

## OBSERVATIONS

## Remitting Diabetes

## A new genetic subgroup?

We describe a previously unreported clinical scenario of remitting diabetes in two young brothers who do not fit existing diagnostic classifications. They may represent a new genetic subgroup of diabetes.

Case 1 presented at 3.6 years with poor linear growth, polyuria, and polydipsia. Diabetes was diagnosed based on a blood glucose value of 11.5 mmol/l and an elevated HbA<sub>1c</sub> of 7.0% (normal 3.8–6.0). During 3 months' observation, hyperglycemia and an elevated HbA<sub>1c</sub> persisted. Working diagnosis was very early type 1 diabetes, and insulin was commenced (0.2 units · kg<sup>-1</sup> · day<sup>-1</sup>). HbA<sub>1c</sub> improved from 7.0 to 5.3%. However, linear growth did not improve.

The family also tested asymptomatic siblings and identified hyperglycemia in the 18-month-old brother. Diabetes was diagnosed on repeated blood glucose values >11 mmol/l and HbA<sub>1c</sub> 9.0%. Although thriving, there was concern of early type 1 diabetes, and he commenced insulin (0.2 units · kg<sup>-1</sup> · day<sup>-1</sup>). HbA<sub>1c</sub> normalized to 5.5% after 16 months. Two additional family members had glucose abnormalities: the 44-year-old father had impaired glucose tolerance (IGT) (glucose 6.4 mmol/l [0 min] and 10.4 mmol/l [120 min] in an oral glucose tolerance test [OGTT]; BMI 29 kg/m<sup>2</sup>), and the 74-year-old paternal grandmother was diagnosed with type 2 diabetes at age 60 years and is on metformin (not overweight, no diabetes complications). The mother's OGTT was normal.

No evidence of autoimmunity was found in either child (insulin, islet cell, and GAD antibodies). After age 1.6 and 2.3 years, respectively, insulin was ceased, as requirements had remained low with normal HbA<sub>1c</sub> and blood glucose. Both boys had OGTTs showing normal glucose tolerance. Interestingly, the older boy had hypoglycemia (glucose 2.0 mmol/l) at 120 min of OGTT, suggesting possible insulin secretion dysregulation.

After 2 years off insulin, HbA<sub>1c</sub> has remained normal (5.4–5.5%).

The cause of diabetes resolution in these boys remains unexplained. Transient hyperglycemia can occur during intercurrent illness, and is not associated with elevated HbA<sub>1c</sub>. Although type 1 diabetes was the initial diagnosis, their subsequent clinical course and absence of autoimmunity markers make this unlikely. Type 1 diabetes may have an extended honeymoon (i.e., partial remission), sometimes up to 2 years, but normal HbA<sub>1c</sub> off treatment 4 years after diagnosis is very unusual. IGT in the father and type 2 diabetes in the paternal grandmother is consistent with autosomal-dominant inheritance suggesting maturity-onset diabetes of the young (MODY); however, no MODY subgroups remit (1). While glucokinase mutations could explain the adults' hyperglycemia, neither child had fasting blood glucose (>5 mmol/l) effectively excluding MODY2. Case 1 tested negative for hepatocyte nuclear factor- $\alpha$  (HNF-1 $\alpha$ ) mutations. Transient neonatal diabetes remits but is excluded as they presented after age 3 months (1.5 and 3.6 years). A remitting form of atypical diabetes is described in black adolescent Americans (2) but not in whites or young children.

In summary, disappearance of diabetes in these young boys is unusual and does not fit clinically recognized syndromes. Two affected siblings suggest a novel genetic syndrome probably altering  $\beta$ -cell function. This could be a recessive condition with coincidental hyperglycemia in adults. Alternatively, it may represent different stages in a dominant disorder, with adults having undetected hyperglycemia during childhood, suggesting that the children may later relapse. This cyclical pattern of diabetes remission and relapse occurs in transient neonatal diabetes, and we hypothesize a novel genetic mutation causing a similar process. We would welcome reports of further cases of remitting diabetes, as they could provide further insights into this potential new genetic form of diabetes.

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## Seroconversion of GAD Antibody in "Unclassified" Diabetes With Long Duration of Disease

Latent autoimmune diabetes in adults (LADA) (1), or slowly progressive insulin-dependent diabetes mellitus (SPIDDM) (2), is a subtype of type 1 diabetes with a slowly progressive course. LADA, or SPIDDM, is diagnosed by the detection of islet-associated autoantibodies such as islet cell antibody (ICA) or GAD antibody (GADA) in the serum; moreover, patients with LADA are usually originally diagnosed as having type 2 diabetes. If islet-associated autoantibodies are not detected in the serum, these patients who are originally diagnosed as having type 2 diabetes cannot be diagnosed as having LADA and are followed as "unclassified" diabetes at present.

In clinical situations, if islet-associated autoantibodies are not initially detected in the serum, these cases are usually followed as type 2 diabetes or "unclassified diabetes" without reevaluation of autoantibodies because it is unknown whether islet-associated autoantibodies will appear later in the disease course. It has been reported that islet-associated autoantibodies are detected within 1 year after onset in ~15% of cases of "classical" type 1 diabetes without islet-associated autoantibodies at the onset of disease (3).

The following case patient, who was confirmed as not having GADAs at 31 years after the onset of diabetes and was followed as having “unclassified diabetes,” is a rare case in whom GADA was detected at 36 years.

The patient was diagnosed as having type 2 diabetes at age 47 years, had an HbA<sub>1c</sub> level of ~7%, and was being treated with a sulfonylurea (glibenclamide). However, glycemic control subsequently worsened despite being treated with 8.75 mg/day of glibenclamide, 150 mg/day of buformin, and 0.9 mg/day of voglibose, and she was admitted to the hospital at age 78. On admission, her height was 155 cm and her body weight was 38.8 kg (BMI 16.1 kg/m<sup>2</sup>), with no history of obesity. According to laboratory findings, her fasting plasma glucose level was 338 mg/dl and her HbA<sub>1c</sub> level was 10.1%. Her insulin secretion was also low (serum C-peptide level 0.3 ng/ml on fasting, 0.9 ng/ml at 2 h after breakfast, and 24-h urine C-peptide level 10.5 μg/day), thus requiring insulin therapy (total 16 units/day at discharge). Based on these findings, it was possible that she had SPIDDM; however, GADA was negative (detection limit <0.4 units/ml; 100% sensitivity and 100% specificity of the assay in the GADA proficiency test [Immunology of Diabetes Workshop], lab ID no. 305), resulting in the diagnosis of “unclassified diabetes.”

At age 83, she was again admitted to the hospital because of acute myocardial infarction. On the second admission, her body weight was 39.4 kg (BMI 16.4 kg/m<sup>2</sup>). Laboratory results indicated that her fasting plasma glucose level was 198 mg/dl, her HbA<sub>1c</sub> level 7.2%, and her 24-h urine C-peptide level 12.5 μg/day. Surprisingly, GADA, which was negative at the time of her first admission, was now positive (144 units/ml), although insulinoma-associated protein 2 antibody was negative. Furthermore, HLA typing detected DR4, which is considered to be a susceptible HLA type for type 1 diabetes (other HLA types: A24, A26, B35, B55, DR8). Based on these observations, she was diagnosed as having SPIDDM.

The frequency of seroconversion of GADA in diabetic patients who were originally diagnosed as having type 2 diabetes is not known, and a more extensive large-scale study is needed to clarify the frequency of seroconversion in this type of diabetes. Based on this case, however, we

would like to emphasize that it is essential to measure islet-associated autoantibodies such as GADA periodically for the precise diagnosis of diabetes, especially in patients given the diagnosis of “unclassified diabetes,” even if the patient has suffered from diabetes for a long period of time.

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## Normal β-Cell Function in Post-Liver Transplantation Diabetes Treated With Tacrolimus

Use of immunosuppressive agents is mandatory after organ transplantations but may be complicated by the development of hyperglycemia or diabetes. The prevalence of diabetes after liver transplantation in adulthood ranges

from 13.6 to 33% (1,2) with a progressive increase in risk that parallels the time after transplant (3). Tacrolimus, a calcineurin inhibitor, is a recent immunosuppressive agent largely used to prevent and treat transplant rejections often following other immunosuppressive failures (4–5). The incidence of post-transplant diabetes mellitus (PTDM) in tacrolimus-treated patients was significantly higher than in those treated with cyclosporine (6,7) and in pediatric-age patients (8). Usually PTDM refers to renal recipients, and only one pediatric case has been reported after liver transplantation (9). PTDM in tacrolimus-treated patients has been related to reduced pancreatic β-cell function and is generally reversed by dose reduction (10–11).

Here we describe the β-cell function in a 15-year-old male liver transplant recipient treated with tacrolimus at the onset of PTDM and 1 year after remission. He underwent liver transplantation at age 7 years for Alagille Syndrome and was subsequently treated with steroids and cyclosporine. Because of acute rejection at age 15, treatment with cyclosporine was switched to tacrolimus and mycophenolate mofetil. One month later, he presented symptomatic hyperglycemia (42 mmol/l) without ketoacidosis; his BMI was 21.3 kg/m<sup>2</sup>, and his HbA<sub>1c</sub> was 9.4% (normal values 3.3–6.0). Initially, the patient required 1.8 units · kg<sup>-1</sup> · day<sup>-1</sup> of insulin. β-Cell function was investigated by glucagon stimulation—basal C-peptide levels were 0.90 nmol/l (normal values 0.165–0.993) and 1.67 nmol/l after 6 min (relative increase 186%, normal values 130–377%). Tacrolimus was substituted by cyclosporine while continuing other immunosuppressive agents. This allowed a gradual decrease of insulin and its withdrawal within 5 weeks. One year later, an oral glucose tolerance test showed normal glucose tolerance (basal levels 4.5 mmol/l, peak 7.7). In addition, stimulated C-peptide response was normal (relative increase 231%), fasting insulin level was 54.6 pmol/l, and HbA<sub>1c</sub> was 5.6%.

The absence of ketoacidosis and the presence of normal C-peptide levels during tacrolimus treatment indicate that β-cell function was normal in our patient, not confirming the β-cell impairment ascribed to tacrolimus (9,10). The high insulin dose required suggests that insulin resistance, which was not due to steroids

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since they were never withdrawn from therapy, may have played a role. Furthermore, because proneness to diabetes depends on several genetic mechanisms, it is possible that immunosuppressive agents play only a triggering role in PTDM. In addition, since most PTDM cases were described after renal transplantations, we cannot exclude a putative role of the transplanted liver itself on the abnormal peripheral insulin action. With the spreading use of tacrolimus in liver transplantation, pediatric diabetes practitioners will probably face many new cases of PTDM.

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## Definition of Microalbuminuria in First-Morning and Random Spot Urine in Diabetic Patients

Measurement of albumin excretion in a 24-h urine collection has long been the “gold standard” for quantitative evaluation of albuminuria in diabetic patients; however, collection errors due to improper timing and missed samples may lead to significant over- and underestimation of albuminuria. For convenience and consistency, the American Diabetes Association (1) and the National Kidney Foundation (2) have recently recommended measurement of albumin-to-creatinine ratio (ACR) in a random spot urine collection for diagnosis of microalbuminuria. Microalbuminuria is diagnosed if ACR ranges between 30 and 300 mg/g creatinine. The guidelines recommended using a first-morning sample because of the potentially higher correlation with 24-h albumin excretion, but a random sample is considered acceptable if a first-morning specimen is not available. Measurement of ACR using a first-morning or random urine sample may differ significantly, as exercise stress, diurnal variation, and other factors may affect urinary albumin excretion. We provide data from a cross-sectional study

evaluating potential differences in ACR obtained from first-morning and random spot urines collected on the same day.

A total of 717 adult diabetic patients with and without nephropathy were recruited from the outpatient clinic of the Diabetes Center, Tokyo Women’s Medical University Hospital, Tokyo, Japan. Patients were instructed to bring a first-morning urine specimen to the clinic and then provide a random urine specimen immediately upon arriving at the clinic on the same day. ACR was calculated from urinary albumin and creatinine concentrations determined using radioimmunoassay and Jaffe’s method, respectively. Paired samples with a random urinary ACR of more than 1,000 mg/g were excluded to provide a more accurate range for estimating the relationship between measurements.

Paired samples were analyzed from 668 patients (289 women and 379 men, mean age 58 ± 12 years, 95% with type 2 diabetes). The majority (75%) of random spot urine was collected during a morning visit (8:30 A.M. to 12:00 P.M.). There was a strong relationship between ACRs measured from first-morning and spot urine samples, yielding a linear correlation on a logarithmic scale:  $\log_{10} \text{ACR (first-morning sample)} = 0.8589 \cdot \log_{10} \text{ACR (random spot sample)} - 0.0604$  ( $r = 0.871$ ). Applying this equation, ACR values of 30–300 mg/g in a first-morning urine specimen would correspond to values of 51–391 mg/g in random spot collection. Using the ACR cutoff value of 30–300 mg/g, 135 patients (20%) would receive a diagnosis of microalbuminuria based on first-morning urine, whereas 234 patients (35%) would receive this diagnosis based on a random spot collection.

This rather large discrepancy between ACR from first-morning and random spot urine may have important implications in the diagnosis of microalbuminuria in diabetes. We advocate strict adherence to the use of first-morning urine or possibly an upward adjustment of the range for diagnosis of microalbuminuria using ACR from random spot urine. Further analysis of the relationship of ACR in first-morning and random spot urines to 24-h urinary albumin excretion, as well as their value in predicting future development of clinical proteinuria, is required.

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## Lipid Levels in Black South Africans With Type 2 Diabetes

### Dispelling misconceptions

**D**yslipidemia in type 2 diabetes typically comprises hypertriglyceridemia and reduced HDL cholesterol, usually associated with hypercholesterolemia (1). Relatively little is known about its occurrence in developing African communities, where the prevalence of type 2 diabetes may escalate dramatically (2). This is important because dyslipidemia constitutes a major risk factor for coronary artery disease (CAD) in type 2 diabetes (3). We therefore assessed serum lipids of South African blacks with type 2 diabetes of differing socioeconomic status and compared levels with those of patients two decades earlier. Our initial expectations were that dyslipidemia would be substantially greater in the higher socioeconomic group due to affluence and that lipids would have risen considerably over time because of increasing urbanization.

Our low socioeconomic community comprised 445 black African patients (241 women and 204 men) with recently diagnosed type 2 diabetes studied between 1994 and 1996. They attended the

diabetes clinic at Johannesburg Hospital and were mostly domestic workers, laborers, and pensioners who were overweight and not undergoing lipid-lowering therapy. The higher socioeconomic cohort consisted of 82 patients (32 women and 50 men), also with recently diagnosed type 2 diabetes studied during 2001–2003. They attended a private diabetes clinic in the same city and were mainly civil servants, clerks, and executives. Again, the majority was overweight and not receiving hypolipidemic drugs. Finally, we reevaluated lipid data from 47 African patients (mainly women, mean age 55 years) with type 2 diabetes who attended Johannesburg Hospital complex in 1976; they were predominantly domestic workers.

Venous blood was collected at ~0800, and although not formally fasting, most subjects had not eaten overnight. Serum was analyzed for total cholesterol, HDL cholesterol, and triglycerides by automated enzymatic methods (4). LDL cholesterol was calculated using the Friedewald formula. (These differed from the 1976 automated techniques [5].) Long-term diabetes control was assessed by HbA<sub>1c</sub> concentrations. Statistical analysis of data between patient groups utilized the unpaired *t* test, with

*P* < 0.05 after Bonferonni adjustment being significant.

Biochemical data (Table 1) showed unimpressive dyslipidemia in women with no significant differences, although total and LDL cholesterol tended to be lower and triglycerides higher in the higher socioeconomic cohort. For men, similar trends emerged (*P* < 0.05 for triglycerides). In both sexes, diabetes control was significantly worse in the Johannesburg Hospital setting.

Comparing mean total cholesterol and triglyceride concentrations in African diabetic patients (three-quarters of them women) from the 1976 survey with African diabetic women attending the same clinic two decades later, serum cholesterol had risen from  $4.8 \pm 1.1$  to  $5.3 \pm 1.3$  mmol/l (*P* < 0.01). Serum triglycerides, however, had not changed significantly ( $1.2 \pm 0.5$  to  $1.5 \pm 1.1$  mmol/l).

Dyslipidemia in the higher socioeconomic cohort of South African blacks with type 2 diabetes was unimpressive and not substantially greater than in their less sophisticated counterparts, apart from mild hypertriglyceridemia; importantly, total and LDL cholesterol tended to be lower. This was our first misconception to be corrected and is explainable by two factors: tighter metabolic control and the likeli-

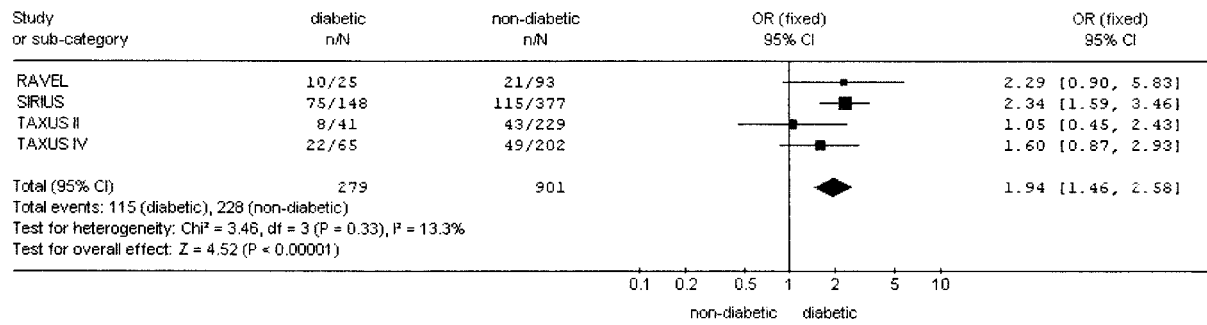
**Table 1—Demographic, anthropometric, and biochemical characteristics of black South African patients with type 2 diabetes of differing socioeconomic status**

	Johannesburg hospital 1994–1996 (Low socioeconomic community)	Private diabetes clinic 2001–2003 (Higher socioeconomic cohort)
<b>Women</b>		
<i>n</i>	241	32
Age (years)	53.6 ± 5.4	53.9 ± 10.8
BMI (kg/m <sup>2</sup> )	31.7 ± 6.6	30.1 ± 5.9
Total cholesterol (mmol/l)	5.3 ± 1.3	4.9 ± 1.0
LDL cholesterol (mmol/l)	3.3 ± 1.4	3.1 ± 1.0
HDL cholesterol (mmol/l)	1.3 ± 0.4	1.4 ± 0.5
Triglycerides (mmol/l)	1.5 ± 1.1	1.9 ± 2.4
HbA <sub>1c</sub> (%)	9.6 ± 3.2*	7.9 ± 1.5
<b>Men</b>		
<i>n</i>	204	50
Age (years)	52.6 ± 4.9*	49.5 ± 9.0
BMI (kg/m <sup>2</sup> )	27.6 ± 4.9	28.3 ± 4.6
Total cholesterol (mmol/l)	4.9 ± 1.3	4.6 ± 1.2
LDL cholesterol (mmol/l)	3.0 ± 1.1	2.8 ± 1.0
HDL cholesterol (mmol/l)	1.2 ± 0.4	1.2 ± 0.7
Triglycerides (mmol/l)	1.6 ± 1.2*	2.2 ± 1.2
HbA <sub>1c</sub> (%)	9.3 ± 3.3*	8.5 ± 2.1

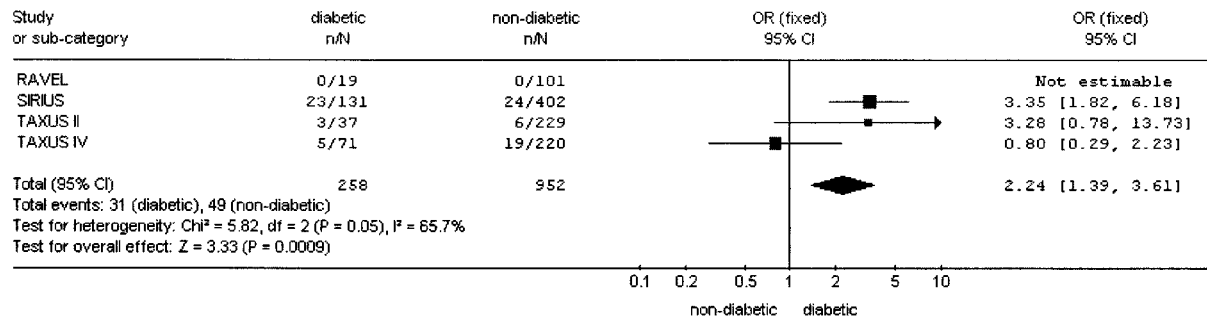
Data are means ± SD. \**P* < 0.05 compared with private diabetes clinic.



### Bare-metal stent



### Drug-eluting stent



**Figure 1**—Meta-analysis of four trials comparing the effects on restenosis of bare-metal stents and drug-eluting stents in diabetic and nondiabetic patients.

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## Major Diabetes Complications Have an Impact on Total Annual Medical Cost of Type 2 Diabetes

**B**randle et al. (1) found that the occurrence of diabetes-related comorbidities in type 2 diabetic patients are associated with an increase in average annual medical cost.

To investigate the medical cost attributable to type 2 diabetes, we conducted a retrospective longitudinal cost-of-care study in a diabetologic center in Italy. A priori, we estimated to validly enroll 300 type 2 diabetic patients with at least 1 year of follow-up. To this aim, we randomly selected 315 type 2 diabetic patients from a base of ~2,000 diabetic patients attending the diabetologic center of Portogruaro during the period from January 2001 to August 2002.

Cost included hospitalizations, visits, diagnostics, and pharmacological therapies and were quantified in the perspective of the National Health Service. We ex-

tracted clinical and demographic information from the electronic database and performed extensive chart review, including the comorbidities retinopathy, cardiopathy (coronary heart disease), vasculopathy (other than coronary heart disease), and nephropathy.

We analyzed the association between diabetes-related comorbidities and average annual medical costs using univariate and multiple linear regression analyses. In the linear regression analysis, cost was transformed using the square-root transformation to better fit a Gaussian distribution.

Sixteen type 2 diabetic patients were excluded because it was found that their follow-up period was <1 year; the main reasons were premature mortality and loss to follow-up. A total of 299 type 2 diabetic patients were considered for this analysis and followed-up for an average of 476 days, totaling 520 person-years of observation. Their mean ( $\pm$ SD) age was  $68.6 \pm 8.8$  years, and 201 (67.2%) were men. The mean systolic blood pressure, diastolic blood pressure, total cholesterol, HDL cholesterol, HbA<sub>1c</sub>, and Hb levels were  $152.5 \pm 20.9$  mmHg,  $82.7 \pm 10.0$  mmHg,  $195.5 \pm 41.6$  mg/dl,  $50.2 \pm 20.3$  mg/dl,  $7.1 \pm 1.5\%$ , and  $13.9 \pm 1.5$  g/dl, respectively. The average annual cost of care was €1,909.67 (i.e., \$2,425 U.S.; exchange rate, 1 Euro = \$1.27 U.S.); 52% of costs were attributable to drugs, 28% to hospitalizations, 11% to diagnostics, and 9% to visits.

A total of 101 (33.8%) type 2 diabetic patients were free of diabetes-related comorbidities, 117 (39.1%) had one complication, and 81 (27.1%) had two or more complications. The more frequent complication was vasculopathy, which affected 89 (29.8%) type 2 diabetic patients, followed by cardiopathy (79 [26.4%]), retinopathy (66 [22.1%]), and nephropathy (65 [21.7%]).

The annual medical costs increased with the number of complications from €1,039.59 (\$1,320 U.S.) to 1,808.17 (\$2,296 U.S.) and to 3,141.21 (\$3,989 U.S.) in type 2 diabetic patients with none, one, and two and more complications, respectively, with the association being statistically significant in both univariate (Kruskal-Wallis test, 73,035;  $P < 0.0001$ ) and multiple linear regression analyses ( $R^2 = 0.21$ ;  $F$  test 82.5,  $P < 0.0001$ ).

We could not assess the impact of di-

agnosis on cost, since the care of type 2 diabetic patients developing end-stage renal disease is not controlled by the diabetologic center.

We did not consider the cost of supplies for self-monitoring of blood glucose, which is, at any rate, minimal ( $\sim$ €100  $\cdot$  patient<sup>-1</sup>  $\cdot$  year<sup>-1</sup>) and is not related to the type of complication.

Our study confirms the findings of Brandle et al. regarding the annual medical cost and its determinants in type 2 diabetic patients. Strategies aimed at preventing the onset of diabetes complications are likely to reduce medical costs in the long term, while improving patients' health.

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## Normal Insulin Sensitivity During the Late Preclinical Stage of Type 1 Diabetes

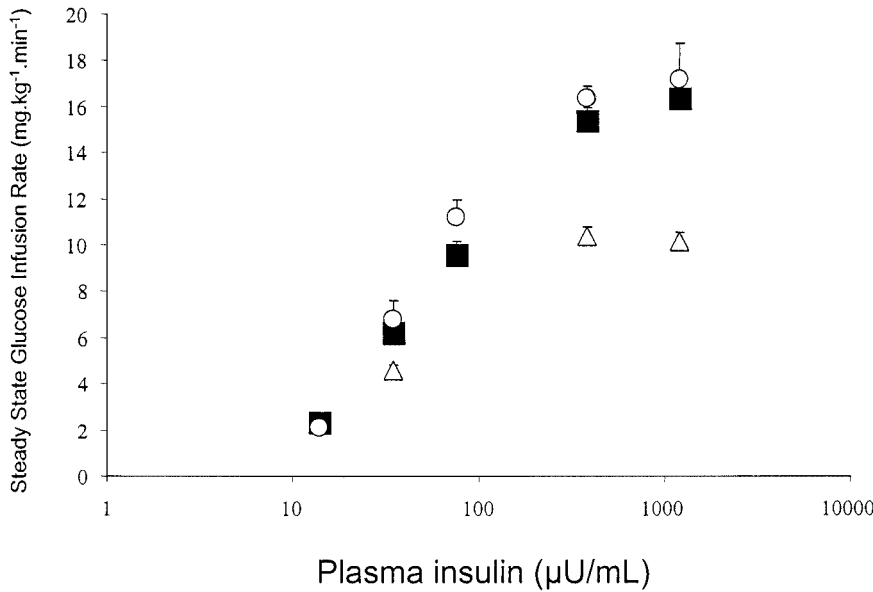
In most cases, type 1 diabetes is the late consequence of a  $\beta$ -cell autoimmune destruction leading to absolute insulin deficiency (1). At onset of clinical diabetes,  $\beta$ -cell mass is thought to be reduced by 80–90% (2), and 73% of adult patients have ketosis or ketoacidosis at diagnosis

(3). Patients with type 1 diabetes have major defects in insulin sensitivity at diagnosis of overt diabetes (4–8). However, the fact that pre-diabetic patients can maintain normal blood glucose levels in spite of dramatically low insulin secretory capacities suggests that their insulin sensitivity is normal.

Here we report that insulin sensitivity, measured by the glucose clamp method in nine patients, remains normal even during the very late preclinical stage of type 1 diabetes. None of these patients had clinical symptoms of overt diabetes, spontaneous weight loss, or ketosis before or at the time of the study. Mean age at entry in the study was 27 years (range 20–41). The mean BMI was 20.9 kg/m<sup>2</sup> (range 16.3–23.2). All patients were islet cell antibody positive, and seven of eight tested had at least one susceptibility HLA haplotype. Mean fasting glucose level was  $7.2 \pm 1.3$  mmol/l (range 5–9.6). Of the eight patients who met the criteria for diabetes, four had fasting blood glucose level <7 mmol/l; in the ninth patient, oral glucose tolerance test disclosed impaired glucose tolerance. The mean HbA<sub>1c</sub> level was  $6.4 \pm 0.8\%$  (range 5.3–7.8; normal values  $5.0 \pm 0.5\%$ ). The sum of 1- and 3-min plasma insulin levels after the intravenous glucose tolerance test was  $15.3 \pm 5.8$  mU/l (range 11–25).

Four patients were treated with insulin immediately after the metabolic explorations reported here. Four others have initiated permanent insulin therapy within 24 months of follow-up. The last patient was still non-insulin dependent when last seen 1 year after the study.

During clamp studies, the insulin dose-response curve of preclinical type 1 diabetic subjects was superimposable to that of 20 healthy control subjects. Maximal glucose infusion rate, at a plasma insulin level of  $1,400 \pm 120$  mU/l, was  $17.2 \pm 1.6$  mg  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup> (Fig. 1). It was  $16.4 \pm 0.6$  mg  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup> in 20 control subjects at a similar plasma insulin level:  $1,500 \pm 100$  mU/l. By contrast, the maximal glucose infusion rate was significantly lower in 15 patients with symptomatic diabetes of recent onset ( $11 \pm 1.4$  mg  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>,  $P = 0.003$  by Mann-Whitney  $U$  test). These results confirm, at an even later stage of the natural history of the disease, those observed in a substudy of the Diabetes Prevention Trial-1 (9). Thus, the onset of overt clinical diabetes may be triggered by the addition of insu-



**Figure 1**—Glucose clamp study. Dose-response curves obtained during the euglycemic-hyperinsulinemic clamps in patients with preclinical diabetes (○). For the purpose of comparison, results obtained in control subjects (■) and in patients with symptomatic diabetes studied within 1–3 week after diagnosis (△) are shown. The latter two are from ref. 7.

lin resistance to insulin deficiency; the triggers may be external or internal factors. In this respect, the seasonal peaks of the incidence of diabetes (10) suggest that viral infections may play a role in the very final act of the preclinical phase by triggering insulin resistance and metabolic storm. The respective parts of insulin deficiency and insulin resistance may be determinants for the onset and duration of the honeymoon period.

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COMMENTS AND RESPONSES

**Comparative Study of Prognostic Value for Coronary Disease Risk Between the U.K. Prospective Diabetes Study and Framingham Models**

Response to Protopsaltis et al.

The comparison by Protopsaltis et al. (1) of the Framingham risk equations and the U.K. Prospective Diabetes Study (UKPDS) risk engine as predictors of coronary risk in diabetes is of interest, as previous analyses have shown that the Framingham equations can underestimate absolute coronary heart disease (CHD) risk in diabetic subjects by a factor of 2 or more (2,3). The sensitivity and specificity analyses presented by the authors, however, are difficult to interpret because of methodological concerns. They examined the incidence of coronary angiographically determined CHD but not “hard” CHD (defined as fatal or nonfatal myocardial infarction) as estimated by the UKPDS risk engine (4). Their use of a retrospective survivor cohort introduces bias, as patients with fatal CHD will have been excluded. This may explain the apparent poor performance of HbA<sub>1c</sub> as a risk predictor, since myocardial infarction is more often fatal in those with higher HbA<sub>1c</sub> (5). The use of a mixed cohort



of type 1 and type 2 diabetic subjects is problematic because the UKPDS risk engine, a type 2 diabetes-specific risk calculator, has not been evaluated in subjects with type 1 diabetes. The UKPDS analysis (6) cited by the authors shows that a 1% decrement in HbA<sub>1c</sub> was associated with a 37% risk reduction in microvascular disease, not a 10-fold reduction (90%).

A full validation of a risk model requires a prospective study of a cohort to which the model is applicable. In the case of the risk engine, a cohort with type 2 diabetes and suitable demographic characteristics (3) is needed. Covariates should be measured at the beginning of follow-up, and the cohort should be monitored for the end points addressed by the model. In the case of the risk engine, these end points would be fatal and nonfatal myocardial infarction and sudden cardiac death. Publication of the observed rate of CHD in the cohort and of the mean predicted rate according to the model would then allow an evaluation of risk tools against true rates of heart disease. An ideal study would also adjust for assay differences, if appropriate, and for regression dilution and competing risks if necessary.

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## Comparative Study of Prognostic Value for Coronary Disease Risk Between the U.K. Prospective Diabetes Study and Framingham Models

Response to Stevens and Holman

We appreciate the comments of Stevens and Holman (1) regarding our analysis comparing the accuracy of the U.K. Prospective Diabetes Study (UKPDS) (2) and Framingham models in the prediction of 10-year risk for coronary artery disease (CAD) in diabetic patients. In our letter, we mentioned that the diagnosis of CAD was established by coronary angiography. In addition, this study was performed in a cohort of patients with type 2 diabetes and included a 10-year follow-up. In the sample of cases with myocardial infarction who were examined during this analysis, fatal and nonfatal cases were included.

We agree that this analysis was retrospective with its disadvantages, and it is absolutely equitable that the variables used by both of these models should have been determined at the beginning of follow-up. However, it is obvious that this study was designed as a retrospective, since the UKPDS prediction model has recently constituted a useful cardiovascular disease (CVD) risk prognostic model. In the epidemiologic analysis of the UKPDS, Stratton et al. (3) showed that the effect of HbA<sub>1c</sub> values on microvascular complications over a range of 5.5–11% was nearly 10-fold, whereas the effect of HbA<sub>1c</sub> on myocardial infarction incidence, over the same range of HbA<sub>1c</sub>, was 2-fold.

Regarding the effect of HbA<sub>1c</sub> on

myocardial infarction incidence, the range of HbA<sub>1c</sub> was from 5.5 to 11%, so we can say that 11% (upper limit) is two times 5.5% or 1 more time 5.5% (lower limit). Therefore 1 refers to one time and not 1%. The percent symbol was added by mistake.

Moreover, as the UKPDS study showed, improved glycemic control had no significant impact in cardiovascular outcomes in patients with type 2 diabetes. The Veterans Affairs Cooperative Study (4) also showed a nonstatistical significant deterioration of CVD events in intensively treated patients compared with those receiving standard treatment.

The exception for reducing mortality from myocardial infarction was in the overweight UKPDS cohort patients treated with metformin (5). However, metformin use was not associated with lower blood glucose levels compared with insulin or sulfonylureas, so it can be assumed that the cardioprotective effects of metformin could be interpreted by its well-known actions in the atherothrombotic risk profile (6) and blood pressure levels through nonglycemic pathways.

Summarizing the previously epidemiologic data, since coronary heart disease is a multifactorial disease and glycemic control is not significantly associated (7,8) with reduced CVD risk in diabetic patients, it can be assumed that the small contribution of chronic hyperglycemia (HbA<sub>1c</sub>) at the incidence of macrovascular complications has a respectively weak contribution on the calculation of coronary heart disease risk by the UKPDS mathematical model.

Finally, we absolutely agree with Stevens and Holman that prospective studies will be needed to determine the validity of the predictive value for both of these models.

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pound necessary for a beneficial health effect. One of the main reasons for this is the fact that nutrient composition tables are under continuing development. A common alternative technique, which we used in the present study, is to rank the study population according to the intakes. In such an approach, the validity of the results depends on the accuracy of the ranking, so absolute intake levels are less important.

In our analyses, the assessment of  $\beta$ -cryptoxanthin intake was based on analyzed values of Finnish foods available in the late 1980s. However, more recent estimates of the  $\beta$ -cryptoxanthin content of oranges have been shown to be much higher than those used in the present study (average orange intake 29 g/day). To ensure the accuracy of our analyses, we recalculated the  $\beta$ -cryptoxanthin intake using more recent published values (3,4). We calculated the  $\kappa$  coefficient between quartiles of the recalculated and the original variables and noted a high level of agreement between these two variables ( $\kappa = 0.9$ ), suggesting that the study participants are very similarly ranked using either the original or the recalculated  $\beta$ -cryptoxanthin intake values. Thus, the inverse association between  $\beta$ -cryptoxanthin intake and diabetes risk presented in our article is justified.

In conclusion, we suggest that the significant inverse association between the intake of  $\beta$ -cryptoxanthin and the risk of type 2 diabetes observed in our study is a valid finding. The importance of this finding in the prevention of type 2 diabetes, however, remains to be established.

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### Twice-Daily NPH or Mixture Insulins Versus Triple Therapy: Apples Versus Oranges

Response to Poulsen et al.

**P**oulsen et al. (1) recently demonstrated that triple therapy (metformin, rosiglitazone, and preprandial insulin aspart) lowered HbA<sub>1c</sub> levels much better than twice-daily NPH or MIX insulin in type 2 diabetic patients. They then claim that the reason for this improvement, compared with the patients treated with insulin alone, is the superiority of specifically treating the three pathophysiological components of type 2 diabetes (peripheral insulin resistance, hepatic insulin resistance, and impaired glucose-stimulated insulin secretion). Given the design of the study, this conclusion is suspect for two reasons.

First, the glycemic goals for the two groups were different. The goals for patients receiving only insulin were a preprandial value of 5–7 mmol/l. The goal for patients receiving triple therapy was a postprandial value of 5–7 mmol/l. Achieving a postprandial goal of 5–7 mmol/l will necessarily lead to better control than achieving the same goal preprandially (since in the latter situation the postprandial glucose concentrations will obviously be higher).

Second, twice-daily NPH injections

are a poor insulin regimen to achieve near euglycemia because there is no short- or rapid-acting insulin to blunt postprandial hyperglycemia. (The authors acknowledge this in their discussion.) How many of the eight patients in the control group were on twice-daily NPH insulin? Even the ones on MIX insulin (I assume this is a premixed insulin) are not on an optimal insulin regimen for achieving near euglycemia. One example illustrates this point. How does one adjust the MIX insulin dose in a patient whose preprandial glucose concentrations before supper are in the lower part of the goal range but whose preprandial lunch values exceed the goal range?

For both of these reasons one would expect higher postprandial glucose concentrations in the control group receiving only insulin (which is borne out in Fig. 2A) and consequently higher HbA<sub>1c</sub> levels. Hopefully these issues will not be ignored in subsequent long-term studies.

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### The Combined Effect of Triple Therapy with Rosiglitazone, Metformin, and Insulin Aspart in Type 2 Diabetic Patients

Response to Poulsen et al.

I have some concerns regarding the results of Poulsen et al.'s (1) study, which suggested that triple therapy with insulin aspart, metformin, and rosiglitazone was superior to continuing treatment



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## A Randomized Trial Evaluating a Predominantly Fetal Growth-Based Strategy to Guide Management of Gestational Diabetes in Caucasian Women

Response to Schaefer-Graf et al.

Schaefer-Graf et al. (1) rightly suggest that the management of women with gestational diabetes mellitus (GDM) should be based on more than glycemic factors alone. However, the study in which they conclude that strict glycemic control is not useful in the absence of the measurements of fetal overgrowth has two unusual features.

The authors' criteria for diagnosing GDM are lower than those of the World Health Organization or the American Diabetes Association, and they may be including women who could be considered normal. This is supported by the fact that there is little difference between the rate of large-for-gestational-age (LGA) babies in both their groups (12.1% above the 90th percentile) and that of the defining nor-

mal population (10%). These women may not have been equally represented in the two groups, as 30% more women in the ultrasound-defined group met their criteria for insulin therapy.

More importantly, the women with larger babies were treated more aggressively. Because their outcome was not different from less aggressively treated women without initially large babies, there is the possibility that the latter might have done better if they had been using the same glycemic targets as the women with large babies. They certainly had higher fasting glucose concentrations, and more of the LGA babies were born to women who did not receive insulin in either group. At the very least, the protocol favors the authors' hypothesis that insulin intervention before the onset of fetal overgrowth is not helpful.

Jovanovic (2) draws attention to the discrepancy in glucose targets but worries that her own policies, based on strict glycemic control and resulting in a lower macrosomia rate in her GDM population than in the local background population, may have achieved this at the cost of an increase in small-for-gestational-age (SGA) babies. For us, in a clinic of predominantly African and Caribbean background, SGA is not an issue. Using Jovanovic's protocols in women diagnosed by World Health Organization criteria, our SGA rate is <5%. Because SGA is defined as babies in the lowest 10th percentile, our current rate is lower than that of the background population.

Schaefer-Graf et al.'s study supports the use of strict glycemic control in women with demonstrably large babies. This is valuable evidence that such problems may respond to intervention with insulin even after the onset of fetal overgrowth. Reassuringly, none of the differences in the rates of SGA in the study approached significance. We would not, therefore, support the authors' suggestion that we abandon glycemic indications for insulin therapy in our population until a randomized prospective trial using similarly strict glucose targets in all groups shows that it does more harm than good.

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2. Jovanovic L: Never say never in medicine: confessions of an old dog (Editorial). *Diabetes Care* 27:610–612, 2001

## A Randomized Trial Evaluating a Predominantly Fetal Growth-Based Strategy to Guide Management of Gestational Diabetes in Caucasian Women

Response to Amiel and Blott

We appreciate Amiel and Blott's (1) interest in our study (2) and thank them for their helpful discussion. They rightly pointed out that the diagnostic criteria used in Germany at the time of our study had been lower than those of the American Diabetes Association. We were also aware that we treated some women who would have been considered healthy in other countries. To demonstrate that the fetal growth-based approach is also safe for women with a more severe glucose intolerance, we repeated the analysis for a subgroup of women who fulfilled the diagnostic criteria of Carpenter and Coustan (3) (80% of our population). Again, there was no adverse outcome in the ultrasound group. The limitation to women who qualified for gestational diabetes mellitus (GDM) based on Carpenter and Coustan criteria diminished the difference in the rate of insulin therapy. Because of the higher degree of glucose intolerance in these women, more women qualified for insulin therapy in the standard group. We also

realized that in the whole population, the rate of women who met the criteria for insulin was higher in the ultrasound than in the standard group. However, this was not because of an unequal representation of fetal macrosomia, as suggested by the authors. The rate of an abdominal circumference of >75th percentile at entry was not different between both groups. It was more likely due to our low diagnostic criteria, which included women with a low degree of glucose intolerance and, therefore, less frequent need of insulin. The low rate of large-for-gestational-age (LGA) babies was an effect of intensive treatment. The studies of Langer et al. (4) and Buchanan et al. (5) demonstrate that a normal LGA rate can be achieved in GDM when we aim for a very tight control.

We were very grateful that Lois Jovanovic's comment (6) emphasized the aspect of an increased risk for intrauterine growth retardation in some women with GDM. When we discuss treatment strategies for GDM, we always focus on how to reduce neonatal macrosomia. When we did a subanalysis comparing the outcome of women with hyperglycemia but normal fetal growth treated with (standard group) or without (ultrasound group) insulin, we also attempted to determine whether withholding insulin would increase the LGA and cesarean section rates. We were surprised when we realized the high rate of SGA in the standard group. The overall rate of SGA was similar in both study groups. We did not conclude that the policy of strict glycemic control is harmful for the general population with GDM. We suggested the use of an additional test, the measurement of the fetal abdominal circumference, to decide who will benefit and for whom a tight glucose control might be harmful due to a reduction of the maternal fuel supply to the fetus. Although the differences between the groups were obvious, when we looked at the outcome of the women who were treated differently according to the study protocol, the small sample sizes resulting from the subanalysis impaired our possibilities of an adequate statistical analysis. In the future, we hope to initiate and cooperate in multicenter studies to gather more evidence to prove our results.

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### Multiple Symmetric Lipomatosis: A Paradigm of Metabolically Innocent Obesity?

Response to Haap et al.

The study of Haap et al. (1) on two patients with multiple symmetric lipomatosis (MSL), also known as the Launois-Bensaude Syndrome, adds interesting new insights into a condition still poorly understood.

As for the conclusions drawn concerning insulin sensitivity in patient 1, we would like to suggest some caution. Our study group has also measured the insulin sensitivity index (ISI) in three subjects

with MSL with the euglycemic-hyperinsulinemic clamp and found the ISI to be higher in one and lower in two male subjects in comparison with sex- and BMI-matched control subjects (2). The good insulin sensitivity in patient 1 in the study of Haap et al. may indeed be related to the low visceral fat mass in this very patient, but it is rather questionable whether this finding is typical in MSL. From five patients with MSL identified in our clinic, computed tomographies of the abdomen had been performed in two case subjects, and the degree of visceral fat was described as comparable with that of healthy subjects. In a systematic evaluation of the fat mass and deposition in 18 patients with MSL by computed tomography, Enzi et al. (3) also did not describe a distinct reduction of visceral fat in these patients. Given this and the considerable phenotypical and clinical variability in patients with MSL (4), the conclusion of a good insulin sensitivity in MSL patients should not be generalized. Studies in larger populations are mandatory, although not easily performed due to the rareness of the disease. In a literature search of our own, we identified about 400 cases published since the first description by Brodie in 1846 (5).

One further aspect on MSL seems worth mentioning: three of the five patients with MSL in our clinic had obstructive sleep apnea syndrome (OSAS). We recently identified (5) the presence of OSAS as an independent risk factor contributing to insulin resistance. Thus, the investigation for OSAS in MSL patients might also be useful in the discussion of insulin sensitivity and of other metabolic aspects of MSL.

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## Multiple Symmetric Lipomatosis: A Paradigm of Metabolically Innocent Obesity?

Response to Harsch, Schahin, and Wiedmann

**W**e have recently suggested (1) that patients with multiple symmetric lipomatosis (MSL) may represent a paradigm for metabolically innocent fat accumulation. Harsch and colleagues (2,3) raise some justified words of caution with respect to the generalization of this statement. It is probably true that we cannot make general metabolic inferences on the syndrome of MSL as such based on our rather limited sample size. But this was not our intention, and we welcome the opportunity to clarify our line of argument.

The original idea was to present a situation where a substantial increase in body fat mass was not accompanied by decreased insulin sensitivity, which is in much contrast to common belief. And in fact, fat accumulation, if confined to the subcutaneous compartment, was not associated with much insulin resistance. By selecting these two specific patients for argument's sake, we may have introduced a bias. But this is beside the point because even if everything we said held true for only these two subjects and no other patient with MSL, our findings would be no less interesting. And this is the reason why we specifically put "paradigm" in the title rather than the syndrome alone. Nevertheless, Harsch et al. (2) appropriately pointed out that fat accumulation in MSL need not necessarily be confined to the subcutaneous compartment and that, without doubt, if it included the visceral compartment, insulin resistance would be present.

Since our observation was accepted for publication, we were able to recruit two more patients with the clinical appearance of MSL and very little visceral fat. The whole-body fat volume of the two subjects was ~14 and 20 l, respectively. The subcutaneous-to-visceral abdominal fat ratio as measured by magnetic resonance imaging was 3.3 and 5.9, respectively, compared with BMI-, age-, and sex-matched control groups (1.6 and 1.4, respectively). Consistent with the small visceral fat mass, liver fat was much lower in both patients. Intramyocellular lipids in soleus and tibialis anterior muscles were also lower than those in the control groups. And again, both MSL patients were substantially more insulin sensitive than their respective control groups. For the sake of completeness we also came across a subject with clinical MSL and type 2 diabetes. But there are a number of reasons, which have little to do with our line of argument, for such a patient to acquire secondary types of diabetes, for example, via alcohol-induced pancreatitis.

Finally, the comment of Harsch et al. regarding a higher prevalence of obstructive sleep apnea syndrome (OSAS) among patients with MSL is interesting and valuable. OSAS seems to be an independent risk factor for insulin resistance (4). Upon reexamination of our small cohort, we indeed identified a man with documented OSAS (not among the ones reported). This patient appeared to be insulin sensi-

tive and otherwise healthy, but due to his extreme obesity (BMI 64 kg/m<sup>2</sup>) would not fit into the magnetom, and we were unable to assess his visceral fat mass. This aspect is not necessarily in conflict with our original hypothesis but just another mechanism to render someone insulin resistant. Probably, among two equally obese subjects with OSAS, the one with only subcutaneous fat accumulation is more insulin sensitive.

In conclusion, at some point the reasoning becomes circular and our way of presenting these selected patients with MSL may be just another way of demonstrating that subcutaneous fat is metabolically more innocent than visceral fat (5).

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## Has RoboCop Got Diabetes?

**W**e received a picture series from Becton Dickinson (Fig. 1A, here transformed to black and white and translated from Swedish) showing how syringes look after one, three, and five injections. We were astonished at how deformed the syringes were after a few injections.

To test the reproducibility of the syringe deformation, one physician and two nurses, all with ordinary builds and without scars or metal implants, tested Becton Dickinson's insulin pen syringes Micro-Fine+ 31 gauge  $\times$  8 mm. We used the syringes 1, 3, 5, and 10 times for injections in the abdominal fat. One syringe was thereafter used to penetrate an ordinary rubber mousepad 100 times, then to cut into a wooden computer table, and, finally, to cut a metal lamp foot. Pictures were taken of the syringes with a Zeiss Axioscope 2.5 $\times$  lens with a lateral light source and a Canon 10D camera with 6.2 mpx resolution. The only syringe that looked similar to the used syringes in Becton Dickinson's picture series was the one that cut into a metal lamp foot. The syringes used 0, 1, 3, 5, 10, and 100 times are without distortion of the tip (Fig. 1B).

Hence, Becton Dickinson has improved the quality of their insulin syringes dramatically since the pictures were published, the syringes have been manipulated to produce false evidence of syringe defects, or Robocop was used as a test subject.

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## Has RoboCop Got Diabetes?

Response to Berger et al.

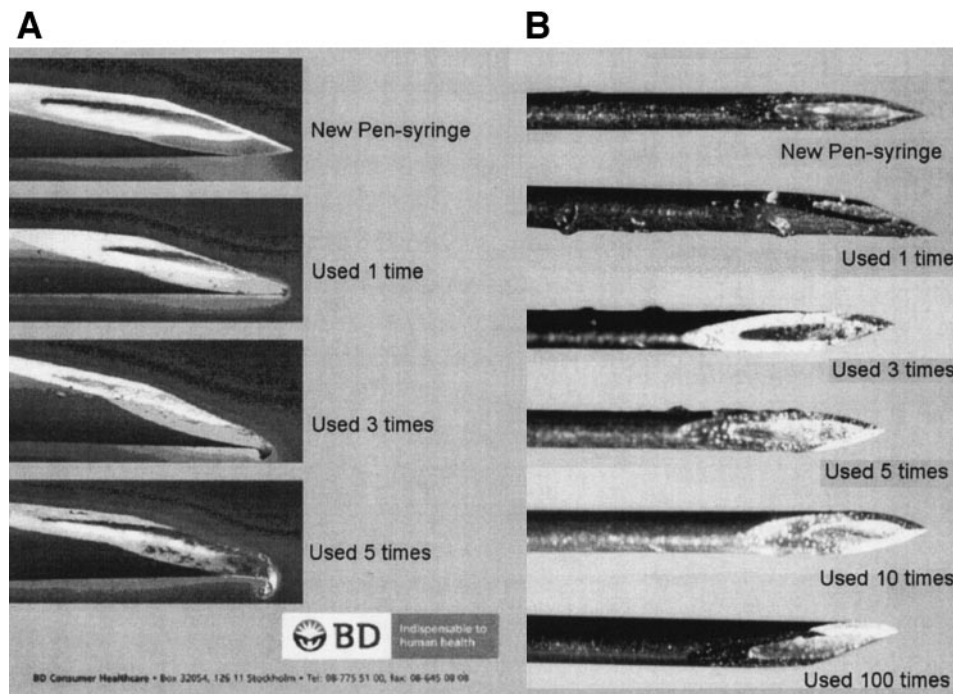
**W**e thank Berger et al. (1) for raising questions about the serious issue of reusing insulin syringes and pen needles. The source of the photographs used by Becton Dickinson is an independent study conducted in 1997 by

Dr. Jacques Garden, Chairman of the Department of Metallurgy at the University of Grenoble, France (unpublished observation).

In Garden's study, 80 diabetic patients from the Diabetes Service of Dr. Dieter Look returned their used pen needles and indicated the number of times each specific needle had been used. All needles were used in a customary fashion and spanned the range of manufacturer types, gauges, and needle lengths. Needles were used from 2 to 38 times. Needle tips were then resterilized for safety reasons and examined by electron microscopy (2).

The tip damage found by Garden ranged from mild bending of the extreme tip to a hook-like distortion of the entire distal shaft of the needle. Loss of the tip was seen on one occasion. Some needles appeared undamaged, even after many reuses. (In this regard Garden's findings agree with those of Berger et al.) However, a clear association was seen between the severity of tip damage and the number of needle reuses.

Among the needles, some looked just like the ones provided by Berger et al. Some were much worse than the ones we have chosen to show the public. We are unsure why the results of Berger et al. differ from our own. Among the possible causes are 1) the magnification used was



**Figure 1**—The picture series distributed by Becton Dickinson (A), and our own pictures of used syringes (B).



