OBSERVATIONS

Itraconazole-Induced Painful Neuropathy in a Man With Type 1 Diabetes

The antifungal agent itraconazole is considered safe in patients with diabetes (1,2) but has been associated with acute painful neuropathy in patients taking vincristine (3–5). We describe a patient with diabetic neuropathy who developed acute painful neuropathy with itraconazole therapy.

A 37-year-old man with poorly controlled type 1 diabetes of 19 years' duration presented with an excematous rash affecting his lower abdomen. Skin scrapings grew *C. albicans*. Itraconazole (200 mg/day) was prescribed, but on the 4th day of treatment he developed acute bilateral leg weakness with stabbing pain in the hips and legs and difficulty walking. He was taking no other medication apart from insulin. He was known beforehand to have peripheral neuropathy with absent ankle reflexes and mild postural hypotension.

On examination, his BMI was 24 kg/m^2, his calf muscles were tender, and he had moderate proximal leg weakness. His muscle tone was normal and knee reflexes preserved. There was no change in postural hypotension or sensory abnormalities. Itraconazole was stopped after 7 days. Over the next 6 months his pain improved, although he lost 6 kg in weight. The power in his legs recovered, but the knee reflexes were lost. Over the next year his pain improved and he became asymptomatic.

At the onset of his symptoms, blood count, erythrocyte sedimentation rate, renal function, and serum creatine kinase were normal. On repeated follow-up, these blood tests and his HbA$_{1c}$ remained unchanged. The vibration perception threshold at the medial malleolus rapidly declined over the next year. Nerve conduction studies of the upper and proximal lower limbs were normal, but conduction velocities were slow in the distal lower limbs. Over the next year, the distal lower limb compound muscle action potential amplitudes reduced, suggesting loss of these nerve fibers. Electromyography (EMG) was normal at presentation, but after 6 months showed signs of lower-limb muscle denervation. There were no features to support lumbar plexopathy. As the abnormalities were most marked in the distal muscles, this suggests axonal degeneration, which tends to affect the longest nerve fibers first.

There are a number of diagnostic possibilities. Acute painful neuropathy generally occurs within days of rapid improvements in glycemic control, which was not the case in our subject. Diabetic amyotrophy often presents with severe anterior thigh muscle pain and weight loss; however, EMG typically shows evidence of lumbosacral plexopathy (6). Acute diabetic radiculopathy can cause acute pain and weakness, but the symptoms are usually in a single nerve root distribution. Diabetic cachexia can be associated with profound weight loss, symmetrical peripheral neuropathy, and autonomic dysfunction but is generally associated with painful dysesthesias without weakness (7).

In this man with preexisting diabetic neuropathy, the sudden onset of neurological symptoms with itraconazole therapy, axonal degeneration on electrophysiological testing, and stabilization after stopping itraconazole suggest that a drug-induced polyneuropathy is the most likely diagnosis. Drug-induced neuropathy is associated with axonal degeneration, lasting weeks or months (8). Discontinuing the administration of the drug does not always lead to improvement, as the damage to neuronal structures or function can be permanent.

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Evaluation of the Portable HealthWear Armband

A device to measure total daily energy expenditure in free-living type 2 diabetic individuals

Lifestyle modifications involving diet and exercise are effective in reducing the incidence of type 2 diabetes (1–3). In particular, lifestyle changes targeted toward increasing daily energy expenditure are a cornerstone treatment of type 2 diabetes (2). In the Diabetes Prevention Research Group study (4), a goal of 150 min/week of physical activity was recommended, and 74% of the patients in this study group achieved this level by 24 weeks. This type of success in exercise modification is made possible in research protocols by intensive individual counseling (5), which may not be easily reproduced in primary care settings. Because of the critical importance of increasing daily energy expenditure and its central role in preventing and/or treating diabetes, one can surmise that instrumentation providing accurate and simple feedback to type 2 patients may have clinical utility.
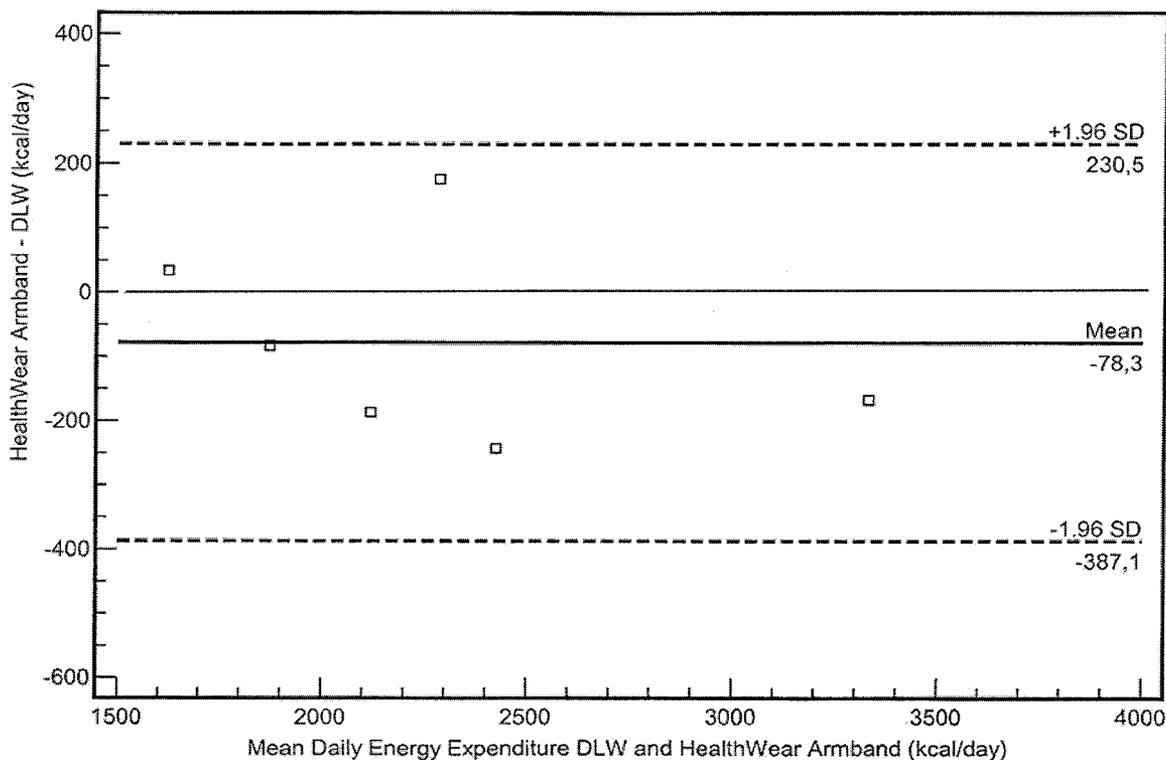
Therefore, we provide preliminary

data on the accuracy of the HealthWear Armband (Roche Diagnostics, Indianapolis, IN), an instrument designed to assess total daily energy expenditure in free-living adults, including those with diabetes, versus the doubly labeled water (DLW) technique. The development of the DLW methodology provides a gold standard from which the accuracy of other devices to measure daily energy expenditure can be determined (6). The DLW method requires little subject cooperation, is unobtrusive, and accurately determines daily energy expenditure throughout a person's daily routine. Unfortunately, the relatively high price of the oxygen-18 water, the need for mass spectrometer instrumentation, and the high level of technical expertise required has limited its widespread application in clinical research. The HealthWear Armband evaluates daily energy expenditure based on a proprietary algorithm. That is, it uses a collection of sensors to gather information such as movement, heat flow, skin temperature, near-body temperature, and galvanic skin response in conjunction with body measurements such as sex, age, height, and weight to calculate energy expenditure. The heat flow sensor uses sensitive thermocouple arrays and measures

the heat dissipated by the body. It is placed between the skin and the side of the Armband exposed to the environment. If such a practical tool was available and validated, it would help the patient monitor or increase their daily energy expenditure levels to lose weight with the ultimate goal of reducing the complications of diabetes.

As part of a larger study, we assessed total daily energy expenditure in six diabetic patients treated with diet only and/or oral hypoglycemic agents. We tested two men and four women, aged 56.5 ± 5.96 years with a BMI of 29.76 ± 4.12 kg/m^2, a fat-free mass of 50.08 ± 12.17 kg, and a fat mass of 31.98 ± 6.99 kg (determined by dual-energy X-ray absorptiometry). All subjects wore the HealthWear Armband simultaneously with the determination of DLW during a 10-day period to measure total daily energy expenditure. The armband was worn around the right arm and was removed only for showering and bathing purposes. "On body time" for the armband was 99% during the 10-day period for all subjects.

In the six diabetic patients, we noted no significant differences (Δ 78.3 ± 158 kcal/day [mean ± SD], 95% CI −87 to 245 kcal/day) in mean daily energy ex-

penditure between the armband (2.237 ± 568 kcal/day) and DLW (2,315 ± 625 kcal/day). Also, the correlation between the armband and DLW reached $r = 0.9696$ ($P = 0.0014$). In addition, the intraclass correlation coefficient (ICC) between the armband and DLW reached ICC = 0.9625, with a technical error of measurement of 104 kcal/day. Fourth, individual comparisons between DLW and the HealthWear Armband were examined using a Bland-Altman plot (Fig. 1). The Bland-Altman plot shows the difference in daily energy expenditure between DLW and the HealthWear Armband versus mean daily energy expenditure determined between DLW and the HealthWear Armband. From these data, limits of agreement between DLW and the HealthWear Armband were calculated (i.e., mean difference between DLW and the HealthWear Armband ±1.96 SD of the difference). We hypothesized a narrow limit of agreement (i.e., ± 100–300 kcal/day) between HealthWear Armband and DLW. The measured range of under- and overestimation of the armband versus DLW was −243 to 176 kcal/day, respectively, suggesting an acceptable level of concordance between the two methods.

Figure 1—*Limits of agreement between DLW and the HealthWear Armband.*

Although these results will need to be confirmed in a larger sample size, preliminary analyses suggest that the Health-Wear Armband is an acceptable device to accurately measure total daily energy expenditure in type 2 diabetic patients over a 10-day period. This information would be useful in counseling patients regarding appropriate levels of daily energy expenditure needed to prevent or offset diabetes and its related complications.

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Hypoglycemia Following a Nateglinide Overdose in a Suicide Attempt

Various drugs are currently used for the treatment of diabetes. Several reports on overdose of these drugs, especially on sulfonylurea and metformin, have been published (1,2); however, few such publications are available on nateglinide, a rapid insulin secreatagogue. We report the first case of attempted suicide by nateglinide overdose. A 30-year-old Japanese nondiabetic woman was transferred to the emergency department of our hospital 1 h after (6:30 A.M.) ingesting 3,420 mg (38 tablets, 90 mg each) of nateglinide, which was prescribed to her diabetic partner. She had a mild psychiatric history and used minor tranquilizers occasionally. Upon arrival to the hospital, she was able to walk unaided though she seemed drowsy. Blood pressure was 120/80 mmHg, pulse rate was 78 beats/min, and peripheral oxygen saturation was 96% on room air breathing. Blood glucose concentration measured at arrival (1 h after ingesting nateglinide: 7:30 A.M.) was 2.0 mmol/l. A bolus dose of 40 ml of 50% glucose was injected intravenously (iv). At 8:30 A.M., blood glucose was increased to 3.1 mmol/l. Another 40 ml of 50% glucose was iv injected again, which resulted in normalization of blood glucose concentration. However, at 10:30 A.M., blood glucose was 1.2 mmol/l. Another 40 ml of 50% glucose was iv injected, and blood glucose concentration returned to 4.2 mmol/l and immunoreactive insulin was 11 μU/ml. At 11:30 A.M., blood glucose concentration was 2.2 mmol/l. At that stage, a bolus of 20 ml of 50% glucose was iv injected, and a 10% glucose drip infusion was started (40 ml/ h). At 12:30 P.M., the blood glucose concentration was 3.0 mmol/l, and at 1:30 P.M., the blood glucose returned to normal range under 10% glucose infusion (40 ml/ h), and no more hypoglycemic episodes were observed. The next day, the blood glucose was 5.5 mmol/l and immunoreactive insulin was 5.0 μU/ml without glucose infusion, and she was discharged without complications. Thus, the prolonged hypoglycemic effect of nateglinide continued for 6 h, and intravenous glucose supplementation (totally 100 g) was sufficient to maintain euglycemia.

Nateglinide is a novel, highly physiologic mealtime glucose regulator recently approved for the treatment of type 2 diabetes. Compared with sulfonylurea, nateglinide causes rapid but short stimulation of insulin secretion. Factitious sulfonylurea overdosages usually result in prolonged hypoglycemia (usually >48 h in a case report [3]), and intravenous glucose supplementation or octreotide injection is necessary to maintain euglycemia. To our knowledge, overdosage of nateglinide has not been previously reported. Repaglinide-induced factitious hypoglycemia has been reported, but the dose taken was equivalent to that used clinically (4). In normal rats fasted for 17 h, oral administration of nateglinide produced a prompt (within 1 h) and dose-dependent reduction in blood glucose, but significant reduction was no longer noticeable after 3 h, even at the dose of 100 mg/kg (5). In comparison, glibenclamide showed a slower onset of its hypoglycemic action and caused a sustained decrease in blood glucose levels for at least 6 h at a dose of 1 mg/kg (5).

In conclusion, an overdose of oral nateglinide elicited prompt but mild, relatively short lived, and reversible hypoglycemia. These features of hypoglycemia resembled the hypoglycemic effects of nateglinide in regular therapeutic dosages.

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Increased Prevalence of Diabetes and Obesity in Patients With Salivary Gland Tumors

It has been recently revealed that type 2 diabetes is a risk factor for tumorous proliferation at different sites (1). Breast and colon cancers were the first tumors for which an epidemiological correlation was demonstrated between this glucose metabolism disorder and tumor incidence (2). The "western lifestyle," first of all obesity, increases the risk of not only type 2 diabetes but also of overall cancer promotion (3).

Swelling of the parotids and a decreased salivary flow rate caused by degenerative alterations in the acinar cells are common concomitants of diabetes and dyslipidemias (4,5). However, no data are available concerning the epidemiological correlation between metabolic disorders and salivary gland tumors.

In the present work, a retrospective controlled study was performed to clarify the possibility of an association between type 2 diabetes, obesity, and salivary gland tumors. Clinical data on 438 inpatients were analyzed on the basis of their case histories. In 224 patients, salivary gland tumors had been surgically removed and histologically diagnosed (SGT group). The mean age of these patients was 51.2 years (range 23–87). A total of 118 were men and 106 were women. Their tumors were predominantly benign (166 cases, 74.2%), and a majority of them were located in the parotid. The rate of malignancies was 25.8% (58 cases), and the most frequent locations were the accessory glands of the palate. Two hundred and fourteen randomly selected patients undergoing dental surgery served as the control group. They had no tumorous lesions in the oral or maxillofacial region. Their mean age was 50.8 years (range 24–80). A total of 104 were men and 110 were women. Fasting blood glucose levels were routinely measured repeatedly within 4 days before the surgical intervention. The level was regarded as pathological only if it was repeatedly higher than normal (>6.9 mmol/l). Patients with known and treated disease or with a newly diagnosed high fasting glucose levels were included in the type 2 diabetic group. BMI was also registered in the case histories. Patients with BMI >30 kg/m^2 were regarded as obese. The χ^2 test was used for the statistical analysis. A probability level of 5% was taken as a limit of statistical significance.

Type 2 diabetes was established in 51 patients (22.8%) of the SGT group and in 14 subjects (6.5%) in the tumor-free control group ($P < 0.001$). Among the diabetic and nondiabetic patients of the SGT group, the rates of histologically malignant tumors were 26.6 and 23.5%, respectively ($P > 0.05$). Obesity was registered in 102 patients (45.5%) in the SGT group and in 38 subjects (17.7%) in the control group ($P < 0.001$). The rates of malignant tumors among the obese and nonobese SGT patients were 27.8 and 23.5%, respectively ($P > 0.05$).

These findings permit a novel hypothesis concerning the epidemiological association between type 2 diabetes, obesity, and salivary gland tumors. However, there were no close correlations between these metabolic disorders and the malignancy rate of the tumors.

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COMMENTS AND RESPONSES

Telecare for Patients with Type 1 Diabetes and Inadequate Glycemic Control

Response to Montori et al.

The insightful study of Montori et al. (1) raises the question of whether telecare can close the gap between the necessary and frequent interventions by health care professionals in order to lower the HbA$_{1c}$ of patients. We would like to comment on the control group and meta-analysis in their study.

Telecare can be embedded into different achievable scenarios, where the leftmost cornerstone considers a control group and where conventional care means no intervention (A). The rightmost cornerstone is to replace face-to-face interventions by telecare with the same

frequency and quality as in the control group (B). In reality, the typical group defining "conventional care" would be situated between these two cornerstones. Due to regional differences, the private situation, and, particularly, the distance to the next specialist, the patients would not be able to achieve the necessary frequency of face-to-face visits that they would if the doctor's office were next door (C).

In a comparative study, medical outcome (HbA_{1c}) and costs would be different depending on whether strategy A or B or something in between was adopted. A cost-effectiveness study is particularly mandatory in strategy B, where the primary outcome parameter would be cost and the secondary parameter HbA_{1c}.

In a randomized cost-effectiveness study (2), we adopted strategy B in order to isolate the effect of telecare and not any effect attributable to the frequency of interventions. A similar study by Chase et.al (3) is also situated closely to strategy B. Both studies came to the conclusion that telecare can save costs while maintaining the quality of care (HbA_{1c}).

In another recent study (4), we tried to adopt an approach that better simulates a patient's "real-life" (C) by having the patients in the control group being educated first in hospital and then returning to their private practitioners. We believe that due to the different goals of the studies and the different control groups, a meta-analysis would ultimately draw equivocal or false conclusions.

In conclusion, we would suggest adding the method of whether a cost-effectiveness analysis or an outcome analysis has been performed to a further meta-analysis in telecare. However, the use of excellent tools such as intention-to-treat analysis and the high degree of transparency makes the report of Montori et al. groundbreaking and a critical starting point for further studies in this field.

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Telecare for Patients With Type 1 Diabetes and Inadequate Glycemic Control

Response to Biermann et al.

We thank Biermann et al. (1) for their kind remarks about the clarity and importance of our research and for proposing a novel taxonomy of telecare interventions by purpose: as a supplement to usual care (A in their taxonomy) or as a replacement of face-to-face visits (sometimes called nonvisit encounters; B or C in their taxonomy).

Two of the trials included in our meta-analysis used, to some extent, telecare as replacement. In their 6-month trial, Chase et al. (2) added telecare encounters to usual care and replaced the face-to-face visit at 3 months with a telecare nonvisit encounter. Biermann et al. (3) replaced all ad hoc visits with telecare encounters but kept face-to-face visits at 2, 4, 6, and 8 months for patients allocated to both telecare and control. These two replacement trials found no significant difference between telecare and control; however, this is not enough to claim that telecare visits are similar or superior (i.e., not inferior) to face-to-face visits.

To determine noninferiority, one needs to evaluate the magnitude of the smallest reduction in HbA_{1c} that is still consistent with the trial data, i.e., the lower limit of the confidence interval (4). Data from the two trials of telecare as replacement were consistent with differences in HbA_{1c} as large as 0.7% in favor of usual care. Thus, evidence of noninferiority from each of these trials alone is inconclusive.

Following the suggestions of Biermann et al. (1), we evaluated a subgroup effect across trials in our meta-analysis by telecare purpose (replacement versus supplement). There was no difference (test for interaction, $P = 0.44$) in pooled treatment effects between trials of telecare as replacement (pooled random-effects estimate 0.5% [95% CI 0.0–1.0%]) and as supplement (0.2% [−0.4–0.8%]). Therefore, the results of our meta-analysis (0.4% [0.0–0.8%]) apply to both types of trials, are not misleading, and suggest that telecare may be noninferior to usual care when it supplements usual care or when it replaces some visits.

We agree that a systematic assessment of costs with attention to the opportunity costs of implementing telecare and to the resulting freed-up resources available to patients who are most likely to benefit from face-to-face visits rather than telecare is critical when considering new technologies. Unfortunately, to our knowledge, a formal cost-effectiveness analysis of telecare as a supplement or replacement to usual care is not available.

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Effect of High-Dose Vitamin E on Insulin Resistance and Associated Parameters in Overweight Subjects

Response to Manning et al.

In the report of Manning et al. (1), patient's plasma peroxides were decreased by 29% at 6 months with a transient reduction in insulin resistance. Consequently, they postulate that vitamin E improves oxidative stress and hepatocellular function in overweight patients and suggest that "vitamin E could have a role to play in delaying the onset of diabetes in at-risk individuals (1)."

The rationale for vitamin E supplements protecting against diabetes is based on the assumption that it becomes depleted by reactive oxygen species and the expectation that vitamin E prevents the oxidative stress events linked to such oxidation. However, administered antioxidants could fail to intercept radical generation from discrete sources (cytoplasm, nucleus, and interstitial space). For example, myeloperoxidase is a major source of reactive oxygen species generation in inflammatory syndromes. However, myeloperoxidase-catalyzed lipid peroxidation is resistant to inhibition by vitamin E (2). Moreover, α-tocopherol may act as a prooxidant drug during lipid oxidation in vivo (2,3).

But theoretical considerations vanish against ethical concerns. Overweight patients have endothelial dysfunction and are "at-risk individuals" not only for diabetes but also for atherosclerosis. In clinical trials with antioxidants, it has been suggested that high-dose vitamin E has an acute toxic effect, and coronary heart disease can be expected (4) with its administration. Other studies (5) have also reported a nonsignificant excess in coronary deaths among those with a history of myocardial infarction who were receiving vitamin E.

In the Manning et al. article, were patients informed in detail before randomization to receive vitamin E that as a consequence of their overweight they could have increased mortality risks from coronary heart disease? Does the transient improvement in insulin resistance justify the authors' suggestion that "vitamin E could have a role to play in delaying the onset of diabetes in at-risk individuals (1)" without alerting them about possible dangers associated with this approach? Scientific advances are difficult to obtain, but ethical constraints should not be forgotten.

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Effect of High-Dose Vitamin E on Insulin Resistance and Associated Parameters in Overweight Subjects

Response to Vale

We take issue with the points Vale (1) has raised. While it is established that vitamin E does not influence myeloperoxidase-catalyzed lipid peroxidation in vitro, this does not exclude possible benefits from vitamin E supplementation in vivo in subjects with increased myeloperoxidase activity and high risk of coronary heart disease. For example, supplementation with vitamin E reduced the risk of myocardial infarction, including sudden death in hemodialysis patients (2). Whether the antioxidant activity of vitamin E is responsible for this improved risk of coronary heart disease is unknown, and other effects of vitamin E may be implicated. As pointed out in our report, vitamin E has a number of effects that are independent of its antioxidant activity, and the mechanism underlying this improvement in insulin sensitivity remains to be determined.

While there is evidence that vitamin E acts as a prooxidant under specific conditions in vitro, there is little direct evidence that it has similar activity in vivo. It is thought that substantial levels of coantioxidants, such as ascorbate, regenerate the tocopherol radical and prevent tocopherol-mediated peroxidation in vivo (3).

Vale claims that high-dose vitamin E may have an acute toxic effect and may increase the risk of coronary death. This is based on the higher number of early deaths in the vitamin E (19/1,035) group compared with the placebo (7/967) group in the Cambridge Heart Antioxidant Study (CHAOS) (4). This study has been criticized because of imbalances in several baseline characteristics, raising the possibility that randomization failed to produce truly comparable groups. In addition, given that the number of cardiovascular end points was small and that the study was of short duration, it has been suggested that the main finding of a 77% decrease in nonfatal acute myocardial in-

farction in the CHAOS was likely due to chance (5). Moreover, the number of early cardiovascular deaths was substantially lower than the total number of nonfatal acute myocardial infarctions, making the finding of an increased risk of early cardiovascular death even more likely to be due to chance. In addition, most of the deaths in the CHAOS were in those taking the lower dose of vitamin E (400 IU/day) (6). This dose is the same as the dose used in the much larger HOPE (Heart Outcomes Prevention Evaluation) study (5), in which there was no early excess of cardiovascular deaths.

It should also be noted that a number of previous studies (7,8) have supplemented individuals at higher risk of cardiovascular events for similar or longer duration and with comparable dosages to those used in our study and have not reported any adverse effects. Minimal side effects have been noted with vitamin E supplementation at doses much higher than those we used and for up to 11 years in some trials (9). Taken together, the available data do not suggest that our overweight subjects who were assigned to vitamin E were at increased risk of coronary death.

We agree that vigilance on the use of vitamin E supplementation should be observed. Patients receiving statin-niacin therapy or anticoagulants should not receive vitamin E supplements. None of the participants in our study (10) were receiving drug therapy.

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Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects

Response to Wackers et al.

We read the results of the DIAD study (1) with great interest and congratulate all of the investigators. However, the study leaves some questions unanswered and raises others.

1) Since there is no nondiabetic control group with similar baseline characteristics, we don't know whether the reported prevalence of silent ischemia (22%) is higher than in nondiabetic patients. Such a comparison is necessary to determine how many scans are needed to diagnose one addional silent ischemia in asymptomatic diabetic patients. Therefore, the clinician is not assisted in determining whether performing myocardial perfusion imaging (MPI) in asymptomatic diabetic patients has any incremental diagnostic and prognostic value.

2) Since patients are asymptomatic, it is unclear whether performing coronary angiogram (its cost, risks, and subsequent revascularization interventions) is cost-effective and/or will improve clinical outcomes.

3) The following factors may overestimate the prevalence of silent ischemia. *i*) Reported silent ischemia (22%; however, only 15.9% had abnormal MPI). Eight subjects (1.9%) had left ventricular dysfunction, which may not indicate silent ischemia. Categorizing transient ischemic dilatation and/or left ventricular dysfunction without perfusion defect as silent ischemia is also debatable. *ii*) Image analysis. Subjects were obese (BMI 31.1 ± 6.3 kg/m^2), and 47% were women. It is not clear whether correction software for scatter, attenuation, and motion were used in the image interpretation. *iii*) Vasodilator stress testing using intravenous infusion of adenosine with simultaneous very-low-level treadmill exercise. The authors provide a rationale for this mode of stress test. However, it is of concern that asymptomatic, relatively young patients (60.7 ± 6.8 years) were not asked to perform an exercise test. False-positive scan rates are higher with vasodilator stress tests because myocardial images are more difficult to interpret due to relatively less myocardial uptake and increased gastrointestinal uptake. How generalizable are these findings in patients undergoing treadmill stress test with SPECT (single-photon emission–computed tomography) MPI? *iv*) Nine patients with transient ST-segment depression. It is not evident from the report whether these were purely adenosine or adenosine with exercise. The significance of electrocardiogram changes in vasodilator stress test with exercise is somewhat uncertain. *v*) Since there are no angiographic confirmations of abnormal scans, the sensitivity

and specificity of positive scans are unclear.

4) Male sex as predictor of abnormal test. Despite the fact that the authors performed multivariate analyses, it would be helpful to know whether men and women differed on baseline characteristics.

In reference to issue *1*, on retrospective analyses of our 231 MPIs in an inner-city hospital, the prevalence of abnormal MPIs among asymptomatic diabetic and nondiabetic patients was similar (20%) (2).

In view of all the above, a large-scale, multicenter, prospective study of asymptomatic diabetic and nondiabetic patients is warranted.

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Detection of Silent Myocardial Ischemia in Asymptomatic Diabetic Subjects

Response to Bhalodkar and Blum

The DIAD study was designed to investigate the prevalence and predictors of silent ischemia, specifically in asymptomatic patients with type 2 diabetes (1), who often present with advanced coronary artery disease (CAD) without prior angina. The DIAD study did not compare the prevalence of asymptomatic CAD in diabetic and nondiabetic patients. Although the relative prevalence of asymptomatic CAD in nondiabetic patients otherwise well-matched for cardiac risk factors is of interest, it will require a much larger study.

Bhalodkar and Blum (2) express concern that the prevalence of silent ischemia in DIAD might be overestimated. We believe this to be unlikely. All single-photon emission–computed tomography (SPECT) studies were interpreted by consensus of a panel of well-recognized experts in nuclear cardiology. Attenuation correction was not applied, and images were read visually along with quantitative analysis. By design, all images with possible attenuation artifacts were interpreted as normal. We would agree that resting left ventricular dysfunction and transient ventricular dilation without perfusion defects may not be due to macrovascular CAD, but these were infrequent findings.

The specificity of SPECT Sestamibi imaging abnormalities in asymptomatic patients with diabetes has not been formally evaluated. However, we previously established a normalcy rate of 97% in normal subjects using the same quantitative analysis method. Importantly, our analysis of the predictors of ischemia focused on patients with moderate or large reversible SPECT defects, which occur rarely in the absence of significant CAD.

Since many patients with diabetes are unable to exercise adequately, vasodilator stress was chosen to ensure that the study was broadly inclusive. Exclusion of patients unable to exercise would select a lower risk and nonrepresentative study group. The literature does not indicate that vasodilator stress has a higher false-positive rate than exercise stress, and adenosine Sestamibi images are not more difficult to interpret than exercise images in experienced laboratories. By study design, poor-quality studies were excluded; however, only 1 of 523 SPECT studies was deemed of poor quality.

The adverse prognostic significance of ST-segment depression with adenosine is well documented in patients referred for evaluation (3,4). Most nuclear cardiologists consider this finding to indicate an increased risk for future cardiovascular events. Of patients with ST-segment depression, 5 of 9 patients with perfusion defects and 13 of 21 patients without perfusion defects performed low-level exercise (P = NS). The second phase of DIAD (to be completed in September 2007) will define the prognostic significance of adenosine-induced ST-depression in asymptomatic patients with diabetes.

We agree that, currently, there are insufficient data to support routine angiography/intervention in all patients with abnormal screening SPECT studies. Physicians who screen patients must use their own judgment in determining individual management at the current time. The follow-up phase of DIAD will lend insight into which patients are at highest risk for future cardiovascular events. However, an abnormal perfusion study should trigger intensive risk factor intervention that is otherwise not commonly achieved, even when patients are treated in the diabetes clinic.

With regard to the unpublished observations mentioned in the letter, caution is warranted in interpreting retrospective data from a referred patient population because of selection bias. We appreciate the interest in DIAD.

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Biological Variation in HbA₁c Predicts Risk of Retinopathy and Nephropathy in Type 1 Diabetes

Response to McCarter et al.

McCarter et al. (1) report that the propensity to glycate hemoglobin, as evidenced by a higher-than-expected HbA$_{1c}$ level for the concomitantly measured mean blood glucose (MBG) level, is itself a risk factor for diabetic retinopathy and nephropathy. They use publicly available data from the Diabetes Control and Complications Trial (DCCT) to calculate a hemoglobin glycation index (HGI) to support their hypothesis. Their results appear to offer a possible explanation for anecdotal reports that some patients with chronically excellent control are nonetheless severely affected by diabetic retinopathy and/or nephropathy, while others with chronically poor glycemic control nonetheless escape these complications.

The data from the National Institute of Diabetes and Digestive and Kidney Diseases–funded DCCT were placed in the public domain to allow other investigators to pursue additional analyses, and we applaud their efforts. However, we the principal investigators of the DCCT cannot accept their conclusion based on the results presented.

The HGI used in these analyses is heavily dependent on the observed HbA$_{1c}$. The authors regress HbA$_{1c}$ on MBG and other factors and then define the HGI as the residual: HGI equals observed HbA$_{1c}$ minus predicted HbA$_{1c}$

from the regression equation. However, the residual is not independent of the HbA$_{1c}$. When HbA$_{1c}$ is regressed on the residual, the slope is 1 (a statistical fact whenever the dependent variable is regressed on the residual). Thus, the higher the residual or HGI, the higher the HbA$_{1c}$. HGI is then simply a surrogate for HbA$_{1c}$. This is a statistical tautology. Their analysis (their Fig. 2) showing that the risk of diabetic retinopathy progression is directly related to HGI is therefore certainly a function of HbA$_{1c}$.

The question that is not addressed is whether HGI is a risk factor for diabetic retinopathy and nephropathy independent of the observed HbA$_{1c}$. In other words, is the difference between the HGI groups in diabetic retinopathy or nephropathy risk attributable in whole or in part to the differences in HbA$_{1c}$ between these groups? This would be addressed by examining the differences between HGI groups after also adjusting for the levels of HbA$_{1c}$. This critical analysis is not presented.

Related questions are whether HGI explains more of the variation in diabetic retinopathy and nephropathy risk than the observed HbA$_{1c}$ and whether HGI is a better and more useful predictor of risk than HbA$_{1c}$ alone.

In the authors' methods report (2) they developed the HGI from numerous self-monitored blood glucose values over the preceding 30 days. However, the only blood glucose values available during the DCCT were the values obtained immediately before the time of the HbA$_{1c}$ collection. HbA$_{1c}$ is an index of MBG over the preceding 4–12 weeks and not necessarily of the MBG determined on the preceding day. For example, a patient with chronically elevated blood glucose levels and a high HbA$_{1c}$ might try hard to have lower blood glucose levels on the test day. This would explain Fig. 3*A*, where subjects with a low calculated MBG but high HGI (meaning high HbA$_{1c}$) are at greater risk for retinopathy. Thus, the regression relationship between the concurrent MBG and HBA$_{1c}$ would be expected to be less than that between the HbA$_{1c}$ and the preceding 4–12 weeks of blood glucose values, data which were not obtained in the DCCT. Accordingly, a better regression estimate and a more accurate HGI index would be obtained from a regres-

sion line generated from each individual DCCT patient's mean DCCT HbA$_{1c}$ versus the mean of each patient's quarterly MBGs over the entire DCCT follow-up.

It is conceivable that a greater tendency to glycate hemoglobin and other proteins adds to the risk of complications above that created by the level of hyperglycemia per se. However, this hypothesis has not been addressed in this report. Moreover, the potential for sampling errors in measuring MBG and, consequently, the poor appreciation of the relationship between MBG and HbA$_{1c}$ remains a major impediment in understanding whether "biologic" variations in glycation truly exist. Until these issues are resolved, the observed HbA$_{1c}$ level still remains the easiest obtained and best proven clinical predictor of the risk of microvascular and neuropathic complications (3).

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Biological Variation in HbA$_{1c}$ Predicts Risk of Retinopathy and Nephropathy in Type 1 Diabetes

Response to Genuth, Lachin, and Nathan

Genuth, Lachin, and Nathan (1) pose several questions regarding the methodology and conclusions of our recent report (2). We are responding in order to clarify the validity of our approach, results, and conclusions regarding the important relationship between biological variation (BV) in HbA$_{1c}$ and mean blood glucose (MBG) and the development of microvascular complications of diabetes.

A key consideration in our hypothesis is the existence of consistent between-patient directional differences over time in HbA$_{1c}$ not accounted for by the associated MBG levels (2). BV in biochemical metabolites is a well-recognized phenomenon in clinical chemistry (3). BV in HbA$_{1c}$ levels has been reported in individuals without diabetes (4), where MBG has little impact on HbA$_{1c}$ levels. In patients with diabetes, the strong correlation between HbA$_{1c}$ and MBG must be taken into account when assessing the impact of BV on HbA$_{1c}$ levels. The hemoglobin glycation index (HGI) was devised for this purpose (2,5). We have used the HGI to demonstrate the presence of directional BV in HbA$_{1c}$ in longitudinal data from patients with diabetes in our own clinic population (5) as well as participants in the Diabetes Control and Complications Trial (DCCT) (2). In repeated measures obtained over the course of both studies, we found that large numbers of patients had consistently nonrandom, large positive or negative deviations (high or low HGIs, respectively) of their observed HbA$_{1c}$ from the predicted HbA$_{1c}$ based on their associated MBG (2,5). Thus, HbA$_{1c}$ levels from patients with diabetes can be shown to be determined by idiosyncratic patient-specific factors as well as by MBG.

Genuth, Lachin, and Nathan (1) do not directly question the existence of between-patient BV in HbA$_{1c}$, but they do offer an alternative explanation for the findings. They suggest that DCCT partic-ipants who usually have poor glycemic control and high HbA$_{1c}$ levels may have been motivated to deliberately improve their glycemic control just on the day they collected their glucose profile set. This would cause lower glucose levels just for that day and result in a misleadingly low MBG. These patients would then appear to have a much higher HbA$_{1c}$ level than would be predicted for their MBG and thus exhibit a large positive HGI. However, it should be kept in mind that there were as many DCCT participants with low HGI as there were with high HGI. By the reasoning of Genuth, Lachin, and Nathan, a similarly large number of patients who usually have good glycemic control with low HbA$_{1c}$ levels deliberately worsened their glycemic control just for the day of the profile set. Thus, leading to HbA$_{1c}$ levels unexpectedly lower than would be predicted from their MBGs and giving a large negative HGI. We believe that this explanation is not plausible. It is unlikely that two-thirds of the DCCT participants consistently and deliberately either improved or worsened their glycemic control just for 1 day each quarter for 7–9 years. Nor is it a plausible explanation for BV in HbA$_{1c}$ levels reported in clinic patients where MBG was estimated from multiple glucose samples obtained over a period of 30 days (5) or in individuals without diabetes (4). We have considered other possible explanations for BV in HbA$_{1c}$ within the discussion of our report (2). Ultimately, the possibility that BV in HbA$_{1c}$ is a manifestation of individual differences in metabolic processes, other than MBG, that influence hemoglobin glycation and development of complications is a hypothesis that deserves further attention (2,5).

Genuth, Lachin, and Nathan point out that HbA$_{1c}$ is a good index of glycemia over a period of 4–12 weeks, while the DCCT MBG is derived from a seven-sample, 1-day glucose profile set and may not provide as good an estimate of the true MBG over the same period of time. To obtain a better estimate of HGI, Genuth, Lachin, and Nathan recommend using an average of MBGs and HbA$_{1c}$ levels over the entire DCCT follow-up. For the purpose of predicting complications, the HGI was indeed computed as an average value for each subject over the course of the DCCT follow-up (2), as Genuth, Lachin, and Nathan recommended. When computed in this way, the HGI rep-resents a measure of each individual's average directional divergence in HbA$_{1c}$ from that predicted over dozens of quarterly measurements; it is not merely a single regression residual.

Furthermore, we note that the association of HbA$_{1c}$ levels with glucose levels is so strong that consistent regression relationships have been demonstrated between HbA$_{1c}$ and an MBG derived from multiple glucose samples obtained over 30 days (5), seven glucose samples obtained over the course of 1 day (6), or even one glucose sample (7). It stands to reason that an MBG calculated from a 1-day, 7-point glucose profile set may not estimate the true MBG as well as an MBG calculated from a more extensive sampling protocol. However, the 1-day DCCT MBG has been shown by DCCT investigators to provide a valid regression relationship with HbA$_{1c}$ (6), and this regression model has been extensively promoted as a way to estimate MBG based on HbA$_{1c}$ assays standardized to the DCCT high-performance liquid chromatography methodology (8). There is no evidence that the 1-day MBG estimates themselves are biased. Furthermore, MBG calculated from the DCCT 1-day profile sets have themselves been successfully used to predict the development of diabetic retinopathy (9). Collectively, this information suggests that the MBG estimates from the DCCT are quite adequate for analysis of BV in HbA$_{1c}$ and risk of complications.

Our main hypothesis tested in the report was that BV in HbA$_{1c}$, after accounting for the influence of MBG, is predictive of diabetic retinopathy and nephropathy (2). The simple approach of including both HbA$_{1c}$ and MBG together in a statistical model for prediction of complications is undesirable, since HbA$_{1c}$ is highly correlated with MBG. Genuth, Lachin, and Nathan point out that HGI and HbA$_{1c}$ are also highly correlated. However, HGI is not correlated with MBG (5) and can therefore be reliably included as an independent variable in a statistical model together with MBG for the prediction of nephropathy and retinopathy. This statistical approach allowed us to successfully demonstrate that BV in HbA$_{1c}$, as measured by HGI, is predictive of retinopathy and nephropathy, independent of the important effect of MBG.

The findings of our report should in no fashion be construed as detracting or

contradicting the important results and conclusions of the DCCT. Nor should they be taken to suggest that HGI should replace HbA_{1c} or deter the clinical use of HbA_{1c} for the assessment of patients with diabetes. If anything, our findings suggest that in addition to reflecting the effects of preceding MBG, HbA_{1c} also contains important information about other processes that influence hemoglobin glycation and the development of complications. We hope that this discussion will promote further study of these processes and their impact on diabetes complications.

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