OBSERVATIONS

Reduction in Foot Ulcer Incidence

Relation to compliance with a prophylactic foot care program

Diabetic foot lesions are one of the most serious causes of morbidity among diabetic people and often require a long hospital stay. Despite intensive therapy, many of these patients will require a lower-extremity amputation (LEA), with a high economic and social cost. The estimated cost due to LEAs in diabetic patients in Spain was 5,289 million pesetas ($39.5 million U.S.) (1). Area 7 in Madrid has the lowest LEA incidence of all Caucasian populations (2), with a progressive decline since 1989, reaching a ≥50% decrease in 1997. Preventive strategies are mainly focused on early peripheral neuropathy detection, diagnosed by a neuropathy disability score (NDS) ≥6. Diabetic people diagnosed with neuropathy are then included in a continuous prophylactic foot care program (FP). This program has been available in our area since 1993. Our study assessed the effectiveness of the FP in reducing the foot ulcer incidence in diabetic patients included in this program between 1993 and 1996 and in the follow-up completed in December 1999.

We designed a prospective clinic-based study in which all diabetic patients who attended the outpatient clinic of the endocrinology service and who were diagnosed as having peripheral neuropathy based on an NDS ≥6 were included in a screening and prophylactic FP. The NDS is included in the standards of medical care for diabetic people from area 7 in Madrid (population of 565,000). The number of people with diagnosed diabetes is estimated to be ~19,000.

The design of the screening program has been described previously elsewhere (3). In short, we recruited diabetic patients with an NDS ≥6 who were considered to be suffering from peripheral neuropathy according to standard criteria (4). All of these diabetic patients were tested for peripheral vascular disease (PVD) and morphological plantar deformities; for visual and motor capacity that enabled them to inspect their own feet; and for self–foot care that included the manner in which they walked barefoot, correct performance of foot hygiene, callus care, nail trimming, water temperature checking, the use of heating pads and other methods to warm up the feet, "bathroom surgery," the use of products for foot care, the method used for inspection of feet and shoes, and the proper use of shoes, socks, and clothes. Patients with severe PVD (grade 2 ischemia or higher), which was defined as the presence of intermittent claudication or the absence of at least one foot pulse (dorsalis pedis or posterior tibial), were excluded because these patients are unlikely to be influenced by FPs. The other patients were included in a continuous FP that consisted of four 90- to 120-min sessions held during 1 week. The first session was individual, and personal characteristics of the foot care of each patient were noted. The main goal of this session was to make the patient realize his/her lack of normal sensitivity in the feet compared with the rest of the body and his/her loss of sensory perception of pain.

Patients should agree that because of the decrease or loss in their protective pain sensation, it should be carefully evaluated. First, visual and motor capacity to inspect their own feet was explored. Patients were considered to have adequate eyesight capacity if they were able to read a letter 0.4 cm in size from 50 cm away (with their usual glasses if necessary) and acceptable physical mobility if they could see the soles of their feet, using a mirror if necessary. The patients were evaluated for the proper use of shoes, socks, and clothes; the manner in which they walked barefoot; the correct performance of foot hygiene; callus care and nail trimming; water temperature checking; the use of heating pads, hot water bottles, and other methods to warm up the feet; bathroom surgery; the use of products for foot care; the time and method used for the inspection of feet and shoes; as well as the use of podiatry services.

These data were collected in a questionnaire (5) adapted from one previously published (6). To enhance their knowledge and to change unsuitable behaviors, patients were included in groups of three to six people and instructed during three consecutive sessions over the course of 1 week. If a patient was unable to inspect his/her feet, one of the patient's relatives was then instructed on how to perform the task or at least monthly access to a chiropody service was provided. A continuous foot care treatment program was performed, including regular monthly visits during the first 6 months to evaluate the changes in the patient's behavior and diabetes treatment. In addition, patients could contact the clinic whenever they felt it necessary to evaluate some finding in their feet. Thereafter, reviews took place at least every 6 months. At least once a year a full clinical review took place, including a thorough neurological examination that followed the American Diabetes Association (ADA) recommendations (7).

Since 1998, a neurothesiometer (Arnold Horwell, London) has been available in our department, and a vibration perception threshold (VPT) was included in the annual review.

Patients were considered as having compliance with the FP if they met the following requirements: completion of the educational program, a change in inadequate foot care behavior during the first 6 months, regular visits to the podiatrist, at least one foot review every 6 months, and an annual medical care diabetic treatment review.

Between November 1993 and December 1996, 3,254 diabetic patients (17% of estimated diabetic population) visited our outpatient setting office. A total of 318 patients (9.2%) with neither past nor recent history of foot lesions were recruited from the screening and included in the study. Of these patients, 223 showed compliance with the FP (group A), whereas 95 patients did not complete the requirements and were placed in group B. Causes for noncompliance with the FP were as follows: 41 did not complete the educational program, 52 did not change their foot care behaviors, and 2 did not visit the podiatrist regularly. Groups A and B were comparable in terms of age, sex, duration of diabetes, and HbA_{1c} levels (Table 1). Because substantial reductions in morbidity can be obtained by instituting an adequate screening as simple as an NDS and enrolling patients in a basic FP, the existence of a control group lacking these requirements was considered ethically unacceptable. This letter compares patients with and without compliance to an FP, bearing in mind that the characteristics of both groups of patients are comparable. In addition, patients from group B received identical screening and an educational program at baseline and were followed in the same office setting, so we believe that this group received a better than conventional treatment. Patients

Table 1—*Characteristics of the diabetic patient groups*

	Group A	Group B	Overall
n	223	95	318
Sex (M/F)	101/122	43/52	144/174
Age (years)	65.4 ± 11.6	70.2 ± 10.3	68.3 ± 10.8
Duration of diabetes (years)	8.6 ± 7.9	9.1 ± 8.9	8.9 ± 7.8
Deaths during follow-up	7	6	13
NDS	6.2 ± 0.02	6.3 ± 0.02	6.2 ± 0.02
Smoker			
Actual	22 (10)	11 (12)	33 (10)
Never	44 (20)	18 (19)	62 (19)
HbA_{1c} (%)*	6.4 ± 1.4	6.3 ± 1.3	6.3 ± 1.3
Annual number of first (all) ulcers			
Year 1	0	4	4
Year 2	1	3	4
Year 3	1	5	6
Year 4	1 (2)	6 (8)	7 (10)
Year 5	2	3 (4)	5 (6)
Year 6	1	5 (6)	6 (7)
Total ulcers	6 (7)	26 (30)	32 (37)
Cumulative all ulcers rate (%)	3.1	31.6†	11.6
Cases (first ulcers) per year (95% CI)	0.5 (0.4–0.6)	6.8 (5.4–8.2)‡	2.1 (1.9–2.3)
Relative risk (group B vs. group A)		13	

Data are *n*, means ± SD, or *n* (%) unless otherwise indicated. *Normal <5.8%; †$P < 0.001$ vs. group A; ‡$P < 0.01$ vs. group A.

were followed between 3 and 6 years (mean 4.6). A χ^2 test was used to evaluate the differences in foot ulcer incidence within both groups.

During the follow-up, 13 patients died (8 men and 5 women, 69 ± 9 years of age [means ± SD]). Of these, 6 died as a result of heart ischemic disease, 3 died because of neoplasm disease (breast, colon, and prostate, respectively), and 3 died of unknown causes. The final patient, who died because of renal failure, had previously suffered an LEA.

In total, 37 foot ulcers were detected in 32 diabetic patients (68.6 ± 17 years of age), with 7 ulcers in 6 patients from group A and 30 ulcers in 26 patients from group B. Of these ulcers, 20 progressed to LEAs (73.2 ± 7.6 years of age), with 19 from group B and 1 from group A. The incidence of first ulcers and the annual distribution are shown in Table 1. The cumulative total foot ulcer rate was 11.6%, with 3.1% from group A and 31.6% from group B ($P < 0.001$). The number of first ulcers per 100 diabetic patients per year (95% CI) for the whole study population was 2.1 (1.9–2.3), with 0.5 (0.4–0.6) from group A and 6.8 (5.4–8.2) from group B ($P < 0.01$). With regards to the VPT, the number of first ulcers per year of diabetic patients with VPT scores >25 V was 4.3% in group B, compared with 0.05% in group A (relative risk 8). The figures for diabetic patients with VPT scores <25 V were 4.4 vs. 0.2% for group B versus group A, respectively (relative risk 22).

Following international recommendations (7,8), educational programs must be offered to diabetic people experiencing a decrease in their protective pain sensation, even though the efficacy may be based on poor evidence (9,10). Our data show that diabetic people who complied with the FP had a 13-fold lower risk of suffering first foot ulcers than people who did not follow the program. This reduction may be higher in diabetic patients with less severe polyneuropathy (VPT <25 V). This finding shows, in a very indicative way, the importance of early intervention. Moreover, the program was designed to be widely applied in all of the ordinary medical office settings, even with limited financial resources. We compared the results from both group A and group B, considering group B as the control group. Thus, the control group (group B) had better than usual medical therapy, but without a continuous educational program. In addition, both groups were matched in relation to other risk factors, so that the difference in foot ulcer incidence might depend on compliance with the FP.

Our study clearly supports the hypothesis that when an FP is present, many patients change their inappropriate foot-care behavior, with at least a 13-fold decrease in foot ulcer presentation. Some peculiar facts in our FP could explain our results. First, following ADA (7) recommendations, intervention was limited to high-risk people with previous neuropathy diagnosed by NDS. Second, continuous education was maintained until the changes in the patient's behavior were achieved, in contrast to other education programs with a rigidly scheduled session or a maximum of 3 months of surveillance. This FP integrates preventive educational and therapeutic strategies in a continuous way. Finally, free podiatry care was provided to all patients unable to perform their foot self-care. These three aspects, altogether, are critical in the program's efficacy.

There are several ways to diagnose a diabetic patient as having neuropathy (4). The NDS had been proven to be useful in epidemiological trials, using simple equipment that is available in any clinic (11,12). In addition, a recent study conducted in the primary care setting in the U.K. (13)—designed to search for risk factors in a large population sample—identified diabetes duration, amputation, and an NDS ≥6 as high-risk categories for foot ulceration, after stepwise multiple regression. Our study confirms that simple clinical measures of neuropathy, particularly NDS, are the best predictors of diabetic foot ulceration and could be applied in any medical office setting.

Moreover, patients with neuropathy that is diagnosed with these methods could have different risk categories. When the foot ulceration rate in people who complied with the program is compared with the rate in people who were noncompliant (according to VPT scores higher or lower than 25 V), diabetic people compliant with the FP and having a VPT score >25 V showed an eightfold lower risk for foot ulceration. This risk decreases even more (22-fold) in diabetic patients with less severe neuropathy (VPT scores <25 V). These results support the hypothesis that program efficacy could be greater when it is applied early, especially in people with less severe neuropathy.

In conclusion, our data suggest that a screening program based on the NDS is useful in detecting people with a high risk of foot ulcer development. Intervention programs based on continuous and well-

organized education, supported by regular podiatry assistance, have demonstrated to be very effective in decreasing the incidence of foot ulceration. Considering how simple the program is, and that prevalence of clinical neuropathy in Spain is 22.7% (12), this program could be extended to any primary care clinic. Based on these findings, an FP in the primary setting is ongoing in Spain.

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Depression Among African-Americans With Diabetes

A dearth of studies

It has been well established that African-Americans have an increased prevalence of type 2 diabetes compared with Whites (10.1 vs. 5.2%, respectively) (1). Both White and African-American women have a 40% greater prevalence rate of type 2 diabetes compared with men (1). African-Americans also have higher rates of morbidity and mortality associated with a variety of diabetic complications, including higher glycemic levels, increased prevalence of microalbuminuria and kidney disease, longer duration of kidney disease, greater likelihood of retinopathy, greater incidence of diabetes-related amputations, and greater incidence of end-stage renal disease (1). It would appear that the psychosocial impact of diabetes on African-Americans is less well characterized.

We recently completed a series of meta-analyses of the literature to determine the prevalence of depression and its associations with glycemic control and diabetes complications. Depression was two times more prevalent in patients with diabetes than in those without diabetes (2). Glycemic control and diabetes complications were each significantly associated with depression in types 1 and 2 diabetic patient samples (3,4).

We reviewed 69 studies gathered for the above-referenced meta-analyses. Of these studies, 11 included African-Americans in samples gathered from U.S. localities, and 2 of the 11 studies examined the relationship of depression and diabetes using race/ethnicity as a grouping variable (5,6). In short, only 3% of all studies that have been conducted on the relationship between depression and diabetes have examined race/ethnicity as a contributing factor.

In light of the disproportionate burden that diabetes places on African-Americans, we were surprised to find so few studies that address the relationship of depression to glycemic control and diabetes complications among African-Americans. The paucity of this literature points to an important gap in our understanding of the impact of diabetes and depression on psychosocial adjustment for these patients. Little is known about cultural or behavioral factors that may contribute to the experience or outcomes associated with depression in African-Americans.

As the prevalence of type 2 diabetes increases among African-Americans and demographic expansion continues, African-Americans can be expected to represent a growing and important segment of the diabetic population. Depression may be a factor in the disproportionate prevalence rates of diabetes in African-American women. The prevalence of depression among African-Americans with diabetes needs further documentation. In addition, studies are needed to determine whether the association of depression with hyperglycemia and diabetes complications

can be found in African-American as well as White samples.

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Evidence of Autoimmunity in Male Twins With Neonatal Diabetes

We report male monozygotic twins who presented with neonatal diabetes mellitus (NDM) within an autoimmune context. They were born to unrelated healthy parents after 36 weeks of uncomplicated pregnancy. Family history was unremarkable. The clinical history of the patients was almost identical; both twins were admitted on the 12th and 25th days of life, respectively, because of poor feeding, dehydration, lethargy, metabolic acidosis, severe watery diarrhea, and persistent hyperglycemia (>17 mmol/l). It was very difficult to stabilize diabetes on the conventional subcutaneous insulin schedule, so intravenous treatment was started in both patients. High levels of thyroid-stimulating hormone were found by routine screening tests, and increased serum levels of anti-thyroglobulin and anti-thyroid peroxidase antibodies were detected. Moreover, islet cell antibody and GAD-reactive autoantibodies were found, whereas insulin autoantibodies, serum enterocyte autoantibodies, antiparietal cells, and anti-endomisium were normal. No serum levels of these autoantibodies were detected in the mother. Extensive testing (lymphocyte subpopulation, CD4-to-CD8 ratio, and mitogenic response) failed to reveal immunological defects. Serologic tests for viral infections were negative. IgE concentration was normal. HLA typing did not show type 1 diabetes–related haplotypes.

The subsequent clinical course was characterized by persistent watery diarrhea (volumes ≤100 ml/kg per day) unresponsive to total parenteral nutrition, a failure to thrive, recurrent infections, and brittle diabetes (values from 5 to 25 mmol/l).

Clinical conditions progressively worsened, and both patients died of sepsis within the third month of life. Postmortem examination showed a marked infiltration of mononuclear cells of the pancreas, intestine, lung, and thyroid.

The infants we have described share several features with an extremely rare X-linked syndrome of intractable diarrhea, polyendocrinopathy, and fatal infection (1,2). Certainly, the most striking outcome of this report is that NDM is associated with immune dysregulation.

It is believed that NDM is not related to an autoimmune phenomenon because autoantibodies have never been reported and because the autoimmune destructive process is a very slow one, and it may last years; therefore, this process would unlikely begin or develop in utero and become clinically evident at birth.

Nevertheless, at least three types of evidence support the autoimmune nature of diabetes in our patients: *1*) the presence of β-cell–reactive autoantibodies, *2*) the association with other typical autoimmune diseases (namely thyroiditis and enteropathy), and *3*) the identification of insulitis with a massive infiltration of mononuclear cells at necropsy.

Undoubtedly, the histological and immunological findings are typical of the autoimmune-type diabetes. A striking finding is that insulitis can be clinically evident very shortly after birth. Nevertheless, it would be very interesting to speculate how these findings relate to the absence of specific HLA antigens of susceptibility. The anti-islet response could be part of a more global immune hyperreactivity caused by the loss of the immune-regulatory function, without apparent requirement for an autoantigenic driving force. Our experience further suggests that NDM includes more than one disorder, so more than one mechanism might be implicated in the etiology. Although it is difficult to formulate a global hypothesis explaining our findings, evidence supports the possibility that autoimmunity might, in someway, be involved in at least selected cases of NDM.

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Does Pioglitazone, Like Troglitazone, Increase Serum Levels of Lipoprotein(a) in Diabetic Patients?

Thiazolidinediones such as troglitazone and pioglitazone ameliorate dyslipidemia in type 2 diabetic patients by improving insulin resistance. The levels of serum triglycerides, nonesterified fatty

acids, total cholesterol, and LDL cholesterol decrease after administration of these agents, while HDL cholesterol increases (1–3). These effects are helpful in preventing the development of atherosclerosis in diabetic patients. On the other hand, troglitazone has also been known to increase serum lipoprotein(a) [Lp(a)] (4,5), a known atherogenic lipoprotein (6). To our knowledge, there is no report on the effect of pioglitazone on serum levels of Lp(a). Therefore, we investigated serum levels of Lp(a) and remnant-like particle cholesterol (RLP-C), a lipid known to act atherogenetically (7), before and after the administration of pioglitazone in type 2 diabetic patients.

Eight type 2 diabetic patients (five men and three women; mean age [mean ± SEM] 60.8 ± 3.7 years) were included. Six enrolled patients had been receiving sulfonylureas, while the other two were on diet therapy only. Because of high levels of HbA_{1c}, pioglitazone administration (15 or 30 mg/day) was added to previous treatment. The patients were instructed not to alter their eating patterns and exercise habits. Their preexisting medications (if any) remained unchanged during the treatment period. HbA_{1c} and serum levels of triglyceride, total cholesterol, HDL cholesterol, Lp(a), and RLP-C were measured before and 3 months after pioglitazone administration. HbA_{1c} levels were measured by a high-performance liquid chromatogrophy method with a normal laboratory range of 4.7–5.8%. Serum levels of triglyceride, total cholesterol, and HDL cholesterol were measured by standard laboratory techniques. Serum Lp(a) levels were measured by latex immunoassay with a rabbit monoclonal anti-human Lp(a) antibody, whereas serum RLP-C levels were measured by immunoadsorption assay using mouse monoclonal anti-human apolipoprotein (apo)B-100 and anti-human apoA-1 immunoaffinity mixed gel (normal range <40 and <7.5 mg/dl, respectively). This study was approved by the institutional review board, and all participants gave their informed consent.

The patient's HbA_{1c} levels were improved from 7.9 ± 0.3 to 7.3 ± 0.3% by the addition of pioglitazone. Pioglitazone decreased serum triglyceride levels (from 191.3 ± 32.2 to 156.3 ± 35.5 mg/dl, $P < 0.05$) and increased serum HDL cholesterol levels (from 49.4 ± 3.9 to 58.6 ± 4.3 mg/dl, $P < 0.05$), whereas serum total cholesterol levels were unchanged (from 225.0 ± 18.0 to 225.0 ± 15.8 mg/dl). Serum Lp(a) levels were essentially unchanged (20.0 ± 6.8 to 19.9 ± 4.9 mg/dl). On the other hand, serum RLP-C levels were significantly decreased from 8.2 ± 1.9 to 7.2 ± 1.9 mg/dl ($P < 0.05$).

Previous studies demonstrated that thiazolidinediones have an inhibitory effect on the development of atherosclerosis through several mechanisms (8–11). This is the first report to clarify the relationship between pioglitazone and serum levels of Lp(a) and RLP-C. While pioglitazone did not influence serum Lp(a) levels, it decreased serum RLP-C levels. Concerning the effect on serum Lp(a), another thiazolidinedione, troglitazone has been known to increase serum Lp(a) levels (4,5). Because Lp(a) is known as an atherogenic lipoprotein (6), pioglitazone is superior to troglitazone in preventing atherosclerosis. Furthermore, pioglitazone may prevent the development of atherosclerosis due to the reduction of serum RLP-C levels. Our patient population was small in this study, so further studies will be needed to clarify the relationship between pioglitazone and serum levels of Lp(a) and RLP-C.

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Efficacy of Oral Sildenafil in the Treatment of Erectile Dysfunction in Diabetic Men With Positive Response to Intracavernosal Injection of Alprostadil

Erectile dysfunction (ED) is a common complication of diabetes and has a multifactorial etiology that includes psychogenic factors, autonomic neuropathy, vascular disease, and drug intake. A number of drugs have been used for the medical treatment of ED in diabetic men.

Table 1—*Scores for questions 3 and 4 of the IIEF questionnaire at baseline and at the end of the 3-month treatment periods with alprostadil and sildenafil*

	Question 3	Question 4
Baseline	1.2 ± 0.1	1.1 ± 0.1
Alprostadil	4.2 ± 0.2*	4.0 ± 0.2*
Sildenafil	3.1 ± 0.2†	3.0 ± 0.2†

Data are means ± SEM. *$P < 0.001$ vs. baseline and sildenafil; †$P < 0.001$ vs. baseline.

Several studies have investigated the effects of the intracavernosal treatment with alprostadil (1,2); 60–87% of diabetic patients included in these studies reported satisfactory sexual activity. Transurethral alprostadil is a less invasive alternative with the advantages of a lower rate of priapism and penile fibrosis. In a recent study, 64.9% of patients treated with transurethral alprostadil had successful intercourse (3). A meta-analysis of seven controlled trials demonstrated that yohimbine is also a therapeutic option for ED when psychogenic causes are identified as the origin (4). More recently, oral sildenafil resulted to be an effective well-tolerated treatment for men with ED (5). A total of 56% of the diabetic patients taking sildenafil reported improved erections compared with 10% of patients taking placebo.

The aim of our study was to assess whether oral sildenafil citrate could be an effective alternative for the treatment of ED in diabetic men with a positive response to intracavernosal injection of alprostadil. We studied 52 men, aged 35–74 years (mean ± SEM 56.7 ± 4.5), with a diagnosis of ED (duration 2.2 ± 0.3 years, range 0.5–5.6) already effectively treated with alprostadil for no longer than 1 year (range 1–11 months). Only men in a stable sexual relationship for at least 6 months were included in the study. All of the patients were affected by diabetes (12 type 1 diabetic patients and 40 type 2 diabetic patients, duration 16.2 ± 1.9 years). No patients had a penile anatomical defect; a history of priapism or prostatectomy; the sickle-cell trait; major hematological, renal, or hepatic illnesses; or coronary artery disease. Other exclusion criteria included treatment with nitrate or anticoagulant therapy and evidence of drug abuse or alcoholism. The cause of ED had been determined from medical history, physical examination, laboratory evaluation, and other diagnostic procedures, including cardiovascular tests for autonomic neuropathy and penile duplex ultrasonography. The etiology of ED was 55.7% neurogenic, 19.2% psychogenic, 9.6% vasculogenic, and 15.3% mixed. The 15-question International Index of Erectile Function (IIEF) had also been administered to all of the patients as part of our standard clinical practice for the diagnosis of ED in the outpatient clinic. At baseline, no patient had successful attempts at sexual intercourse.

The mean interval between the baseline and the beginning of our study was 7 months (range 2–16). On entry into the study, the patients were asked to treat their ED for 3 months with intracavernosal self-injection of alprostadil (no more than three times a week). They were instructed to document the number and the effectiveness of sexual attempts. The optimal dose of alprostadil had been established by titration. After a 15-day wash-out period, the patients were transferred to oral treatment with sildenafil. They were instructed to take sildenafil (50 mg) ~1 h before sexual activity, no more than once a day, and to increase the dose to 100 mg based on two consecutive unsuccessful attempts at sexual intercourse. The IIEF questionnaire was self-administered again at the end of the alprostadil and sildenafil treatment periods.

The efficacy of the two treatments was assessed using responses to the following questions from the IIEF: question 3, "When you attempted sexual intercourse, how often were you able to penetrate your partner?" and question 4, "During sexual intercourse, how often were you able to maintain your erection to completion of intercourse?" Responses to the two questions were rated on a scale ranging from 1 to 5, with five response options: 1 = almost never/never, 2 = a few times (much less then half the time), 3 = sometimes (approximately half the time), 4 = most times (much more than half the time), and 5 = almost always/always. At the end of the two 3-month periods of treatment, patients used a mean dose of 16.8 ± 1.4 μg (range 7.5–30) alprostadil and a mean dose of 86.5 ± 0.5 mg sildenafil.

Both treatments were associated with significantly higher scores for question 3 (frequency of penetration) and question 4 (maintenance of erection after sexual penetration) than baseline ($P < 0.001$). The mean scores for questions 3 and 4 were significantly higher after treatment with alprostadil than after treatment with sildenafil ($P < 0.001$) (Table 1). Of all the attempts at sexual intercourse, 79% (850 of 1,083) were successful during alprostadil treatment as compared with 48.7% (485 of 995) during sildenafil treatment ($P < 0.001$). All of the patients reported at least one successful attempt at sexual intercourse during alprostadil treatment as compared with 63.5% successful attempts during sildenafil treatment ($P < 0.001$). Glycated hemoglobin, blood pressure, etiology of ED, and prevalence of autonomic neuropathy of patients who responded to sildenafil were similar to those found in patients who did not respond to sildenafil. After alprostadil injection, at least one episode of penile pain was reported by 38.4% of men. However, only one patient discontinued treatment because of pain during the study period, and mild hematomas occurred in four patients (7.6%). One episode of prolonged erection was reported by two men (3.8%). During the sildenafil treatment period, 36.5% of the patients reported at least one episode of transient headache, 28.8% reported flushing, 5.7% reported dyspepsia, and 3.8% reported rhinitis. These adverse effects were sporadic, and no patient withdrew from the study because of these side effects. None of the seven patients using drugs that have the potential to interfere with the metabolism of sildenafil (one on diltiazem, one on verapamil, one on nifedipine, and four on statins) showed side effects related to a prolongation of the half-life of sildenafil (6). Because of insufficient response, six patients discontinued therapy with sildenafil before the end of the treatment period.

Unlike previous studies, our investigation considered the efficacy of sildenafil treatment in a group of diabetic patients already effectively treated with intracavernosal alprostadil. Sildenafil was associated with a significant increase, with respect to baseline, in the mean end-of-treatment scores for questions 3 and 4 of the IIEF. It is not surprising that alprostadil appeared to be more effective than sildenafil, because the patients enrolled in our study had already showed a positive response to intracavernosal treatment with alprostadil. We did not study diabetic patients who did not respond to alprostadil; therefore, it is possible that some of these patients could have been successfully treated with sildenafil.

It is known that some patients treated with intracavernosal alprostadil discontinue treatment because they recover erectile function. Therefore, in our study, the previ-

ous treatment with alprostadil could have increased the efficacy of sildenafil treatment.

Both treatments were well tolerated in our patients. Pain was common after alprostadil injection, but in most instances, it was mild. The optimal dose of alprostadil was accurately individualized by titration in the Diabetes Unit; this procedure reduced prolonged erections and avoided priapism.

Penile fibrosis did not occur in our study; this side effect of prolonged intracavernosal treatment is less frequent when using alprostadil rather than papaverine (7). Moreover, in our patients, the period of intracavernosal treatment was short.

In conclusion, sildenafil represents an effective treatment of ED in diabetic men already treated with intracavernosal alprostadil. Alprostadil showed a higher grade of effectiveness than sildenafil. Nevertheless, therapy with intracavernosal alprostadil is more invasive, has heavier side effects, and needs accurate instructions for self-injection. Sildenafil is a reliable therapy with minimal side effects and good patient acceptance; it is simple to use, and it permits discreet administration.

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Treatment With Human Analog (Gly^{A21}, Arg^{B31}, Arg^{B32}) Insulin Glargine (HOE901) Resolves a Generalized Allergy to Human Insulin in Type 1 Diabetes

Allergic reactions to insulin are rare now that recombinant human insulin is clinically available. However, certain patients still suffer from insulin allergy, even with human insulins. We report herein the case of a 45-year-old type 1 diabetic Japanese man (weight 62 kg, BMI 19.3 kg/m^2) with generalized allergy to human insulin, who was successfully treated with human analog (Gly^{A21}, Arg^{B31}, Arg^{B32}) insulin glargine (HOE901). He was diagnosed with type 1 diabetes because of the high titer of anti-GAD antibody (65 U/ml, normal range <5) and poor C-peptide responses after glucagon loading (0.43 ng/ml).

In 1985, his first insulin therapy was started. Although he had no history of past illness, including any type of allergy or atopic background, the first subcutaneous injection with pork insulin (semi-lente type) induced allergic reactions, including transient skin rash, itching all over the body, and facial edema. Several days later, injection was restarted once daily with beef insulin (semi-lente type). However, beef insulin also induced generalized allergic reactions. Fortunately, the allergic reactions to beef insulin were far less intense than those to pork insulin. In 1989, the insulin therapy was switched from beef to human insulin. However, the allergic reactions presented yet again. An antihistaminic drug reduced the allergy, but did not eliminate the reactions.

A blood examination did not show any evidence of allergic reaction to insulins. The percentage of eosinophils in the peripheral white blood cell count was 3.1% (normal range <7). Total IgE was 142 U/ml (5–419), and insulin-specific IgE and IgG were not detected. Drug-induced lymphocyte stimulation tests for regular and NPH human insulin were negative. However, intradermal tests showed positive skin reactions to human regular insulin, NPH insulin, and crystalline insulin zinc. The patient did not show any positive skin reaction to concomitant material or any preservatives.

Insulin glargine was recently developed as a new human insulin analog with protracted action, and it may be an ideal preparation for maintaining basal insulin substitution (1). As the prick test of insulin glargine was negative, we initiated treatment with insulin glargine. The patient tolerated subcutaneous insulin glargine without any evidence of allergy. Subsequently, we started an intensive insulin therapy with regular insulin before each meal and insulin glargine at a bedtime. Intensive insulin therapy using 8 U/day of insulin glargine was administered for >6 months. During the treatment, the HbA_{1c} levels decreased from 9 to 7%. No other allergy was noted, even with regular insulin; therefore, antihistaminic drugs were no longer required.

His allergic epitopes appear to contain both human insulin A-chain and animal insulin (Ala^{B30}), because all of the pork, beef, and human insulins induced allergic reactions, and both epitopes are modified in insulin glargine. The tolerance of insulin glargine appeared to suppress the allergy to human regular insulin. The epitope spreading of the tolerance by peptide therapy in autoimmune diabetic mice has recently been reported (2). Similar anergic epitope spreading may have occurred in the insulin allergy. Although the precise mechanism to induce the tolerance across other insulins remains unclear, this is the first report to demonstrate that insulin glargine allows generalized insulin allergy to be overcome.

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The Continuing Increase of Diabetes in the U.S.

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Diabetes is a major cause of morbidity and mortality in the U.S. (1). The health care direct and indirect costs associated with diabetes in 1997 were an estimated $98 billion (2). Evidence from several studies indicates that obesity and weight gain are associated with an increased risk of diabetes (3,4). Obesity continues to increase rapidly in the U.S. The prevalence of obesity (BMI ≥30 kg/m^2) increased from 12.0% in 1991 to 17.9% in 1998 (5).

Recently, we reported that the prevalence of diagnosed diabetes in U.S. adults increased from 4.9% in 1990 to 6.5% in 1998 (6). To determine whether this increase is continuing, we used 1999 data from the Behavioral Risk Factor Surveillance System. The results were striking: the prevalence of diabetes increased to 6.9% in 1999, a 6% increase in 1 year (Table 1). Average weight increased from 76.2 kg in 1998 to 76.7 kg in 1999 (84.3–85.0 kg among men and 68.5–68.7 kg among women).

Diabetes is clearly a growing public health threat in the U.S. This update is consistent with our earlier prediction of the epidemic nature of diabetes. Specifically for diabetes, much of the impact of the continuing increase in obesity will be manifested in future years because of the substantial delay between the onset of obesity and the subsequent development of diabetes. Public health strategies to limit this increase and address its impact are urgently needed.

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Table 1—*Changes in diabetes prevalence from 1998 to 1999 by selected characteristics*

	1998	1999
Total	6.5 (0.11)	6.9 (0.12)
Sex		
Male	5.5 (0.15)	6.0 (0.17)
Female	7.4 (0.16)	7.6 (0.16)
Age-groups (years)		
18–29	1.6 (0.12)	1.9 (0.16)
30–39	3.7 (0.18)	3.4 (0.17)
40–49	5.1 (0.22)	5.6 (0.24)
50–59	9.8 (0.38)	10.0 (0.38)
60–69	12.8 (0.45)	12.8 (0.44)
≥70	12.7 (0.39)	14.4 (0.44)
Race		
Caucasian	5.9 (0.11)	6.2 (0.12)
African-American	8.9 (0.39)	9.9 (0.42)
Hispanic	7.7 (0.48)	8.0 (0.50)
Other	6.6 (0.73)	7.7 (0.70)
Education		
Less than high school	11.6 (0.41)	11.9 (0.45)
High school	6.4 (0.19)	6.9 (0.20)
Some college	5.9 (0.20)	5.9 (0.20)
College graduate or more	4.4 (0.17)	5.1 (0.19)
Weight category		
Underweight	3.5 (0.63)	4.3 (0.61)
Normal	3.5 (0.12)	4.0 (0.14)
Overweight	6.6 (0.19)	6.5 (0.19)
Obese	13.5 (0.38)	13.7 (0.36)
Smoking		
Never	5.8 (0.14)	6.4 (0.15)
Ex-smoker	9.3 (0.27)	9.6 (0.28)
Current	5.0 (0.20)	4.9 (0.20)

Data are % (SEM).

COMMENTS AND RESPONSES

Cost-Free Prevention to Asymptomatic Bacteriuria in Diabetic Women

Two hands, two towels

We read with interest the article of Geerlings et al. (1) that analyzed asymptomatic bacteriuria as a complication in diabetic women. It is known that urinary tract infections (UTIs) are an important problem in diabetic individuals, and bacteriuria is more common in diabetic women than in nondiabetic women (2) because of several factors that predispose diabetic individuals to infection (3). Furthermore, many UTIs are asymptomatic, and, as observed by Vejlsgaard (4), it is not clear if symptomatic infections are preceded by asymptomatic bacteriuria (ASB). Several studies confirm that there is a higher prevalence of ASB in diabetic women than in nondiabetic women (1). Unfortunately, ASB is not easily detected, even if there are some elements and clinical signs that indicate the presence of ASB. Furthermore, as reported by Mizock (5) and Perschel et al. (6), many stress factors, such as infections, burns, or trauma, are associated with alterations in carbohydrate metabo-

lism, inducing a need for higher insulin doses or insulin injection in patients normally on oral medication. Therefore, it is important to investigate the presence of possible stress factors such as infections in diabetic patients with suspicious elevation of glycemia.

During the last year, in the diabetes outpatient clinic of Santo Spirito Hospital in Rome, we observed 148 diabetic women with an increased average glucose value of 2.2 mmol/l (range 0.5–5.51); this variation of glycemia was present throughout each day for a period of several days. There were no significant variations in HbA_{1c} levels. After this observation, we interviewed the patients about possible stress factors, including UTIs and ASB that was defined as the presence of at least 10^5 colony-forming units (cfu)/ml of one or two bacterial species in a clean-voided midstream urine sample from individuals without symptoms of a UTI (7).

ASB was found in 79 of the 148 patients with alterations of glucose values; all 79 patients were postmenopausal. Furthermore, 69 patients had type 2 diabetes (age 58 ± 14.9 years), and the other 10 had type 1 diabetes (age 47.3 ± 7.4 years); all of the patients suffered from habitual UTIs or ASB.

As observed in other studies, *Escherichia coli* was the most frequently isolated microorganism (42 patients [53%]) (1,8). In addition, *Klebsiella oxytoca* was found in 18 patients (22.7%), *Enterobacter cloacae* was found in 12 patients (15.1%), and *Proteus mirabilis* was found in 7 patients (8.8%). ASB disappeared after successful treatment with specific antibiotics.

Moreover, we investigated the hygiene habits of the 79 patients with ASB. We found that 68 patients used one hand and one towel to wash and dry both the genital and anal regions. The remaining 11 patients used both hands to wash, one for the genital and one for the anal region, but only one towel to dry the two different regions. The anatomical characteristics of women may facilitate the migration of intestinal microorganisms in the urinary tract. Therefore, we recommended that the 68 patients change their habits and use both hands and two different towels to wash and dry the two different regions.

After 6 months of these hygiene modifications, we repeated the midstream urine analysis and found that only 16 (20.2%) of the 79 patients had ASB. *E. coli* remained the most frequently isolated microorganism, with 11 cases (68.7%); *Klebsiella oxitoca* was found in 3 of the 16 patients (18.7%), and *Enterobacter cloacae* was present in 2 cases (12.5%). None of the patients had ASB caused by *Proteus mirabilis*.

In conclusion, careful hygiene habits in diabetic women could present an easy and cost-free way to help prevent ASB and UTIs. Unfortunately, published studies of this kind are uncommon. We often forget that a patient's quality of life can sometimes be improved by adopting simple solutions.

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Response to Cantagallo and Castelli

We read with interest the letter of Cantagallo and Castelli (1), which describes the prevalence of asymptomatic bacteriuria (ASB) in women with diabetes before and after hygiene modifications. They showed that even after the modification of hygiene habits, diabetic women still had a 20.2% prevalence of ASB, which is comparable with the prevalence of ASB in our study group of diabetic women, but much higher than the prevalence of ASB in our nondiabetic control subjects (2). We would like to know why ASB was treated in these patients and how long they remained free from bacteriuria. In contrast to patients in the U.S. (3), most diabetic patients with ASB in Europe are not treated (4). Furthermore, many patients (with and without diabetes) have recurrent bacteriuria despite treatment (5,6). The contradiction in treatment recommendations between the U.S. and Europe is the result of a lack of follow-up studies of diabetic women with untreated ASB. In a long-term follow-up study of our diabetic patients, we hope to discover whether ASB affects renal function and whether treatment can prevent this.

Cantagallo and Castelli (1) underline specific hygiene habits that can help prevent ASB and urinary tract infections (UTIs). General measurements to prevent ASB and UTIs were previously described for all patients, including nondiabetic patients (7). Nevertheless, the authors are correct that most studies show results of trials with different antimicrobial treatment regimens and do not describe simple cost-free ways to prevent bacteriuria. Therefore, the study described in the letter by Cantagallo and Castelli (1) is a welcome addition to the research on ASB and UTIs in diabetic women.

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Catch-22

In response to the article by Rohlfing et al. (1), in which HbA_{1c} testing was suggested as a suitable screening test for undiagnosed diabetes, Herman et al. (2) took issue by relying on the 2-h glucose value on the oral glucose tolerance test (OGTT) of 11.1 mmol/l (200 mg/dl) as the "gold standard" for the diagnosis of diabetes, as previously described by many other studies evaluating the fasting plasma glucose concentration as the diagnostic criterion. We need to look closely at how this gold standard was initially selected and to reveal its subsequent relationship to HbA_{1c} levels. A total of 1,213 subjects were given OGTTs and followed for the development of retinopathy over the next 3–8 years (3). Of these subjects, 77 developed retinopathy, and the gold standard for the diagnosis was based on their 2-h glucose values. Analyzing the Third National Health and Nutrition Examination Survey data set, my colleagues and I have shown that ~70% of subjects with 2-h glucose values of 11.1–13.3 mmol/l (200–239 mg/dl) on the OGTT had normal HbA_{1c} levels (4). Because I believe that the diagnosis of diabetes is untenable in a person with a normal HbA_{1c} level, this raises serious questions about the validity of the OGTT gold standard, which is based on the results of only 77 subjects. After all, a number of prospective studies have clearly demonstrated that the microvascular complications of diabetes are associated with elevated HbA_{1c} levels and that intervening to lower these values results in less complications, and as pointed out by Rolfing et al. (5), there are no data "suggesting that normoglycemic individuals are at significant risk for development of diabetic complications, as long as GHb levels remain within the nondiabetic range." Are we not in a catch-22 situation by comparing diagnostic criteria for the diagnosis of diabetes with a glucose standard that is associated with a normal long-term index of glycemia in up to 70% of individuals?

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Response to Davidson

We appreciate the interest of M.B. Davidson (1) in our study on the use of GHb as a screening test for diabetes (2). We agree with the author's contention that "diagnosis of diabetes is untenable in a person with a normal HbA_{1c} level," because these individuals are not at significant risk for development and/or progression of diabetic complications. It is important to note, however, that GHb can only be a reliable indicator of outcome risks, and therefore a useful alternative to fasting plasma glucose or oral glucose tolerance testing for diabetes screening, if GHb results are directly traceable to those of the Diabetes Control and Complications Trial (DCCT) and the U.K. Prospective Diabetes Study (UKPDS), where relationships to outcome risks have been established (3,4).

As noted in our report, the American Diabetes Association Expert Committee on the Diagnosis and Classification of Diabetes Mellitus did not recommend the use of GHb for diabetes screening or diagnosis in 1997, mainly because of the "many different methods for the measurement of GHb," and because "nationwide standardization of the GHb test had just begun" (5). However, the National Glycohemoglobin Standardization Program (NGSP), initiated in 1996, has been highly successful in certifying GHb assay methods as traceable to the DCCT/UKPDS reference (6). Most GHb assay methods currently in use are NGSP-certified, and recent College of American Pathologists survey data show substantial improvement in the comparability of GHb results between various methods (7).

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Catch-22

A response to Davidson

> "Orr was crazy and could be grounded. All he had to do was ask; and as soon as he did, he would no longer be crazy and would have to fly more missions. Orr would be crazy to fly more missions and sane if he didn't, but if he was sane he had to fly them. If he flew them he was crazy and didn't have to; but if he didn't want to he was sane and had to."
>
> — *Catch-22*, Joseph Heller (1)

Davidson (2) argues that the plasma glucose (PG) obtained 2 h after a 75-g oral glucose load cannot be an appropriate criterion for the diagnosis of diabetes, because subjects with elevated 2-h PG levels may have normal HbA_{1c} levels, and the diagnosis of diabetes is untenable in people with normal HbA_{1c} levels. This line of reasoning presents an impasse, a "catch-22," yet it is not consistent with the way we have traditionally defined disease states.

Population studies have demonstrated both normal bell-shaped curve distributions and bimodal distributions of physiologic measures. When physiologic measures are normally distributed, values greater than or less than the mean plus 2 SDs have been used to define abnormal glucose tolerance. When physiologic measures are bimodally distributed, one distribution may be used to define normal and the other to define abnormal glucose tolerance. Numerous population studies have demonstrated that measures of glycemia are bimodally distributed (3). In such instances, the lower distribution defines normal glucose tolerance, and the upper distribution defines diabetes. When there are alternative measures that can be used to define normal and abnormal glucose tolerance, the optimal measure for diagnosis is that which provides the most clear-cut distinction between the two populations. We and others (3,4) have demonstrated that compared with fasting plasma glucose (FPG) and HbA_{1c}, the 2-h PG provides the best differentiation between normal and abnormal glucose tolerance.

We agree that diabetes reflects more than abnormal glucose levels. Diabetes confers a predisposition to unique microvascular and neuropathic complications. Clearly, it is reasonable to consider these risks when defining diabetes. Nevertheless, the argument that a small minority of patients with incident or prevalent retinopathy determines the diagnostic cut point for diabetes ignores the fact that both the presence and absence of complications determine sensitivity and specificity. Data from the entire population are informative. In addition, complications arise as a function of the degree and duration of hyperglycemia and as a result of individual susceptibility. Not everyone will develop complications. Consequently, the analysis of population distributions of glycemia, rather than the prediction of complications, may be the best approach to defining diabetes.

Finally, we believe that issues of diagnosis and treatment must be clearly distinguished. The first task is to make a diagnosis, and the second task is to contemplate therapy. Glucose homeostasis is the result of a complex feedback system involving a hormone, insulin, and its regulatory substrate, glucose. In endocrine systems, if autonomous hyperfunction is suspected, the diagnostic approach is to physiologically suppress the system. If hypofunction is suspected, the preferred diagnostic approach is to physiologically stimulate the system. To the extent that diabetes is a condition of absolute or relative insulin deficiency, a stimulated (2-h PG) rather than a basal measure (FPG or HbA_{1c}) is most likely to unmask the abnormality.

We are not persuaded by the argument that there is no value in labeling an abnormality if it is not severe enough to require treatment. Because treatment goals change over time, this approach is problematic. In addition, we disagree with the assertion that diabetes with normal HbA_{1c} levels does not require treatment. The Diabetes Control and Complications Trial found no evidence of any threshold below which a lower HbA_{1c} level was not associated with a lower risk of the development or progression of complications (5). These data suggest that a more aggressive treatment is beneficial.

In summary, we believe that Davidson's apparent catch-22 arises from the belief that "a diagnosis of diabetes is untenable in a person with a normal HbA_{1c} level" (2). Basing diagnostic cut points for diabetes on the 2-h PG level is supported by general principles of disease definition and endocrine testing, and the impasse is prevented if issues of diagnosis and treatment are distinguished.

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