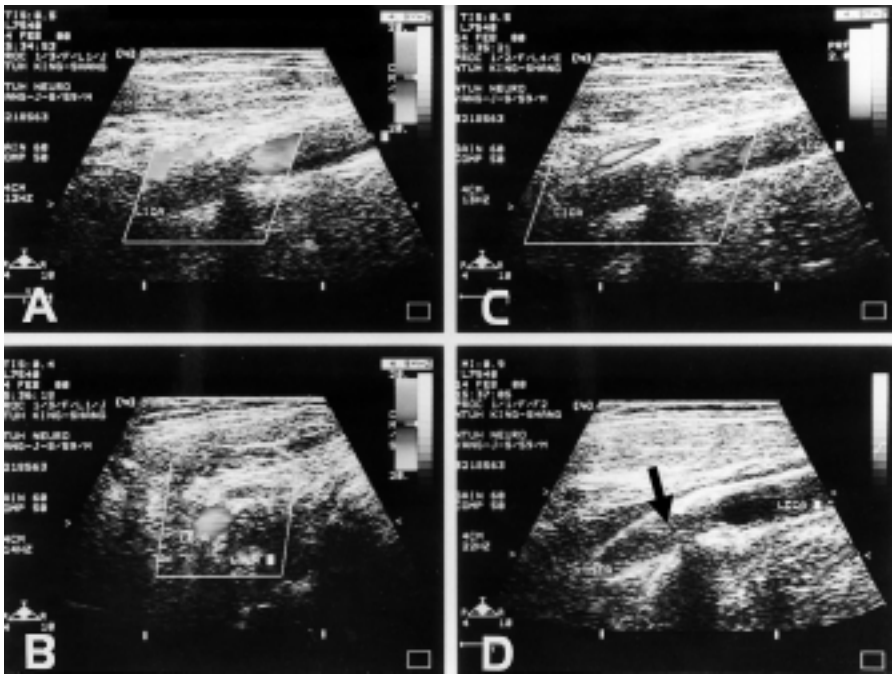

Figure 2—*Carotid duplex scan of the bifurcation of the left common carotid artery.* A*: The color-coded B-mode image showed total occlusion at the origin of the ICA.* B*: No stenosis was found at the external carotid artery.* C*: Carotid duplex artery Doppler scan.* D*: Carotid duplex examination showed dense plaque (as indicated by arrow) in the ICA distal to the bifurcation.*

therapy, buflomedil 150 mg 3 times a day for reducing risks of myocardial infarction, stroke, and oral hypoglycemic antihypertensive lipid-lowering agents.

Atheromatous lesions were found to be present in the ipsilateral arteries of 88% of patients presenting with retinal ischemia, and there was a trend toward higher incidence of more severe lesions on the ipsilateral side (2,3). Asymmetric retinopathy occurs in 5.2–10.1% of diabetic patients with proliferative diabetic retinopathy (PDR) (4–6). Although the incidence of severe carotid artery disease was only 0.8–20% (4,7), we learned from this case and other studies that reported that even in asymptomatic patients, significant ipsilateral carotid occlusion disease is an important risk factor for asymmetric pre-PDR and PDR (7).

It is estimated that more than 2 million Americans have ≥50% stenosis of the carotid artery without being aware of any attendant symptoms (8), and carotid artery stenosis accounts for ~20% of occlusive strokes in the carotid distribution (9). Our patient's asymptomatic ICA occlusion was found unexpectedly by routine screening with nonmydriatic fundus photography because of the presence of significantly asymmetric retinopathy. We therefore strongly recommend searching for underlying lesions in cases of asymmetric diabetic retinopathy (including pre-PDR and severe PDR). We suggest that both carotid vessels should be examined routinely in patients with asymmetric diabetic retinopathy.

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Effectiveness of a Diabetes Education Program Adapted for People With Vision Impairment

The rising prevalence of people with vision impairment associated with diabetes (estimated between 570,000 and 2.3 million affected individuals) requires adapted diabetes education services (1–3). The availability of diabetes programs delivering these services is limited. A comprehensive program for people with both diabetes and vision impairment enabled participants to master self-care skills, such as administration of insulin injections and blood glucose monitoring (4–6). We evaluated the outcomes of this program extended to a more diverse population over a 10-year period.

From 1989 through 1998, visually impaired participants were referred to the St. Louis University Health Sciences Center. Diabetes educators specializing in adaptive diabetes techniques met with the individuals to *1*) assess visual function, *2*) evaluate and update general diabetes knowledge, and *3*) assist in the selection of appropriate self-management devices. The number and content of the sessions varied according to the level of preexisting diabetes knowledge and time needed for acquisition of self-care skills.

Assessment of visual function was obtained from medical records as well as from direct questioning about the subjects ability to read standard and large-print materials, their need for special lighting, and their ability to recognize large objects or subtle details. Before introducing adaptive self-care skills, the educators provided instructions in basic diabetes knowledge and self-care. Visual function and manual dexterity were taken into consideration when choosing the most appropriate adaptive devices among the available options. Adaptive equipment included syringe magnifiers, syringe loading devices, and glucose monitoring systems with speech capability and tactile aids for proper blood sample placement (7–10). Subjects returned for final follow-up after procuring their own equipment. Demonstration of proficient self-care technique was considered a successful outcome. The protocol was approved by the Institutional Review Board of St. Louis University.

Data were analyzed by nonpaired tests and one-way analysis of variance, with subgroup analysis performed by the method of the Newmann-Keuls post hoc test. Comparisons of proportions were performed by χ^2 tests. All data are described as means ± SD.

There were 163 participants. The participants' mean age was 55.9 ± 14.5 years, the duration of diabetes was 17.5 ± 9.8 years, and the duration of vision impairment was 5.5 ± 9.2 years. There were 28 people with type 1 and 135 with type 2 diabetes. There were 43 men and 120 women; 36% were African-American and 64% were white. There were 99 subjects who had "early" visual impairment (defined as legal blindness with some retained functional vision) and 64 subjects had "late" visual impairment (defined as light perception only or total blindness).

There were 112 participants (72%) who succeeded in learning the specialized techniques. Five refused training, 1 had a stroke, and 1 was lost to follow-up. Those who were successful were younger (53.9 ± 14.0 years of age) compared with those who were unsuccessful (61.0 ± 14.9 years of age, P = 0.006). When the population was divided into quartiles by age distribution, those in the highest quartile (>66 years of age [53%]) were the least successful in mastering the skills (χ^2 9.8, P = 0.02). Those

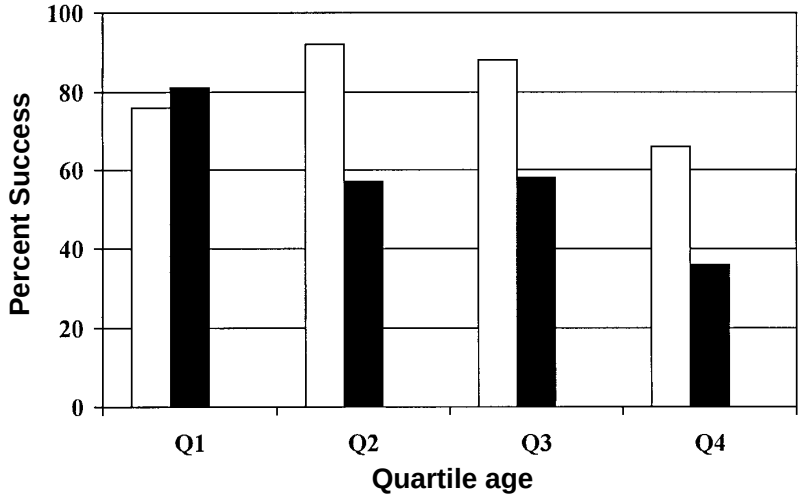

Figure 1—*Success rate of acquiring self-management skills for the visually impaired. The rates are shown for age-groups in quartiles (Q), where Q1 is 22–47, Q2 is 48–56, Q3 is 57–65, and Q4 is 66–89 years of age.* □*, Early visual impairment;* ■*, late visual impairment. Overall, those in Q4 had a significantly lower success rate than the other groups,* P = *0.02.*

with late visual impairment had a poorer success rate (57%) compared with those with early visual impairment success rate of 81% (χ^2 10.3, df = 1; $P = 0.001$). There was an overall trend for poorer success with both advanced age and advanced visual impairment ($r = -0.95$, $P = 0.05$) (Fig. 1).

Before the program, 49 people were attempting to manage their diabetes by themselves, 89 required the help of a family member, and 18 required professional home health care. The latter group, who were predominantly in the fourth age quartile, had the poorest success rate.

In conclusion, this adaptive diabetes education program demonstrated effectiveness in restoring independent diabetes self-care practices among a diverse population. Those individuals least likely to succeed were the elderly with the most advanced degree of vision impairment. Even so, approximately half of the elderly were able to complete the program successfully. Younger individuals with advanced stages of vision loss were less likely to be deterred.

Individuals with early visual impairment were more successful in completing the program, suggesting that reliance on remaining vision may have facilitated acquisition of self-care skills. Early intervention in the course of vision loss may empower the individual with confidence and self-reliance to maintain learned skills as the vision loss progresses.

National standards for diabetes education do not emphasize rehabilitative training and self-care techniques (11,12). However, an adaptive diabetes self-care program allows individuals the opportunity to participate in their diabetes management with the same expectations as their sighted peers (7,9). This leads not only to improved self-reliance and quality of life, but also alleviates the burden on the family and the home health care system (13). With appropriate instruction, independent self-care is possible for the majority of individuals, including many elderly people and those with the severest degrees of vision loss.

All diabetes educators should have an understanding of the resources available for visually impaired patients. The cost of acquiring all necessary adaptive demonstration devices may be prohibitive for private offices and smaller centers (19). However, all major diabetes programs should function as regional referral centers, offering the appropriate demonstration devices and trained educators.

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Which Screening Test Is the Best for Gestational Impaired Glucose Tolerance and Gestational Diabetes Mellitus?

The glucose challenge test (GCT) has been widely adopted as a screening test for gestational diabetes mellitus (GDM). However, because the test is quite labor-intensive, some researchers have investigated other less complex screening methods. Reichelt et al. (1) recently demonstrated that fasting glucose levels predict gestational impaired glucose intolerance (GIGT) with a sensitivity of 81% and a specificity of 49% when using a threshold of 4.5 mmol/l. So far, there has been no study to compare the prediction of GIGT with other less laborious tests. Therefore, we examined several screening tests in the prediction of GDM and GIGT and determined the optimal cutoff threshold for each screening method.

A total of 1,031 pregnant women were recruited from the prenatal clinic at the Prince of Wales Hospital. A 50-g GCT was scheduled between 24 and 28 weeks of gestation. Plasma spot glucose was measured before the test and all patients were scheduled to have a 75-g oral glucose tolerance test (OGTT) 2–4 weeks thereafter, regardless of the initial GCT results. A blood sugar series that included fasting, 2-h postbreakfast, 2-h postlunch, 2-h postsupper, and midnight plasma glucose measurements was also performed either immediately before or 1 week after the OGTT. Plasma fructosamine was also measured during the blood sugar series. A total of 942 (91.4%) women completed the study after the initial recruitment. Glucose intolerance (GIGT and GDM) was diagnosed in 122 subjects (13.0%). The diagnostic criteria of GDM and GIGT were based on the recommendations of the World Health Organization (2). The accuracy of predictions of GDM/GIGT using the 1-h GCT, fasting plasma glucose, spot glucose, postbreakfast glucose, and plasma fructosamine values were compared by receiver-operator characteristic (ROC) analysis using the test devised by DeLong et al. (3).

There were 706 (68.5%) nulliparous and 325 (31.5%) multiparous women. Of these women, 734 (71.2%) were older than 25 years and 152 (14.7%) had a BMI >27 kg/m^2. There were 145 (14.1%) women with a family history of diabetes and 15 (1.5%) women with a previous macrosomic baby. Only 1 patient (0.1%) had a previous history of GDM. The incidence of glucose intolerance was significantly higher in women who were >25 years of age, were obese, or had a family history of diabetes; the odds ratios were 2.64 (95% CI 1.55−4.51), 1.71 (1.07−2.73), and 1.79 (1.11−2.88), respectively. There was no significant increase in incidence among those with a previous macrosomic baby.

Each of the areas under the ROC curves for the GCT (0.773, SEM 0.025), fasting glucose (0.766, SEM 0.026), and 2-h postbreakfast glucose levels (0.743, SEM 0.025) were significantly greater than that for random spot glucose and plasma fructosamine measurements. The areas under the curves were not significantly different among the GCT, fasting glucose, and 2-h postbreakfast values.

The optimal cutoff values were 7.0, 4.1, 5.0, and 4.7 mmol/l for the 1-h GCT, fasting glucose, 2-h postbreakfast, and spot glucose, respectively. The selection of the cutoff value is guided by the Youden index, which is, in general, a compromise between the sensitivity and the specificity. As we were looking for a good screening test, the highest Youden index in which the sensitivity was >70% was selected.

If the policy of selective screening currently recommended by the American Diabetes Association (ADA) (4) were adopted, the number of blood tests could be reduced by 23%. However, the sensitivity would drop to 65.6, 64.8, and 63.1% for the GCT, fasting glucose, and 2-h postbreakfast tests, respectively, using the cutoff values previously determined. If selective screening were performed according to the ADA recommendation of using the GCT cutoff of 7.8 mmol/l, a sensitivity of only 50% would be achieved.

Therefore, our findings support recommendations to offer universal screening to high-risk ethnic groups. Furthermore, the GCT has several disadvantages over the more convenient use of a fasting glucose or postbreakfast value, which have similar predictive values. Hence, we propose to discontinue the use of this nonphysiological test. Although both fasting and postbreakfast glucose levels performed as well as GCT in the prediction of GIGT and GDM, fasting glucose is more convenient administratively, as it does not require timed blood collection. Therefore, we recommend the use of fasting glucose to replace the GCT as a screening test for GIGT and GDM.

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Short-Term Oral Ascorbic Acid Improves Endothelium-Dependent Vasodilatation in Women With a History of Gestational Diabetes Mellitus

Cardiovascular complications are the principal cause of morbidity and mortality among patients with type 2 dia-

betes, primarily as a result of acceleration of atherosclerosis and increased thrombosis (1). One of the early signs in the development of atherosclerosis is endothelial dysfunction; abnormal endothelial function has been observed in patients with conditions predisposing to the development of atherosclerosis, including diabetes (2). The mechanisms of endothelial dysfunction in diabetic individuals are not known, but there is strong evidence that inactivation of nitric oxide by increased oxygen-derived free radicals could be responsible. There are studies in humans that show that abnormal endothelial function in type 2 diabetes has been restored by treatment with antioxidants, e.g., ascorbic acid (3). Women with a history of gestational diabetes mellitus (GDM) represent a group of individuals who have insulin resistance and increased risk to develop type 2 diabetes later in life (4). We have recently shown that these women have markedly abnormal endothelial function, even in the presence of normal glucose tolerance (5). Because ascorbic acid improves endothelial function in patients with type 2 diabetes, we hypothesized that abnormal endothelium-dependent vasomotor function in such subjects in a prediabetic state might be improved by ascorbic acid.

Seventeen women with a history of GDM (mean age 36 ± 3.9 years) randomly selected from a cohort of women, in whom endothelial dysfunction has previously been reported (5), were enrolled in this study. Ten of these women were nonobese (BMI 23.5 ± 1.9 kg/m^2) and 7 were obese (BMI 34.3 ± 5.1 kg/m^2). All of the women were otherwise healthy nonsmokers who were not taking any medication at the time of the study. Basal insulin resistance was calculated using homeostasis model assessment (6). Each subject was assessed double-blindly on 2 visits, 3–6 months after delivery. On day 1, baseline flow–mediated dilatation of the brachial artery was estimated (7), and 2 g ascorbic acid (Cebion, Merck, Germany) or similarly appearing placebo tablets were given orally; 2 h later, flow-mediated dilatation and nitrate-induced dilatation were estimated. It is known that oral ingestion of 2 g ascorbic acid normally leads to plateau plasma levels after 2 h; these remain elevated for 5 h after ingestion. In addition, the 2-g dose produces a significant increase in plasma ascorbic acid levels within the physiological range. This dose and timing were thus selected, as previously recommended (8). One week later (day 2), measurement of baseline flow–mediated dilatation of the brachial artery was repeated and the opposite treatment (placebo or ascorbic acid) was administered; 2 h later, flow-mediated dilatation and nitrate-induced dilatation were assessed. Measurements obtained at baseline, after ascorbic acid, and after placebo, were compared by analysis of variance for repeated measurements with Newman-Keuls post hoc test comparison of group mean values. Statistical significance was taken at a P value <0.05.

Fasting glucose concentration, glycosylated hemoglobin, and oral glucose tolerance tests were all within normal range. Administration of ascorbic acid had no effect on heart rate, blood pressure, resting blood flow, resting artery diameter, and the degree of reactive hyperemia. Ascorbic acid resulted in a significant improvement of endothelium-dependent flow-mediated dilatation from 2.6 ± 2.7 to 9 ± 3.3%, whereas there was no improvement after placebo administration (3 ± 2.3 to 2.6 ± 1.9%) ($P < 0.05$). Regarding the possible effects of ascorbic acid on arterial smooth muscle cell function, sublingual nitroglycerin produced arterial dilatation that was similar in the ascorbic acid and placebo groups (24 ± 9.3 vs. 22.8 ± 6%, NS), indicating the absence of a beneficial effect of ascorbic acid on smooth muscle cell response to nitric oxide.

These findings suggest that ascorbic acid improved nitric oxide bioavailability in conduit arteries in response to hyperemic flow in women with previous GDM; the scavenging of free radicals and reduction of the oxidative stress explain the improvement observed after administration of ascorbic acid. We have recently shown (5) that women with previous GDM have markedly abnormal endothelial function that is independent of obesity; an interesting possibility is that endothelial dysfunction in this setting could be related to the chronic insulin resistance known to characterize this group. A positive correlation between basal vascular endothelial nitric oxide production and insulin sensitivity has been reported in healthy individuals (9), suggesting a direct physiological link between endothelial function and insulin. An interesting finding in our previous work (5) was an inverse correlation of serum uric acid levels and flow-mediated dilatation, indicating that oxidative stress in women with previous GDM plays a role in the pathogenesis of endothelial dysfunction. It is known that activation of the xanthin/xanthinoxidase system causes generation of vascular oxygen radicals, which results in reduction of endothelium-dependent vasodilatation, because xanthinoxidase also generates uric acid; elevated serum uric acid levels appear to be a marker of increased oxidative stress (10). Nitric oxide is inactivated by oxygen-derived free radicals, particularly superoxide anion, leading to endothelial dysfunction (11). Ascorbic acid is an effective antioxidant, which has the ability to scavenge excess superoxide anions and thereby decrease nitric oxide inactivation (12).

In conclusion, oral ingestion of ascorbic acid acutely improves endothelial dysfunction observed in women with previous GDM, suggesting that oxygen-derived free radicals may play a role in the pathogenesis of abnormal endothelial function in these women. Restoring endothelial function may have important implications for reducing the risk of atherosclerosis in these subjects. Further studies examining the effects of the long-term administration of ascorbic acid on endothelial vasomotor activity will be required before vitamin C supplementation can be recommended in women with previous GDM and abnormal endothelial function.

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Assessment of Insulin Sensitivity From a Single Sample

Comparison of homeostasis model assessment (HOMA) and Ln(HOMA) with minimal model analysis

Assessment of insulin sensitivity provides a basic understanding about common metabolic disorders. Various methods have been proposed to evaluate insulin sensitivity in vivo. The euglycemic clamp study and minimal-model analysis (MINMOD) are the standard methods of estimating insulin sensitivity, but the procedures are rather complex and expensive (1–3). There is a need for simple indexes that assess insulin sensitivity from a single sample at diabetes clinics and in large-population studies. The insulin resistance index assessed by homeostasis model assessment defined as the product of fasting plasma insulin and glucose divided by 22.5 (HOMA-IR) is an estimation of insulin sensitivity from a single sample (4). Matthews et al. (4) demonstrated that HOMA-IR is closely correlated with insulin resistance index assessed by euglycemic clamp (clamp IR) in type 2 diabetic patients. This estimation is suitable for large-population studies. Very recently, Emoto at al. (5) and Bonora et al. (6) also reported that HOMA-IR and log-transformed HOMA-IR (Ln[Homa]) provided a good correlation in the clamp studies. In the present study, we applied MINMOD during frequently sampled intravenous glucose tolerance tests to compare the estimates of insulin sensitivity with HOMA-IR and Ln(HOMA).

We examined 103 Japanese subjects with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and type 2 diabetes to assess insulin sensitivity. Glucose intolerance was diagnosed based on the criteria of the World Health Organization (7). The BMI of the subjects with NGT, IGT, and type 2 diabetes were 13.4–38.3, 17–39.3, and 17.2–25.3 kg/m^2, respectively. MINMOD-derived insulin sensitivity index (SI) was estimated as previously described (8–10). The statistical analysis was performed with the StatView 5 system (Berkeley, CA).

We observed a significant correlation between HOMA-IR and MINMOD SI in all of the subjects examined in this study (r = 0.45, $P < 0.0001$). Because visual inspection suggested a hyperbolic relationship between HOMA-IR and SI, we also analyzed the correlation of Ln(HOMA) with SI. Ln(HOMA) correlated more strongly with MINMOD SI than did HOMA-IR per se (r = 0.61, $P < 0.0001$). To investigate the reason why HOMA-IR and Ln(HOMA) show differences in correlation coefficients, we analyzed the relationship of HOMA-IR and Ln(HOMA) with SI across the range of HOMA-IR. We divided the subjects into 3 groups according to the HOMA-IR values (HOMA-IR: <1, from 1 to 2, and >2). The relationship of HOMA-IR and Ln(HOMA) with MINMOD SI is shown in Table 1. There was only a slight difference between the correlation coefficients of HOMA-IR and Ln(HOMA) with MINMOD SI when the HOMA-IR was <1 (r = 0.49, $P < 0.005$ vs. r = 0.49, $P < 0.005$). There was also only a slight difference between the correlation coefficients of HOMA-IR and Ln(HOMA) with MINMOD SI when the HOMA-IR was between 1 and 2 (r = 0.40, $P < 0.01$ vs. r = 0.37, $P < 0.05$). In contrast with HOMA-IR values <1 and from 1 to 2, the correlation coefficient becomes higher and the P value becomes significant when HOMA-IR is log-transformed in subjects with HOMA-IR >2 (r = 0.33, P = 0.10 vs. r = 0.49, $P < 0.05$). Because the HOMA-IR value is a product of blood glucose and insulin levels, it is possible that the estimates are slightly exaggerated and the values are scattered to a wide range, compared with the standard estimates MINMOD SI when the metabolic status of each individual increases both glucose and insulin levels. There is a frequent need of assessing insulin sensitivity for clinicians during the diet, exercise, and/or drug therapy. In addition, HOMA-IR is a widespread index of insulin sensitivity and a simplified evaluation without exaggeration *as a number* is

Table 1—*Comparison of HOMA-IR and Ln(HOMA) with MINMOD SI*

	All subjects	HOMA-IR<1	1<HOMA-IR<2	2<HOMA-IR
HOMA				
r	0.45	0.49	0.40	0.33
P	<0.0001	<0.005	<0.01	0.10
Ln(HOMA)				
r	0.61	0.49	0.37	0.49
P	<0.0001	<0.005	<0.05	<0.05

Data are correlation coefficients (*r*) and *P* values (*P*) of HOMA-IR and Ln(HOMA) compared with MINMOD-derived SI.

necessary (11,12). When the subjects are examined whose metabolic circumstances cause the value of HOMA-IR to increase, the log-transformed HOMA will be a better prediction of insulin sensitivity.

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Prevalence of Glucose Intolerance Among Malays in Brunei

In newly industrialized countries, dramatic changes in economy and lifestyle may result in changed eating habits, reduced physical activity, and increased frequency of obesity. These changes appear to lead to metabolic abnormalities, such as glucose intolerance, hyperinsulinemia, dyslipidemia, hypertension, and obesity. As a consequence, type 2 diabetes, heart disease, and stroke have become major causes of mortality in many of these countries (1).

In Brunei (North Borneo), the socioeconomic development and the increase in wealth over the last 3 decades have led to rapid modernization processes. During this time, Bruneians, particularly the ethnic group of Malays who constitute the majority (75%) of the population, have adapted to an affluent lifestyle resulting from Western influences. Among other things, this new lifestyle has been characterized by a change in diet and very little exercise.

Previous publications have indicated that a relatively high prevalence of glucose intolerance correlates with the level of social development in this area. In West Malaysia, Malays with an urban lifestyle have been reported to show a considerably higher prevalence of type 2 diabetes compared with Malays living a more rural way of life (8.2 vs. 2.8%, respectively) (2). Likewise, Malays in Singapore showed a relatively high prevalence of type 2 diabetes (9.1 and 6.1%, men and women, respectively) (3). These observations emphasized the need for assessing the risk of glucose intolerance among Bruneian Malays.

We performed an oral glucose tolerance test on 100 randomly chosen Bruneian Malay volunteers between 25–55 years of age (57:43, men:women). Our selection criteria were ethnic origin and age, whereas the exclusion criteria were pregnancy, cancer, treatment with oral steroids, recent surgery, and recent serious illness. Venous blood (10–20 ml) was collected just before the glucose challenge (75 g glucose/300 ml H_2O) and 30, 60, 90, and 120 min afterward. Using the diagnostic criteria of the World Health Organization and the National Diabetes Data Group, we classified each subject as having normal glucose tolerance, impaired glucose tolerance, or type 2 diabetes. Serum insulin levels were measured with an immunoradiometric assay not susceptible for proinsulin cross-reactivity (Medgenis, Fleurus, Belgium), and serum C-peptide measurements were determined with a radioimmunoassay (Biolab/Serone, Milan, Italy). Statistical analysis of the insulin and C-peptide response to oral glucose was based on one-way analysis of variance with repeated measurements followed by post hoc Tukey's test.

We observed that 13.5% of the total group was impaired glucose tolerant and 6.5% was type 2 diabetic. Only the diabetic subjects showed increased fasting serum insulin and C-peptide levels. However, both diabetic and impaired glucose-tolerant subjects revealed a delayed insulin and C-peptide response to oral glucose and a significantly prolonged exposure to elevated serum insulin and C-peptide levels during the 2-h testing period. The prevalence of glucose intolerance in relation to age was found to be 15, 19, and 25% in the groups 25–34, 35–44, and 45–55 years of age, respectively.

In addition, we determined weight, height, waist and hip circumference, and fat distribution based on bicep, tricep, subscapular, and suprailium skin-fold measurements with a caliper. Anthropometric

classification of the subjects according to the percentage of body fat (%BF) indicated that 54% of all male subjects and 96% of all female subjects were overweight or obese. Alternatively, classification according to BMI revealed that 53% of all men and 56% of all women were overweight (BMI 25–30 kg/m^2) or obese (BMI >30 kg/m^2). Remarkably, we found that 42.5% of the women who were classified as overweight or obese based on %BF showed a BMI <25 kg/m^2. Of all female subjects, 67.5% showed a waist-to-hip ratio ≥0.8. A combination of a relatively high %BF and a high waist-to-hip ratio has been shown to be related to upper body obesity, which is considered a major risk factor linked to diabetes and cardiovascular disease (4). The specific phenomenon of too much central body fat, even in women with a BMI <25 kg/m^2, has been found in Vietnamese (5) and Chinese (6) women as well.

This cross-sectional study represents the first population-based data collection on the prevalence of glucose intolerance among the Malay inhabitants of Brunei, and it indicates a high frequency of type 2 diabetes and impaired glucose tolerance. Although we cannot exclude a predisposition for glucose intolerance in Bruneian Malays, environmental factors, such as diet and physical activity, might contribute to the development of a multifactorial disease such as type 2 diabetes. Our results support previous findings on diabetes epidemiology in newly industrialized countries.

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Frequency and Patients' Reported Awareness of Diabetic Retinopathy Among Type 2 Diabetic Patients Admitted to Internal Medicine Wards

Although diabetes is one of the major causes of blindness, diabetic retinopathy can be prevented in most cases (1–8). While successful treatment is dependent on early intervention, irreversible damage has often already occurred before symptoms appear. According to guidelines issued by the American Diabetes Association and the American Academy of Ophthalmology (9), patients with type 2 diabetes are advised to have an initial screening examination for diabetic retinopathy shortly after being diagnosed as diabetic. After the primary fundus evaluation, annual examinations are recommended unless more frequent examinations are indicated. Several studies point out that there is low awareness and low compliance to these guidelines for various reasons (10–14). In many cases, ophthalmic surveillance of high-risk patients with diabetes is inadequate, and advanced disease is often present at initial presentation.

Regardless of the reason for admission, the hospitalization of a diabetic patient offers an opportunity to screen for diabetic retinopathy. The objective of this study was to assess the awareness of diabetic retinopathy among hospitalized patients with diabetes and the adequacy of the ophthalmic surveillance given to these patients. All patients with type 2 diabetes hospitalized in the internal medicine wards of one hospital during one month were candidates for inclusion in the study, regardless of the reason for hospitalization. Of these patients, 165 were suitable and agreed to be interviewed and to undergo funduscopic examination. The patients were asked if they knew about possible ocular involvement in diabetes and if they ever underwent ophthalmologic evaluation. All had a dilated fundus examination. Each patient received an explanation regarding diabetic retinopathy, was informed of the results of the present examination, and was given a letter for the family physician noting the results of the funduscopic findings and the required treatment or recommendations for annual follow-up.

A total of 58 patients (35%) reported being unaware of diabetes-associated ocular complications; 88 (53%) reported never having had a dilated examination. Only 57 patients (35%) reported undergoing dilated examination during the 12 months before hospitalization. Diabetic retinopathy was found in 73 patients (44%). Of the 37 (22%) patients who required laser treatment, 13 (35%) were unaware that diabetes could cause ocular problems. Of the 58 patients who were unaware of diabetic ocular complications, 26 (45%) had diabetic retinopathy (22% required laser treatment). Regarding awareness, our results are in accordance with previous studies (11,14). Ophthalmic surveillance findings resemble the results of several studies (12, 14,15), but are poorer than those reported by others (16,17).

Our results indicate that ophthalmologic examination of hospitalized diabetic patients may be an effective means for providing greater awareness of diabetic retinopathy and for screening, early detection, and identifying cases of diabetic retinopathy. Routine dilated funduscopic examination for all admitted patients by an ophthalmologist may be a viable means for overcoming the low compliance found in numerous studies (10,12,14,15,18). This should not replace routine ophthalmologic screening managed by the patient's physi-

cian, but it should serve as a supplement aimed at those patients who are not under the recommended ophthalmic surveillance.

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GAD65 Autoantibodies, β-Cell Function, and Insulin Resistance in Japanese-Brazilian Adults

Outside of Japan, Brazil has the largest population of individuals of Japanese origin. Although it has been shown that diabetic Japanese-Brazilian individuals between 40 and 79 years of age who were analyzed in the Japanese-Brazilian Study Group of Bauru City, São Paulo, Brazil (1), had a smaller mean BMI than the nondiabetic Brazilian population (2), they had a higher prevalence of diabetes (18%) than the the overall age-matched Brazilian population (7.6%) (3).

In the pathogenesis of type 2 diabetes, instead of obesity affecting both insulin secretion and insulin resistance, we know that obesity may vary the relative importance of insulin deficiency and insulin resistance in different ethnic groups (4).

To compare diabetes in Japanese-Brazilians with type 2 diabetes in non-Japanese Brazilians, we evaluated anthropometric data, fasting plasma glucose measurements (glucose oxidase method), total plasma insulin levels with a radioimmunoassay (RIA) kit (Insulin-CT; CIS Bio International, Cedex, France), β-cell function with the homeostasis model assessment (HOMA) ([20 × insulin (μU/ml)/ glucose (mmol/l) – 3.5]), and insulin resistance (HOMA-IR) ([insulin (μU/ml) × glucose (mmol/l)/ 22.5]) applied to fasting insulin/glucose pairs in each individual. The GAD65 autoantibodies were measured in the fasting serum by an RIA procedure using a commercial reagent kit that used ^{125}I–human recombinant GAD65 (Kronus, San Clemente, CA).

These variables were studied in a sample of 49 Japanese-Brazilians with diabetes, 50 Japanese-Brazilians without diabetes, 47 non-Japanese Brazilians with type 2 diabetes, and 45 non-Japanese Brazilians without diabetes.

The Ethics Committee of the São Paulo Hospital of São Paulo Federal University approved the study. The classification of the patients and the control subjects was in accordance with World Health Organization criteria (5).

All groups were of the same age range (40–67 years). The diabetic Japanese-Brazilian (25.8 ± 4.5 kg/m^2) and the nondiabetic Japanese-Brazilian (23.6 ± 3.1 kg/m^2) populations had similar BMIs, but both populations had BMIs lower than both the non-Japanese–Brazilian population with type 2 diabetes (28.8 ± 4.4 kg/m^2) and the non-Japanese–Brazilian population without diabetes (26.4 ± 4.4 kg/m^2, $P < 0.05$).

The GAD65 prevalence (upper limit of normal 0.79 kU/ml [mean + 3 SD of that found in nondiabetic non-Japanese Brazilians]) was similar among each of the groups: 3 of 50 (6%) diabetic Japanese Brazilians, 3 of 51 (5.9%) nondiabetic Japa-

nese Brazilians, and 3 of 47 (6.4%) of the type 2 diabetic non-Japanese Brazilians.

β-Cell function was lower in patients with diabetes (median 85.7%, range 1.1–617.7, and median 134.3%, range 18.1–445.9, in diabetic Japanese Brazilians and type 2 diabetic non-Japanese Brazilians, respectively) than in control subjects (median 307.9%, range 41.8 −1,669.0, and median 320.5%, range 121.5–1,958.6, $P < 0.05$, in nondiabetic Japanese Brazilians and nondiabetic non-Japanese Brazilians, respectively).

Measurements of HOMA-IR were higher in type 2 diabetic non-Japanese Brazilians (median 8.4, range 2.8–28.8) than in nondiabetic non-Japanese Brazilians (median 5.1, range 1.9–51.9, $P < 0.05$), and were similar in diabetic Japanese Brazilians (median 7.6, range 0.2–25.9) and nondiabetic Japanese Brazilians (median 5.6, range 0.6–21.3).

In the diabetic Japanese-Brazilian population, the presentation of the disease sometimes prevents one from easily performing a clinical etiological characterization. Some of these patients have an abrupt onset of disease, whereas others have a slower onset that seems to represent insulin necessity but not insulin dependence.

The HOMA score explores the spontaneous homeostatic characteristics of a metabolic system by inferring the degree of β-cell function and insulin sensitivity that is compatible with a particular blood glucose level. Although this method has some limitations, comparing β-cell function and insulin resistance by HOMA is advantageous when individuals have similar basal fasting glucose levels (6).

Our patients, diabetic Japanese Brazilians and type 2 diabetic non-Japanese Brazilians, were age-matched (median 57 years, range 42–67, and 57 years, range 40–65, respectively), they were within the same range of metabolic control (fasting plasma glucose levels 8.8 ± 3.2 and 8.5 ± 3.0 mmol\l), and their times of clinical diagnosis of diabetes were similar (median 2.0 and 1.6 years, respectively).

The degree of HOMA-IR in type 2 diabetic non-Japanese Brazilians was higher than that in their matched control subjects, nondiabetic non-Japanese Brazilians. On the other hand, as a total group, it was found that the degree of HOMA-IR was similar in diabetic Japanese Brazilians and nondiabetic Japanese Brazilians. This similarity also persists when taking their BMI into account. However, intragroup analysis shows that the rise in BMI was associated with an increase in HOMA-IR only in the diabetic cohorts, type 2 diabetic non-Japanese Brazilians, and diabetic Japanese Brazilians. These data reinforce that, in both diabetic groups, obesity is only one factor among others, such as hyperglycemia, that is responsible for the difference in the insulin resistance level between diabetic and healthy nondiabetic individuals when they become obese.

When this study was performed, as expected in a clinical phase of diabetes, the diabetic Japanese-Brazilian and the type 2 diabetic non-Japanese–Brazilian groups had lower β-cell function in comparison with their matched control groups, nondiabetic non-Japanese Brazilians and nondiabetic Japanese Brazilians, respectively.

The 3 Japanese-Brazilian healthy control subjects who were GAD65 autoantibody–positive had no diabetic first-degree relatives and they were without autoimmune disease. Therefore, without conducting follow-ups, we are unable to explain this unexpected positivity to GAD65 autoantibodies in these subjects.

The mean positivity for GAD65 autoantibodies in type 2 diabetic non-Japanese Brazilians was 5.9%, which is similar to findings of many studies of the literature (7,8), and it varies from 2.8 to 9% in this type of diabetes.

Interestingly, we found an inverse association in the entire Japanese-Brazilian group between the tendency of reduction of the β-cell function and the titers of GAD65 autoantibodies. The group of GAD65 autoantibody–positive individuals had lower levels of β-cell function than the GAD65 autoantibody–negative individuals ($P < 0.05$).

When we performed a backward stepwise regression analysis of all of the individuals included in the 4 study groups, by considering the β-cell function as the dependent variable and through the combination of the variables, we could predict in the diabetic Japanese-Brazilian group GAD65-autoantibody titers ($r = -0.242$, $P = 0.0104$) and the time of diabetes diagnosis ($r = -0.287$, $P = 0.022$). In the type 2 diabetic non-Japanese–Brazilian group, though, only the time of diabetes diagnosis could be predicted ($r = -0.223$, $P = 0.015$).

In conclusion, these results show that, in comparison with non-Japanese Brazilian adults with type 2 diabetes, the Japanese-Brazilian individuals with diabetes showed the same prevalence of GAD65, similar insulin resistance, and similar β-cell function. In this sample of 40- to 67-year-old Japanese Brazilians, the individuals with diabetes showed a lesser degree of β-cell function once they had the same degree of insulin resistance as their matched control subjects. We can speculate that in the Japanese-Brazilian group, the GAD65 antibody levels, as well as the time of diagnosis of diabetes, is a factor that could be related to low β-cell function.

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COMMENTS AND RESPONSES

Assessment of Insulin Sensitivity and Insulin Secretion From the Oral Glucose Tolerance Test in Nonobese Japanese Type 2 Diabetic Patients

Comparison with minimal-model approach

The ability to dispose of carbohydrates depends on insulin sensitivity and pancreatic β-cell function. To estimate these 2 factors simultaneously is important in the pathogenesis of type 2 diabetes, because the estimate of β-cell function is influenced by the degree of insulin resistance (1,2). In this context, the minimal model approach shown by Bergman (1) enables us to estimate these 2 factors simultaneously. This technique, however, requires many blood samples (~30) to be collected and cannot be applied to large population studies. Thus, a simple method to estimate the 2 factors simultaneously is needed. Stumvoll et al. (3) recently disclosed that the oral glucose tolerance test (OGTT) can assess insulin sensitivity and insulin secretion in nondiabetic subjects when compared with the results derived from the euglycemic and hyperglycemic clamp studies. Moreover, they concluded that insulin sensitivity from euglycemic clamp procedure was best correlated with the metabolic clearance rate of insulin (MCR) and the insulin sensitivity index (ISI) predicted from the OGTT-derived equations. In addition, they confirmed that the ISI (composite) proposed by Matsuda and DeFronzo (4), the Ins 120, and the homeostasis model assessment insulin resistance (HOMA-IR) shown by Matthews et al. (5) were also correlated to euglycemic clamp–derived insulin sensitivity in nondiabetic subjects. On the other hand, β-cell function derived from the hyperglycemic clamp method was best correlated with values predicted by equations from the OGTT followed by area under the curve (AUC) Ins/AUC Gluc, ΔIns30/Glu30, HOMA β-cell function proposed by Matthews et al. (5), and ΔIns30/ΔGlu30. However, to our knowledge, the validity of the OGTT to evaluate insulin sensitivity and insulin secretion has not yet been investigated in diabetic subjects. To accomplish this, we calculated insulin sensitivity and insulin secretion from the results of the OGTT and then compared them with those obtained from the minimal-model approach in the Japanese diabetic populations.

There were 25 nonobese type 2 diabetic patients who participated in the study, after provision of informed consent. Their age and BMI were 45.4 ± 2.3 years (mean ± SEM) and 20.2 ± 0.6 kg/m^2 (range 13.5–25.3), respectively. Their HbA_{1c} levels were 7.2 ± 0.3% (range 5.1–11.3). Type 2 diabetes was diagnosed based on the criteria of the World Health Organization (6). The duration of the diagnosis of diabetes was 3.3 ± 0.8 years (range 0.1–17). Five type 2 diabetic patients were treated with sulfonylureas and the rest were treated with diet alone. None of the participants in this study consumed alcohol or performed heavy exercise for at least 1 week before the test. For at least 3 days before the test, their body weight was stable. All subjects had ingested at least 150 g carbohydrate for the 3 days preceding the study.

After an overnight fast, a butterfly needle was inserted into the antecubital vein and maintained by a slow drip of physiological saline. Subjects were allowed to rest quietly for at least 15 min before blood sampling began. Baseline samples for glucose and insulin assays were obtained at −3 min. Glucose (300 mg/kg body wt) was administered intravenously within 2 min and insulin (20 mU/kg body wt) was infused from 20 to 25 min after intravenous glucose injection (7). The samples were obtained from the contralateral antecubital vein at frequent intervals until 180 min as previously described (7). Plasma was frozen and stored at −20°C for subsequent analysis. The subjects' plasma glucose levels were measured in duplicate with an automatic analyzer (Kyoto-Daiichi-Kagaku, Kyoto, Japan) by the glucose oxidase method. Immunoreactive insulin was assayed in duplicate in using a Phadeseph insulin radioimmunoassay kit (Shionogi, Osaka, Japan). Insulin sensitivity was estimated by the minimal-model approach (1,7). Insulin secretion was expressed as the area under the insulin curve between 0 and 10 min after an intravenous glucose injection. The integrated area of plasma insulin above basal level was calculated using the trapezoidal method (8). The statistical analysis was performed with the StatView 5 system (StatView, Berkeley, CA). Pearson linear regression analysis and analysis of variance determined correlation. $P < 0.05$ was considered significant.

ISI obtained from the minimal-model approach was best correlated with the ISI (composite) ($r = 0.677$, $P < 0.001$), followed by root HOMA-IR ($r = -0.542$, $P < 0.001$), log HOMA-IR ($r = -0.502$, $P = 0.011$), Ins 120 ($r = -0.492$, $P = 0.013$), and HOMA-IR ($r = -0.459$, $P = 0.021$) in our type 2 diabetic patients. On the other hand, insulin secretion during intravenous glucose tolerance test was best correlated to ΔIRI 30/ΔGlu 30 ($r = 0.663$, $P < 0.001$), followed by ΔIRI 30/Glu 30 ($r = 0.660$, $P < 0.001$), HOMA β-cell function ($r = 0.646$, $P < 0.001$), and ΔIRI 30 ($r = 0.619$, $P < 0.001$) in our type 2 diabetic patients. From these results, it may be concluded that our nonobese Japanese type 2 diabetic patients can estimate insulin sensitivity and insulin secretion from the results during the OGTT. Moreover, it may be inferred that HOMA-IR and HOMA β-cell function are also a reliable ways to estimate insulin sensitivity and insulin secretion in nonobese Japanese type 2 diabetic patients who do not perform the OGTT.

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Assessment of Insulin Secretion From the Oral Glucose Tolerance Test in White Patients With Type 2 Diabetes

We have recently proposed a method to assess insulin sensitivity and insulin secretion using the oral glucose tolerance test (OGTT) in nondiabetic subjects (including those subjects with impaired glucose tolerance [IGT]) (1). The euglycemic-hyperinsulinemic and the hyperglycemic clamp technique validated the models, respectively. In the letter by Taniguchi et al. (2), the idea was extended to include Japanese subjects with type 2 diabetes. Their models were validated by the minimal model approach (3). They found that insulin sensitivity was best predicted by insulin sensitivity index composite (4) and insulin secretion by $(Ins_{30}–Ins_0)/(Gluc_{30}–Gluc_0)$. We applied the analogous methodology to determine if insulin secretion as measured by the hyperglycemic clamp can be estimated from the OGTT in white patients with type 2 diabetes.

After obtaining informed written consent from the subjects, we studied 28 white patients with type 2 diabetes (World Health Organization criteria [5]) using the OGTT and hyperglycemic clamp (10 mmol/l, 180 min) as previously described (1). Their age (mean ± SEM) was 54 ± 2 years, BMI 27.7 ± 0.9 kg/m^2, fasting glucose 7.0 ± 0.2 mmol/l, 2-h glucose 14.0 ± 0.5 mmol/l, and fasting insulin 88 ± 9 pmol/l. Plasma insulin was determined by radioimmunoassay (Pharmacia, Piscataway, NJ) or microparticle enzyme immunoassay (Abbott Laboratories, Tokyo), and plasma glucose was determined using a glucose analyzer (YSI, Yellow Springs, OH, or HemoCue, Aengelholm, Sweden). Individual phases of insulin secretion were determined as previously described (1). In brief, the first-phase insulin secretion was considered to be the sum of plasma insulin concentrations at 2.5, 5, 7.5, and 10 min of the hyperglycemic clamp experiment minus the mean basal plasma insulin concentration, and the second-phase insulin secretion was taken as the average plasma insulin concentration during the last hour of the hyperglycemic clamp minus the mean basal plasma insulin concentration.

Simple and stepwise multiple linear regression was performed with first- and second-phase insulin release as the dependent variables and demographic parameters and glucose and insulin concentrations during the OGTT. The homeostasis model assessment (HOMA) secretion index was calculated as $Ins_0 \cdot 3.33/(Gluc_0 - 3.5)$ (6). The statistical software package Sigmastat (SPSS, Chicago) was used.

With simple linear regression, clamp determinations of first and second phases of insulin release were best correlated with AUC_{Ins}/AUC_{Gluc} (r = 0.70 and 0.74, respectively; $P < 0.001$), followed by HOMA (both r = 0.69; $P < 0.001$) and $(Ins_{30}–Ins_0)/Gluc_{30}$ (r = 0.64 and 0.69, respectively; $P < 0.001$). Among single insulin concentrations, Ins_{120} was best correlated with first-phase (r = 0.62; $P < 0.001$) and second-phase insulin release (r = 0.67; $P < 0.001$). Using stepwise multiple linear regression, 2 parameters entered the equations: first phase predicted = $-59 + 24.1 \cdot AUC_{Ins}/AUC_{Gluc} - 0.98 \cdot Ins_{90}$ (multiple r = 0.81; $P < 0.001$); second phase predicted = $-0.41 + 8.1 \cdot AUC_{Ins}/AUC_{Gluc} - 0.27 \cdot Ins_{90}$ (multiple r = 0.78; $P < 0.001$).

We conclude from these results that in this white diabetic population, insulin secretion as determined by a hyperglycemic clamp can be estimated from the OGTT. The equations derived from multiple linear regression analysis yielded the highest correlation coefficient but are different from those obtained in subjects with normal glucose tolerance or with IGT. Together with our results from the nondiabetic population, the AUC_{Ins}/AUC_{Gluc} appears to be the single best parameter to assess β-cell function during an OGTT in Caucasians. Under circumstances in which an OGTT is impractical, HOMA also provides an accurate estimate of β-cell function.

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Advanced Glycation End Products and Coronary Heart Disease in Type 2 Diabetes

We read with interest the recently published article by Kilhovd et al. (1). The authors investigated to determine if serum levels of advanced glycation end products (AGEs) and the glycoxidation product N^{ε}-(carboxymethyl)-lysine (CML) are increased in subjects with type 2 diabetes when compared with nondiabetic control subjects, and whether levels of AGEs and CML differed in their cohort of 53 subjects with type 2 diabetes when coronary heart disease (CHD) was present or absent. Levels of AGEs and CML were significantly increased in patients with type 2 diabetes compared with control subjects. Moreover, AGEs were significantly higher in subjects with type 2 diabetes with associated CHD than in subjects with type 2 diabetes without CHD. The authors suggest that AGEs may be involved in the development of CHD in this population. Although this is plausible, we feel that the methods used to screen for the presence of CHD in this study are not sufficiently sensitive to discriminate between the presence or absence of CHD in this population.

This last conclusion is based on the capacity to evaluate accurately the presence of CHD in subjects with type 2 diabetes (2). At baseline, the investigators diagnosed CHD on the basis of the following: *1*) clinical examination and medical history of angina pectoris or myocardial infarction, *2*) resting electrocardiogram (ECG) measurements, and *3*) exercise ECG measurements. During follow-up (median 5 years), CHD was diagnosed solely according to resting ECG measurements and new symptoms suggestive of angina pectoris. No exercise ECG was performed. The total number of patients with CHD corresponded to the addition of subjects at baseline and at follow-up. Unfortunately, the authors did not provide the number of new cases of CHD.

It is well known that diabetes is associated with silent ischemia (2,3), and subjects with type 2 diabetes can often have a normal resting ECG and still have suffered a previous myocardial infarction. Furthermore, exercise testing and/or cardiac-imaging techniques should be used to detect silent ischemia without symptoms or exercise ECG ST segment changes (3–6). In the same issue of *Diabetes Care*, Janand-Delenne et al. (7) have effectively demonstrated that a significant number (21%) of patients with type 2 diabetes, with the absence of clinical or ECG symptoms suggestive of CHD, had significant (>50%) angiographic lesions. Moreover, 50% of the subjects with type 2 diabetes were considered ineligible for exercise testing, thus putting even more emphasis on the imaging technique to properly unmask the presence of CHD in this population (3,7).

In summary, the absence of exercise testing and/or cardiac imaging to detect CHD at follow-up make problematic the suggestion that AGEs were higher in the patients with diabetes with CHD. Therefore, the importance of AGEs in the pathophysiology of CHD in subjects with type 2 diabetes needs to be revisited.

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Advanced Glycation End Products and Coronary Heart Disease in Type 2 Diabetes

Response to Poirier and Eckel

We appreciate the comments by Poirier and Eckel (1) to our paper. Advanced glycation end products

(AGEs) have been linked to the development of atherosclerosis in the arterial wall. So far, none of the diagnostic tools available for in vivo use, perhaps with the exception of intracoronary ultrasound, can describe this process directly. Hence, all diagnostic tests are surrogate measurements and in clinical practice, we will often use combinations of tests. The diagnostic procedures for coronary heart disease (CHD) in the present study probably underestimate the number of patients with coronary atherosclerosis. However, this will apply to the whole population, and, in our view, should not invalidate our findings.

We agree that the data regarding the importance of AGEs in the development of CHD in patients with diabetes are scarce so far. Further and larger studies in this field are in progress.

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Is Testing Children for Type 2 Diabetes a Lost Battle?

The American Diabetes Association recently issued a consensus statement on type 2 diabetes in children (1). Although the consensus panel acknowledges that there are insufficient data to make evidence-based recommendations, it also recommends testing for type 2 diabetes in children ≥10 years of age who are overweight and have at least 2 other risk factors. Risk factors include the following: *1*) having a family history of type 2 diabetes in first- or second-degree relatives, *2*) belonging to certain race or ethnic groups, and *3*) having signs or conditions associated with insulin resistance, e.g., acanthosis nigricans, hypertension, dyslipidemia, or polycystic ovary syndrome. Fasting plasma glucose is the preferred test.

We assessed the implications of the panel's recommendation and used data from the third National Health and Nutrition Examination Survey (2) to estimate the number of U.S. adolescents who would qualify for testing as recommended. Fasting serum glucose was measured in 1,081 adolescents 12–19 years of age without known diabetes.

In the period 1988–1994, 10% (95% CI 8–13) of U.S. adolescents 12–19 years of age were overweight and had at least 2 of the other risk factors (3–5) (Table 1). Thus, ~2.5 million adolescents would potentially qualify for type 2 diabetes testing.

Among those who met the criteria for testing, 73% (67–79) were from minority populations, 48% (38–58) had a family history of type 2 diabetes, 26% (9–43) had hypertension, 73% (67–80) had dyslipidemia, and 5% (0–27) had impaired fasting glucose (IFG) or undiagnosed diabetes, all in addition to being overweight. Because of the small number of cases, we could not estimate the number of adolescents with diabetes, but we still can use the survey sample to illustrate these figures. There were 199 of 1,081 adolescents who met the criteria for testing. Within that group of 199, 1 adolescent had undiagnosed diabetes (fasting glucose >7 mmol/l) and 4 others had IFG (>6 mmol/l). None of the 882 adolescents who did not meet the criteria for testing were diagnosed with diabetes, but 16 had IFG.

The recommendations for testing children for type 2 diabetes lead to testing a very large number of children, while offering a rather small yield, due to the low prevalence of diabetes. To make matters potentially worse, we underestimated the number to test. Acanthosis nigricans, polycystic ovary syndrome, and family history in second-degree relatives for children <17 years of age were not assessed in the survey, children 10–11 years of age did not have glucose measured, and we did not consider high triglyceride and low HDL cholesterol levels. In addition, although it is likely that the prevalence of type 2 diabetes in children has increased since 1988–1994, the prevalence of most of these risk factors probably followed a similar trend.

It is well demonstrated that type 2 diabetes is a devastating disease with lifelong complications and control efforts are badly needed, especially for children (6). Rather than challenging the need for testing children whose clinical features strongly suggest type 2 diabetes, the figures we present here highlight at least the need for refining the criteria for case finding in general. Efforts at early detection may, however, not be cost-effective, and may divert resources away from more important and cost-effective interventions.

Table 1—*Prevalence of risk factors, and number of U.S. adolescents 12–19 years of age with these risk factors, to consider for testing for type 2 diabetes*

Conditions	Prevalence (%)	95% CI	*n* (millions)
Obesity (BMI ≥ age- and sex-specific 85th percentile)	28	22–34	6.6
Individuals other than non-Hispanic whites	36	30–42	8.6
Family history*	20	15–24	4.7
Hypertension†	7	5–10	1.8
Dyslipidemia‡	36	32–40	8.6
To test for type 2 diabetes	10	8–13	2.5

*Restricted to mother or father for 12- to 16-year-olds, and first- or second-degree relatives for others. †Blood pressures (mean of 3 measurements) ≥90th percentile for height, age, and sex, for 12- to 17-year-olds (4), or =130/85 mmHg for others, or a positive history of hypertension. ‡Cholesterol ≥170 mg/dl, LDL ≥110 mg/dl (5), or a positive history of high cholesterol.

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Is Testing Children for Type 2 Diabetes a Lost Battle?

Response to Fagot-Campagna et al.

Fagot-Campagna et al. (1) opine that the recently published American Diabetes Association (ADA) consensus panel recommendations on testing children at risk for type 2 diabetes will lead to massive overtesting, and they indicate that criteria for better case-finding need to be refined. The consensus report did, in fact, note that school or community-based studies should be carried out to demonstrate the value of individual tests and to establish the strength and risk level of various factors that might be influential in the development of type 2 diabetes. It was also emphasized that the studies should be carried out in populations with sufficient numbers of children who are at high risk. This would also provide an indication of the frequency of undiagnosed type 2 diabetes in children, which is presently unknown outside certain Native American groups.

The data provided by Fagot-Campagna et al. (1) neither detract from the recommendations of the consensus panel nor suggest alternatives. The data are difficult to accept as representative or sufficient to derive the estimates that are provided.

Even though the consensus panel recommendations on case-finding recognize the need for a population-based study of their application, their immediate value and importance is to emphasize to the clinician the importance of testing children who have the noted risk factors. In fact, Fagot-Campagna et al. (1) state that they do not challenge the need for testing children whose clinical features strongly suggest type 2 diabetes. This is consistent with the recommendations regarding the identification of cardiovascular risk factors in obese children, as suggested by their colleagues at the Division of Nutrition and Physical Activity at the Centers for Disease Control and Prevention (2). The most important reason for placing these recommendations before the public is to communicate an awareness of the risk factors and the need to test those at risk.

The ADA consensus panel chose to not make its recommendations restrictive by suggesting that clinical judgment should be used to test patients who may not meet these criteria. The criteria were: overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height) plus two other risk factors—family history of type 2 diabetes in first- or second-degree relative; American Indian, African-American, Hispanic, or Asian/Pacific Islander ethnicity; or signs of insulin resistance or conditions associate with insulin resistance such as acanthosis nigricans, hypertension, dyslipidemia, or PCOS. It was recommended that testing begin at 10 years or at the onset of puberty if earlier, with a frequency of every 2 years, and the preferred test was the fasting plasma glucose measurement. This is hardly a prescription for rampant overtesting.

The importance of the clinical judgment disclaimer is emphasized by the last 10 patients diagnosed with type 2 diabetes in our clinic. None had symptoms of diabetes. Five were under 10 years of age, 6 were white, and 4 had only one other risk factor besides obesity (a family history of type 2 diabetes) that resulted in their being tested. The rest were diagnosed because of the incidental finding of glucosuria in 2 patients, which was found while being studied for vaginitis or dysuria (J.H. Silverstein, personal communication). Such early detection by alerting primary practitioners holds the promise of forestalling complications, which appear to be particularly accelerated in this patient group, and preventing hospitalization or death from hyperosmolar nonketotic coma.

Testing children for type 2 diabetes is most assuredly not a losing battle. Recognizing that children and adolescents with type 2 diabetes are frequently asymptomatic, case-finding in the at-risk population should be considered good practice.

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Delineating the Relationship Between Stress, Depressive Symptoms, and Glucose Intolerance

In recent issues of *Diabetes Care*, several studies have reported a relationship between stressful life events and glycemic control (1) and between depressive symptoms and glycemic control among clinical (2) and population-based studies (3–5) of diabetes. In their study, Gary et al. (4) reported that behavioral factors (e.g., diet, exercise, and self-monitoring behavior) did not explain the relationship between the Center for Epidemiologic Studies-Depression scale (CES-D)-assessed depressive symptoms and metabolic control. They offered a possible explanation for the observed relationship: that it might be

manifested via a causal pathway that is independent of behavioral factors (4). Other investigators have also suggested that behavioral factors cannot fully explain the relationship between stress, depression, and metabolic control (6–9).

Most recently, Mooy et al. (10) reported a significant association between stressful life events and prevalence of undetected type 2 diabetes in a population-based study. We take particular interest in this study because of our own observations among a population-based sample of Native Hawaiians (11). We reported that CES-D–assessed depressive symptoms were associated with glycemic control, even after patients with a prior diagnosis of diabetes were excluded from analysis (11). The exclusion of patients with prior diagnoses of diabetes in both of these studies suggests that neither behavioral factors, such as treatment compliance, nor psychological reaction to a chronic condition can fully explain these associations. Furthermore, longitudinal studies have demonstrated that depressive symptoms and depression may increase the risk of developing type 2 diabetes (6–8).

Our observations and those of Mooy et al. agree with the theory by Bjorntorp et al. (9) that stressful life events or chronic psychological stress are associated with glucose intolerance. Several biological mechanisms have been posited to explain the association. For example, depressive disorders are associated with disruption of the sympathoadrenal system and disregulation of the hypothalamopituitary adrenal axis, each of which may impair carbohydrate uptake, thereby leading to increased blood glucose and glucose intolerance. Alternatively, glucose intolerance and/or insulin resistance may cause changes in the neuroendocrine system that subsequently affect perceived stress or mood-state. Elevated glucose levels may cause a heightened state of arousal, which may be reported as stress or depressive symptoms (e.g., fatigue or lack of concentration). Finally, depressive symptoms and glucose intolerance may share a common pathogenesis. Bjorntorp et al. reported that a common polymorphism of the glucocorticoid receptor gene was associated with abdominal obesity, insulin resistance, and hypertension. A study examining whether or not individuals with these abnormalities are sensitive to environmental stressors is currently underway (12).

In conclusion, the causal relationship of stress and depressive symptoms with glucose intolerance has not been adequately delineated. Although several recent longitudinal studies have assessed baseline depressive symptoms as predictors of diabetes, none of these studies examined the converse relationship. In other words, no longitudinal study has examined the effect of baseline glucose and insulin on either changes in mood or response to stress. Additional population-based studies, in which glucose tolerance and insulin resistance is assessed for a cohort of individuals, are necessary to better elucidate the causal relationships of the biological factors discussed here.

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Association Between Socioeconomic Factors and the Metabolic Syndrome in Women With Prior Gestational Diabetes Mellitus

In the December issue of *Diabetes Care*, Wamala et al. (1) reported that lower levels of education are associated with an increased risk for metabolic syndrome in middle-aged women. This result confirms recent reports suggesting the link between socioeconomic factors and cardiovascular disease and diabetes or its late complications (2–4). Because prior gestational diabetes mellitus (GDM) seems to be associated with the components of the metabolic syndrome, or even is a predictor of it (5,6), it may be of importance to gain some information about a similar relationship between socioeconomic factors and metabolic syndrome in women with prior GDM.

To study the previously mentioned connection, we analyzed follow-up data of 108 women with GDM 8 years after delivery (mean [± SD] age, 37.4 ± 6.0 years; 71% of the patients were treated with insulin during pregnancy), randomly selected from a cohort of women cared for by our interdisciplinary team between

1985 and 1990. During this period, women with GDM who were considered to be in need of special care were referred to our center. For the evaluation of metabolic syndrome, the same components and methods (dyslipidemia, central obesity, hypertension, glucose intolerance) were used as in the study of Wamala et al. (1), although the exact definitions differed. Hypertension, however, was defined as blood pressure ≥160/90 mmHg or if the subjects were on blood pressure–lowering medication and glucose intolerance as antidiabetic therapy or abnormal result of a 75-g OGTT according to the World Health Organization criteria (7). Socioeconomic status (SES) was measured by education level (primary school, high school, or college/university), current employment, and marital status, or according to permanent residence (urban or rural).

At least 2 components of the metabolic syndrome were detected in 49 (45%) women at follow-up (dyslipidemia 80%, obesity 69%, glucose intolerance 88%, and hypertension 57%). Patients with lower education ($P < 0.01$) or who were unemployed ($P < 0.01$) had a higher risk for metabolic syndrome (univariate comparisons); however, marital status and residence showed no significant connection to it. The age-adjusted odds ratio for metabolic syndrome was 7.05 (95% CI, 1.68–29.46) between the lowest and highest educational levels, whereas it was 4.27 (1.39–13.14) when comparing unemployment with employment. In a multivariate analysis (logistic regression including age, education, employment, and residence), only lower education level ($P < 0.05$) and unemployment ($P < 0.05$) entered the model as independent covariates.

In a homogenous cohort of relatively young women with prior GDM, an almost 4-times-higher frequency of metabolic syndrome was found in comparison to the results of Wamala et al. (1). Because the selection criteria for this study were related to the patients' metabolic state, there is no reason to suppose that selection bias occurred during analysis. Our results not only confirm the results of Wamala et al. found in healthy women, but also suggest that a similar relationship exists in women with prior GDM (i.e., low education and unemployment might increase the existing risk of women with GDM for metabolic syndrome) (1,5,6). Screening for GDM, follow-up, and care for women later in life is therefore of utmost importance, especially in those with lower SES to prevent clustering of cardiovascular risk factors.

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Preventing Amputations Among Patients With Diabetes on Dialysis

We read with interest Drs. McGrath and Curran's (1) observations from New Zealand about the high amputation rates in Maori people with diabetes after they began dialysis. We had similar findings in our work to reduce diabetic foot complications in Native American communities in northern Minnesota. As we instituted measures to identify and protect diabetic community members with high-risk feet, we saw amputation rates decrease from 29 to 21 per 1,000 diabetic person-years in the periods from 1986–1989 to 1990–1993. We then introduced treatment guidelines to stage, treat, and refer foot ulcers according to well-defined clinical pathways called Staged Diabetes Management, and amputation rates decreased to 15/1,000, as published previously (2). When we reviewed our registry of amputations, we realized that the residual amputations largely occurred among those on dialysis.

We postulated that dialysis patients often lost contact with care outside the dialysis setting. Preventive foot care, early detection of foot problems, and follow-up care for foot ulcers after hospitalization off-reservation were not always a part of routine dialysis care. Accordingly, we instituted an outreach wound care clinic to follow those who had been referred off-reservation for management of severe foot ulcers, and we extended these services to diabetic patients who were receiving dialysis in the local reservation facility. In the 3 years (1997–1999) after instituting this outreach program, amputation rates decreased to 7/1,000 ($P < 0.001$ vs. baseline).

These observations also led us to ask if our experience was unique. Medicare hospitalizations in which a lower-extremity amputation was performed were used to assess non-traumatic lower-extremity amputation in all Medicare end stage renal disease patients (3). The overall amputation rate for dialysis patients in the U.S. was 4.9/100 in 1994 and, for those ESRD beneficiaries with diabetes, the annualized

amputation rate was 13.8/100. Native Americans with diabetes had the highest rates. Among nondiabetic dialysis patients, African-Americans experienced the highest amputation rates. Thus, it appears that all dialysis patients, particularly those with diabetes, are at very high risk for lower-extremity amputation.

In summary, we found that McGrath and Curran's (1) observations are consistent with ours. Dialysis patients with diabetes and those on dialysis for other reasons have both neuropathy and vascular disease that predispose them to foot ulcers, poor wound healing, and the cascade of events that lead to amputation. Foot care is often not a priority in settings that are busy providing dialysis. When we recognized the problem and extended foot care specifically to the dialysis setting, we observed a decrease in amputation rates in diabetic community members. Diabetic individuals worldwide receiving renal replacement therapy are at high risk for amputation and the rates can be reduced with interventions designed to reach them.

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D.G. is a paid consultant to the Indian Health Service and has accepted honoraria from Bayer Pharmaceuticals.

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Response to Rith-Najarian and Gohdes

Thank you to Drs. Rith-Najarian and Gohdes (1) for their interest in our letter (2) and for providing data of high amputation rates in diabetic Native Americans on dialysis similar to those we found in New Zealand Maori.

We have also instituted an intensive podiatric and orthotic service for our diabetic dialysis patients in the year since our study was completed. The lower-extremity amputation (LEA) rate in this group of patients has fallen from 14 patients for the previous 2 years to 2 per year.

Only 1 of the 2 dialysis patients who required an LEA had seen our podiatrist before their amputation.

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