OBSERVATIONS

Sauna-Induced Diabetic Ketoacidosis

Continuous subcutaneous insulin infusion (CSII) has become a popular mode for long-term treatment of patients with type 1 diabetes, and implantable insulin pumps are currently tested in many countries. We report on an unusual cause of diabetic ketoacidosis that occurred in a patient on CSII.

A 32-year-old woman had type 1 diabetes for 6 years. Because she planned to be pregnant, her treatment was optimized, and CSII was instituted. The patient was well-educated to manage her treatment and performed four to six capillary blood glucose determinations per day. During the preceding year, her HbA_{1c} was 6.2–7.2% (normal range 4–6%). Her insulin needs were about 35 U/day (0.58 U · kg^{-1} · day^{-1}). During a weekend holiday, she tried a sauna for the first time. On Saturday afternoon, just before entering the sauna, her capillary blood glucose was 7 mmol/l. She stayed for ~45 min in the room, where the temperature reached 70°C for ~10 min. During the afternoon, her capillary blood glucose rose to 11 mmol/l, and then to 17 mmol/l after a meal, despite the bolus administration of 6 U of insulin. During the evening, she began to feel sick, and she experienced vomiting during the night. On Sunday morning, her capillary blood glucose was 21 mmol/l, and her clinical condition had worsened, with repeated vomiting, abdominal cramps, and extreme fatigue. Urine analysis revealed a 4+ ketonuria. The patient thought that she had diabetic ketoacidosis. The pump functioned apparently well, and there was no inflammation at the site of the infusion. Because she had forgotten to bring insulin pens, the patient repeatedly administered extra insulin through the pump, for a total of 25 U, but she noticed no improvement in either her physical condition or the biological parameters. She eventually decided to change the infusion set and to use a new vial of insulin. Her condition improved dramatically within the following hours: normoglycemia resumed in 6 h, and ketonuria disappeared within 18 h.

A combination of circumstances explains the rapid occurrence of diabetic ketoacidosis in this usually well-controlled diabetic patient. First, exposure of insulin to high temperature leads to the formation of insoluble fibrils and aggregates of biologically inactive insulin (1). Second, after interruption of CSII and acute insulin withdrawal, glucose and ketone body blood concentrations rise rapidly (2), and the occurrence of ketoacidosis has been reported in such circumstances. Third, plasma concentrations of several counterregulatory hormones, including growth hormone and glucagon, are increased by exposure to hyperthermia (3). Lastly, although the patient knew that any unexplained prolonged hyperglycemia can be due to a pump dysfunction, she could not administer extra insulin using a pen. Patients should be warned not to stay in a sauna bath while bearing an insulin infusion device.

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Long-Term Prognosis of Islet Cell Antibody–Negative Ketosis-Onset Diabetes With Subsequent Non-Insulin Dependency

In 1995, we reported islet cell antibody (ICA)-negative ketoacidosis (DKA)-onset diabetes with subsequent non-insulin dependency (1), which may be classified as non-autoimmune type 1 diabetes (type 1, idiopathic), or acute-onset type 2 diabetes (2). Similar, atypical diabetes has also been reported by others (3–5). We report here the long-term prognosis of such atypical diabetes.

Criteria for this type of diabetes were set as follows: *1*) diabetes developed acutely as DKA or ketosis without precipitating events, *2*) negativity in ICA and/or anti (α) GAD antibody (ab) at the onset, *3*) establishment of non-insulin dependency (HbA_{1c} <7.0% without insulin injection) within 3 months and continued presence of it for at least 1 year, and *4*) three or more urinary ketone bodies and/or plasma β-hydroxybutyrate (βHB) >2 mmol/l: the value is the mean – 2 SD βHB in untreated patients with DKA (6). We experienced nine such patients, and two (patients 4 and 5) were lost during the follow-up at 1.9 and 1.2 years, respectively, when they were euglycemic without pharmacological treatment. The rest (n = 7) were followed up for the minimum of 3 years (Table 1). The initial status of patients 1–6 has been previously described (1,7). For patient 1, we restarted insulin 4.3 years after the initial event because glycemic control had been gradually worsened with glyburide. Patient 2 experienced the second episode of DKA 1 year after the initial event, which was again followed by non-insulin dependency: this occurred without precipitating illnesses and with negativity in ICA. Insulin injection was resumed in this patient 5 years after the initial event. Insulin secretion has progressively declined in patient 1, but has been maintained in patient 2 (Table 1). In patient 6, whose HbA_{1c} is continuously <6%, a minimum amount (0.06 U · kg^{-1} body wt · day^{-1}) of insulin has been continued, in hopes of providing β-cell protection. In this patient, a 75-g oral glucose tolerance test (OGTT) has been repeated yearly, and he has been normoglycemic, with significantly reduced insulin response (Table 1). In patient 8, a minimum amount of insulin (0.05 U · kg^{-1} body wt · day^{-1}) had been continued, with HbA_{1c} <6.0% until 1.2 years. At that time, however, the insulin dose was increased to 0.14 U · kg^{-1} body wt · day^{-1} because HbA_{1c} was persistently >8.0%. In the other three patients (3, 7, and 9), excellent glycemic control has been maintained without pharmacological treatment (Table 1). Positive family history of diabetes (all are adult-onset mild type 2 diabetes) and overweight were common

Table 1—*Prognosis of the patients*

Patient	Age at onset (years)	Sex	Follow-up period (years)	BMI (kg/m²) Maximum	BMI (kg/m²) Onset	BMI (kg/m²) Current	HbA_{1c} (%)	Treatment	Other characteristics
1	29	F	9.2	21.0	15.2	20.2	8.5	Insulin 17 U + glyburide 7.5 mg	Progressive lowering of serum C-peptide immunoreactivity; 2-h postprandial value is currently 1.1 ng/ml
2	33	F	8.7	28.0	25.2	28.7	6.9	Insulin 68 U + voglibose 0.6 mg	Urinary C-peptide immunoreactivity currently 59 μg/day; progressive weight gain
3	36	M	6.5	27.5	23.5	23.9	6.0	No drug	Later developed Graves' disease
4	24	M	1.9	33.0	31.2	27.7	5.6*	No drug	Normal glucose tolerance at 75-g OGTT, lost for follow-up
5	16	M	1.2	39.0	31.9	36.0	5.5*	No drug	Lost for follow-up
6	28	M	4.1	27.2	24.6	25.3	5.7	Insulin 5 U	Normal glucose tolerance at 75-g OGTT with very low $\Delta I_{30}/\Delta G_{30}$ (14.0)
7	17	M	11.7	21.0	16.0	19.4	4.5	No drug	—
8	23	F	3.6	38.5	33.2	28.0	5.6	Insulin 10 U	—
9	27	M	3.1	25.1	20.9	27.0	5.5	No drug	—

Patients 1–5 are DKA-onset, and 6–9 are ketosis-onset. Excessive intake of soda pop was documented in patients 2–5 and 8; family history of diabetes was positive in patients 2, 3, 5, 7, and 8; and influenza-like symptoms were present at the onset in patients 3–5, 7, and 9. The insulin dose ($U \cdot kg^{-1}$ body wt $\cdot day^{-1}$) in patients 1, 2, 6, and 8 is 0.35, 0.83, 0.06, and 0.14, respectively. *Including unstable fractions as well. $\Delta I_{30}/\Delta G_{30}$ (pmol/l per mmol/l), the ratio of change in insulin to change in glucose from 0–30 min on a 75-g OGTT (normal value >43.2).

(Table 1). However, weight loss was not an absolute requirement for resumption of non-insulin dependency (Table 1). All patients are currently normoalbuminuric, without diabetic retinopathy, and without clinical evidence of diabetic neuropathy. α-GADab determined during the follow-up period was negative in all. Accumulation of HLA types common in Japanese patients with IDDM was absent (data not shown).

To date, similar atypical diabetes was reported by three other groups (3–5); however, its long-term prognosis was unknown. Banerji et al. (4) reported on 21 African-Americans with GADab-negative NIDDM (type 2 diabetes) with DKA. They found increased frequency of IDDM-related HLA types, but we did not. Umpierrez et al. (5) reported 35 obese African-Americans with similar diabetes; however, HLA typing was not performed. Yamada et al. (3) reported similar Japanese patients, and speculated that diabetes might have been induced by excessive soda pop intake. As shown here (Table 1) and in other reports (4,5), however, excessive soda pop intake is not a prerequisite for the development of this type of diabetes. People regularly drinking a large amount of soda pop will drink it excessively when they feel thirst during the early stage of diabetes, and when they do so, it will further aggravate already developed diabetes. Positivity in ICA in IDDM at the disease onset is considerably lower in Japanese and African-Americans than in Caucasians (8,9), and currently described atypical diabetes is exclusively reported in the former two ethnic groups (1,3–5,7). Therefore, acute non-autoimmune β-cell insult might be not uncommon in these groups. Provided the disease process does not cause severe irreversible β-cell damage, patients may develop atypical diabetes as described here. Regarding stage of glycemia, insulin injection was "required for survival" in these patients only at the onset. Therefore, this type of diabetes may well be classified as atypical type 2 diabetes (2). Banerji et al. (4) claimed in the original publication that their patients had NIDDM, but later (and in another publication) described the same patients as being in the "honeymoon phase of IDDM" (10). Umpierrez et al. (5) concluded that diabetes in their patients was NIDDM because the patients became non-insulin dependent shortly after the initial treatment. Among newly diagnosed patients with IDDM, insulitis was found only in 44% (8 of 18) by pancreatic biopsy, irrespective of positive or negative ICA (11), indicating that the distinction between autoimmune type 1 (type 1a), non-autoimmune type 1 (type 1b), and ketosis-onset type 2 diabetes is far more blurred than generally assumed. Other evidence for an etiologic overlap of type 1 and type 2 diabetes includes *1*) co-occurrence of the two in the same family, or even in the same family sharing a common single diabetogenic gene (12), *2*) ICA-positive type 2 diabetes (12), *3*) α-GADab-positive patients with maternally inherited diabetes with deafness (12), and *4*) increased expression of GAD in the islet β-cells exposed to high glucose in vitro. Taken together, we hypothesize that type 1 and type 2 diabetes are not mutually exclusive (7). In conclusion, long-term prognosis of currently described atypical diabetes is favorable as to glycemia and vascular complications. Nevertheless, this type of diabetes exemplifies complex pathogenesis and difficulty in classification of common diabetes.

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ACE Inhibitor–Induced Cough in Hypertensive Type 2 Diabetic Patients

The average prevalence of ACE inhibitor (ACE-I)–induced cough is estimated to be <8% (1). However, subgroups of patients show a different susceptibility to the side effect: black patients and Asians experience it more frequently than whites, suggesting that the genotype may be relevant. Patients with heart failure share the same problem; however, the attribution of the symptom to the drug or to a disease-related bronchial congestion is not always easy. The available data for diabetic patients rely on large trials in which the focus was placed more on efficacy than on tolerability, which, in this setting, may appear better than it is, due to the unconscious pressure on keeping the patient in the study (and thus minimizing problems that arise); furthermore, side effects (including cough) are rarely specifically investigated and may be reported only when leading to the interruption of treatment.

Thus, we conducted a survey to obtain an accurate estimate of the prevalence of ACE-I–induced cough in type 2 diabetic patients, in whom the use of ACE-Is is widespread and still expanding.

All patients reporting to the Diabetes Clinic of our university hospital during morning consultation hours in the period from 28 March to 31 July 1998 were interviewed by a physician-led questionnaire. The questionnaire gathered information on whether the patient had a history of pharmacologically treated hypertension, whether the treatment included at present or in the past an ACE-I, and whether the patient had experienced—after starting the antihypertensive agent(s)—any of eight side effects presented in alphabetical order.

Patients were not aware that the questionnaire was focused on cough, and when the symptom was declared, specific questioning was aimed at detecting the cause-effect relationship between drug and symptom (inclusive of disappearance after drug discontinuation) and excluding other causes.

In the 4-month period, a total of 2,074 interviews were performed. Some 1,079 patients declared treated hypertension (52% of the total population): their mean age was 69.7 ± 9.6 years, 61.9% were women, and mean duration of diabetes was 13.3 ± 10.6 years.

Of treated subjects, 64% (n = 691; 264 men, 427 women) received a therapeutic regimen that included an ACE-I, and among them, 14.9% (95% CI 12.2–17.5; n = 103) declared the presence of persistent dry cough while on the drug. Prevalence of ACE-I–induced cough did not differ between men (12.9%) and women (16.2%) (NS). In a logistic regression, no factors among those considered in the questionnaire (age, duration of diabetes, smoking status, insulin/oral hypoglycemic treatment) showed a relationship to the appearance of cough. Some 4.7% of the ACE-I–treated population interrupted treatment because of coughing, the symptom thereafter disappearing. Cough was declared by 4.1% of patients treated by antihypertensive drugs other than ACE-I; however, no relationship could be determined between the symptom and the relevant drug treatment.

The prevalence of cough observed in this study is twice ($P < 0.05$ by χ^2) the 7.4% found in a similar survey we conducted on more than 1,500 ACE-I–treated nondiabetic hypertensive patients homogenous with the present population for race (white) and region of residence (2). The sex-related significantly different prevalence then observed (10.5% in women vs. 4.4% in men) has now disappeared, suggesting that diabetes is such an overwhelming factor that it overshadows other predisposing conditions. The reasons for this are unclear.

Cough is now recognized as a side effect of ACE-I treatment, but in clinical practice, physicians do not always conduct a specific investigation on its appearance. On the other hand, spontaneous reporting depends on the recognition by the patient of a cause-effect relationship with the drug; although some patients, mainly after reading the package information, may reach this conclusion, others do not. Therefore, coughing, masked as a

common nonspecific event, may continue undisclosed and undetected, surfacing only at a time at which it significantly affects the quality of life. Interestingly, the withdrawal rate of ACE-I in our coughers has a striking similarity to that observed in a recently published substudy of the U.K. Prospective Diabetes Study (3). This suggests that <5% of the cases present such a severity of the symptom that action is called for. Incidentally, patients who interrupted treatment in our survey were the only ones aware of the symptom as a side effect of ACE-I treatment.

In other cases, cough of lesser intensity, if detected, may be judged by the physician as a price to pay for possible future benefits, and treatment is continued; nevertheless, during chronic treatment, a new symptom, irrespective of severity, is not desirable. Spontaneous disappearance or attenuation, determined by as yet unknown factors, has also been reported, and a wait-and-see policy could also be considered by the physician.

To overcome ACE-I–induced cough, some therapeutic options are available (4), but these maneuvers require first the recognition of the side effect.

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Anti-HCV Antibodies in a Population of Insulin-Dependent Diabetic Children and Adolescents

Besides the indolent but progressive liver damage, chronic hepatitis C virus (HCV) infection may give rise to a large array of autoimmune diseases, such as mixed cryoglobulinemia, membranoproliferative glomerulonephritis, and endocrinologic disturbances (1). A high prevalence of diabetes was found in patients with HCV-related cirrhosis (2), and a significantly increased rate of HCV infection was detected in diabetic adults (3), with a particularly high frequency of genotype 2a, which is preferentially linked to extrahepatic clinical manifestations of HCV (4). However, the issue is still a matter for debate because most HCV-infected patients had non-insulin-dependent diabetes, anti-islet cell autoantibodies were rarely detected, and a convincing temporal relationship between HCV infection and development of diabetes is lacking (5). Indeed, type 1 diabetes manifested at 7 years of age in one of our children with vertically acquired HCV infection (6). To gain further insight on the possible correlation between HCV infection and diabetes, we evaluated anti-HCV antibodies and alanine aminotransferase (ALT) levels in a group of 187 unselected consecutive children and adolescents with type 1 diabetes attending our outpatient clinic during the period from July to December 1998. None of the subjects had history of acute hepatitis, hemocromatosis, or previous blood transfusion. Sex distribution (97 boys, 90 girls), mean age (9.3 ± 5.5 years), and duration of type 1 diabetes (7.1 ± 4.5 years) mirrored that of the entire population of 324 diabetic children followed at our center. Serological testing for anti-HCV antibodies was performed by a third-generation enzyme immunoassay (Abbott HCV EIA 3.0; Abbott Laboratories, Chicago). Informed consent was obtained from all patients and/or their parents.

None of the 187 diabetic patients were positive for HCV antibodies. Mild elevations of ALT concentrations were found in four adolescents, all with very poor metabolic control (glycated hemoglobin >12%).

The data obtained clearly indicate that HCV infection is rare among children with type 1 diabetes, suggesting that the virus does not play a key role in the pathogenesis of the disease. Several considerations may account for the discrepancy in the prevalence of hepatitis C between children and adults affected by diabetes. First, the frequency of HCV infection increases with age and is low before adolescence, when it rises sharply (7). Second, autoimmune complications are common in chronic diseases as a result of the continuous stimulation of the immune system, the reactivity of which is reduced in children compared with that in adults. Existing evidence indicates that the progression of HCV infection is slower in the former, presumably as a result of their weaker immune response (8). Therefore, the occurrence of HCV-related disorders is expected to be lower in children than in adults. Third, there is a long latency period between acquisition of HCV infection and appearance of autoimmune diseases. Thus, an HCV-infected child will develop such disorders only during adolescence or young adulthood. In fact, age of contamination and duration of HCV infection are independent predictors for diabetes (4,5). In conclusion, HCV does not seem to represent a significant risk factor for type 1 diabetes in childhood, and extensive testing for anti-HCV antibodies is consequently not recommended in diabetic children. In our experience, the only diabetic child with hepatitis C acquired the infection from the mother. After the introduction of blood screening for HCV, vertical transmission has become the dominant route of HCV infection in children (9). Whether the risk of associated complications, including type 1 diabetes, is higher in patients infected as newborns than patients infected at an older age remains to be elucidated.

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Cardiovascular Risk Factors in African-Americans With Varying Degrees of Glucose Intolerance

Comparison of new American Diabetes Association versus old World Health Organization diagnostic criteria

Recently, an expert committee of the American Diabetes Association (ADA) (1) published its report on the diagnosis and classification of diabetes, meant to replace the old World Health Organization (WHO) and National Diabetes Data Group (NDDG) criteria (2–4). The main goal of the new diagnostic criteria and classification was to place more emphasis and reliance on fasting plasma glucose levels that are found to be associated with diabetic microvascular diseases rather than cardiovascular disease (CVD) in several populations. The new ADA classification calls for screening of high-risk populations, such as African-Americans, Native Americans, and first-degree relatives of patients with type 2 diabetes, that are genetically predisposed to diabetes or in women who have had prior gestational diabetes (1,2). In this regard, type 2 diabetes and its associated complications are more prevalent and more severe in African-Americans compared with white Americans (5,6). In addition, nondiabetic African-Americans manifest greater insulin resistance and severe hyperinsulinemia compared with white Americans (7). It is uncertain, however, whether the new diagnostic classification would have significant impact on cardiovascular risk factors, the major cause of morbidity and mortality, compared with categorization by WHO and NDDG criteria.

To examine the impact of the new ADA and old WHO criteria on cardiovascular risk factors in African-Americans with varying degrees of glucose intolerance who are genetically predisposed to type 2 diabetes, we studied 220 African-Americans with family history of type 2 diabetes (age range 25–66 years, 178 females and 42 males) using both standard oral glucose tolerance testing and frequently sampled intravenous glucose tolerance test (Bergman's minimal model method). As shown in Table 1, mean age was not significantly different among the groups. However, the obesity indices increased as glucose tolerance worsened. Mean fasting serum glucose levels were lowest in normal glucose tolerance (NGT) 1 and 2 groups, intermediate in the NGT 3 and impaired glucose tolerance (IGT) groups, and highest in the diabetic patients. The mean 2-h postprandial serum glucose levels were lower in the NGT 1 and 2 groups, intermediate in NGT 3 and IGT groups, and highest in the diabetic patients. Fasting serum insulin was lowest in the NGT group, intermediate in the IGT group, and highest in the diabetic patients. Among the NGT groups, fasting serum insulin was not significantly different in the NGT 1, 2, and 3 groups. The 2-h postprandial serum insulin levels were, however, greater in the NGT 2 and NGT 3 groups compared with those for NGT 1. Among the diabetic patients, there were no significant differences in the fasting and 2-h postprandial serum insulin in the diabetes 1, 2, and 3 groups, respectively. Serum fasting and poststimulation C-peptide followed the same trend as that of the insulin responses.

The mean insulin sensitivity index (S_I), as assessed by Bergman's minimal model, was significantly decreased by 30% in the NGT 2 and NGT 3 groups and by 50% in the IGT group compared with NGT 1 (Table 1). S_I values were significantly lower in the diabetic patients (50–82%) than in the NGT 1 and IGT groups, and were similar among the diabetes 1, 2, and 3 subgroups, irrespective of analysis by ADA or WHO criteria. In contrast to S_I, glucose effectiveness (S_G) values were similar across the spectrum of glucose intolerance, ranging from NGT to IGT to diabetes, but was not influenced by either ADA or WHO criteria.

Mean serum cholesterol, triglycerides, and LDL and HDL cholesterol levels were similar in NGT and IGT. The diabetic subgroups had higher serum triglycerides and lower HDL cholesterol levels compared with the NGT and IGT groups. Among the diabetic subgroups, lipids and lipoproteins were similar, irrespective of analysis by ADA or WHO criteria.

CVDs account for 75% of all deaths in patients with type 2 diabetes (5,8). It is well known that the risk factors for macroangiopathy are complex and multifactorial. As shown in Table 1, the mean age and obesity indices as well as blood pressure (systolic and diastolic) increased as the glucose tolerance deteriorated in our population, despite the similar ages among the three main categories of glucose intolerance. Both ADA and WHO criteria identified subjects (NGT 2 and 3) who were intermediate between NGT 1 and IGT subjects and were distinctly different from NGT 1 subjects. The S_I was lower in NGT 2 and 3 compared with NGT 1 subjects. Mean S_I worsened as the glucose tolerance worsened in the IGT and diabetic groups. We found that S_I in the NGT, IGT, and diabetic groups were not significantly different as defined by ADA and WHO criteria. Thus, in high-risk African-Americans, insulin resistance, a major risk factor for CVD, predates the development of IGT and diabetes, irrespective of ADA or WHO criteria.

Table 1—*Clinical and biochemical parameters of African-American subjects with varying degrees of glucose intolerance*

	NGT			IGT (FSG <140/	Diabetic		
	1 (FSG <110)	2 (FSG <126)	3 (FSG <140)	2-h 140–199)	1 (FSG >126)	2 (FSG >140)	3 (2-h >200)
n	173	204	210	31	16	10	23
Age (years)	42.1 ± 0.9	42.3 ± 0.6	42.3 ± 0.5	46.2 ± 1.78	45.8 ± 2.1	46.0 ± 2.6	44.6 ± 1.8
Body weight (kg)	88.6 ± 1.6	90.8 ± 1.63	91.3 ± 1.5	97.2 ± 2.9*	109.2 ± 5.76*	110.4 ± 10.3*	108 ± 4.9*
BMI (kg/m^2)	31.6 ± 0.52	32.4 ± 0.56	32.5 ± 0.5	34.7 ± 1.1	36.8 ± 2.0†	36.56 ± 2.1†	38.2 ± 1.4†
Waist-to-hip ratio	0.91 ± 0.03	0.90 ± 0.01	0.90 ± 0.07	0.94 ± 0.01	0.90 ± 0.03	0.92 ± 0.02	0.90 ± 0.01
Body fat mass (%)	38.7 ± 0.70	39.2 ± 0.68	39.44 ± 0.66	42.6 ± 1.78	45.4 ± 2.46*	44.50 ± 3.67*	46.6 ± 1.83*
Blood pressure (mmHg)							
Systolic	124 ± 1.1	123.4 ± 1.18	123.5 ± 1.12	128 ± 2.9	133.9 ± 4.21*	137.6 ± 6.8*	141.0 ± 3.5
Diastolic	81.4 ± 0.80	77.3 ± 0.89	77.35 ± 0.85	81.4 ± 2.20	81.3 ± 3.15*	82.60 ± 2.96*	82.0 ± 2.50
Oral glucose tolerance test							
Glucose (mg/dl)							
FSG	81.5 ± 1.4	80.0 ± 0.94	100.5 ± 0.68*	86.1 ± 1.8	149.2 ± 3.3‡	158.0 ± 6.10‡	123.8 ± 6.3‡
120-min	97.2 ± 1.6	112.6 ± 3.3	159.0 ± 14.8*	158.3 ± 3.1†	182.7 ± 11.9‡	266.0 ± 8.7‡	249.6 ± 8. 2‡
Insulin (μU/ml)							
Fasting serum insulin	13.3 ± 0.8	14.9 ± 0.91	15.19 ± 13.07	16.5 ± 1.8	23.0 ± 3.26§	21.03 ± 1.00§	28.0 ± 6.0§
120-min	76.9 ± 4.8	85.9 ± 4.9	85.8 ± 9.22	122.9 ± 14.3‖	86.4 ± 17.4	86.96 ± 5.56	74.2 ± 12.8
C-peptide (ng/ml)							
Fasting serum C-peptide	2.82 ± 0.10	2.81 ± 0.10	2.87 ± 1.40	3.05 ± 0.22	3.6 ± 0.35§	3.45 ± 0.12§	3.62 ± 0.39§
120-min	10.42 ± 0.30	10 ± 0.28	10.0 ± 3.96	11.42 ± 0.77	9.6 ± 0.99	9.2 ± 1.13	7.98 ± 0.61
Minimal model parameters							
S_I [$\cdot 10^{-4} \cdot min^{-1} \cdot (\mu U/ml)^{-1}$]	2.93 ± 0.20	1.90 ± 0.22*	1.89 ± 3.20*	1.41 ± 0.17†	0.7 ± 0.8‡	0.48 ± 1.17‡	0.99 ± 0.16‡
S_G ($\cdot 10^{-2} \cdot min^{-1}$)	2.62 ± 0.10	2.30 ± 0.18	3.20 ± 2.50	2.24 ± 0.34	2.0 ± 0.6	2.58 ± 1.19	1.92 ± 0.44

Data are means ± SEM. FSG, fasting serum glucose; 2-h, 2-h post-glucose challenge. *$P < 0.05$, diabetes and IGT vs. NGT; †$P < 0.01$, IGT vs. diabetic subjects; ‡$P < 0.001$, diabetic subjects vs. NGT; §$P < 0.05$, diabetic subjects vs. NGT and IGT; ‖$P < 0.05$, IGT vs. NGT and diabetic subjects.

Previous studies have demonstrated that the major metabolic mediators of atherosclerosis and coronary artery disease are atherogenic lipoprotein profiles in diabetic and nondiabetic populations. African-American women are disproportionately affected by type 2 diabetes and the associated cardiovascular mortality and mortality than their white counterparts (5,8). However, because the levels of atherogenic lipoproteins in African-Americans with type 2 diabetes and coronary artery disease are not often different, and indeed are more favorable with respect to atherosclerosis than those in white Americans (9), we can postulate that other factors, such as the higher rates of hypertension, insulin resistance, and hyperinsulinemia, and obesity and as yet unknown genetic factors, could explain the differences in the rates of CVDs in African-Americans with type 2 diabetes when compared with white Americans. We found that the subjects in the NGT 1, 2, and 3, and IGT groups had normal serum lipids and lipoproteins, despite the varying degrees of S_I, insulin responses, and obesity indices. However, we observed worsening of multiple cardiovascular risk factors, such as hypertriglyceridemia, lower S_I, and increases in systolic and diastolic blood pressure and obesity indices, as glucose intolerance worsened in our high-risk African-American subjects with type 2 diabetes and CVD. Of interest, the findings in the present study are similar to those of the Framingham Offspring Study in Caucasian patients with high risk for CVD (10).

We conclude that the ADA criteria do not confer any advantages in detection of conventional CVD risk factors compared with WHO classifications in high-risk African-American individuals. Thus, we recommend that prevention of risk factors for CVD should target high-risk African-Americans with fasting serum glucose remarkably lower than the diagnostic cutoff point of 126 mg/dl for diabetes recommended by the ADA expert committee (1).

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Pancreatic Amyloid Proteins and Their Relation to Clinical Diabetes, With Special Reference to Serum Insulin Secretion

Amylin is the major constituent of pancreatic islet amyloid in the majority of patients with type 2 diabetes mellitus (1–2) and has been reported to inhibit insulin secretion from β-cells (3). However, whether deposited amylin in the islets inhibits the secretion of insulin in diabetic subjects has not been reported. Recent studies have found that amylin fibers are toxic to islet cells in vitro, and that the cell death occurs within 24 h by apoptosis (4). In this study, pancreatic amyloid deposits were investigated pathologically postmortem, and their severities were compared with serum insulin response prior to death.

Some 44 autopsied type 2 diabetic patients were studied (32 men and 12 women; aged (mean ± SEM) 65.8 ± 2.5 and 76.7 ± 2.8 years, respectively). Serum C-peptide–like immunoreactivity (CPR) or immunoreactive insulin (IRI) response during a breakfast meal (~400 kcal) was measured within 3 years and studied up to 1 month before death. These individuals had no evidence of nephropathy or severe liver dysfunction. Blood samples at 0, 60, and 120 min were assayed for serum IRI or CPR. Amyloid protein in the tail of pancreas was stained by Congo red or Masson stains. To determine the amyloid deposit extent, 50 islets in the pancreas were checked and graded: (++), >10 amyloid-positive; (+), 2–9 islets positive; (±), 1 positive; and (–), none. Of the 42 patients, (++) and (+) patients were 50%. Mean serum Σ IRI for 2 h during breakfast in the amyloid protein (++) or (+) group and in the (±) or (–) group was 59.3 ± 12.0 (n = 6) or 72.5 ± 24.1 μU (n = 5), respectively ($P < 0.58$). No significant difference in serum Σ glucose was found between these two groups. Mean serum Σ CPR in the (++) and (+) groups was 5.87 ± 0.52 ng (n = 3) and 5.10 ± 1.69 ng (n = 5) in the (±) and (–) groups ($P < 0.66$). In four patients with high amylin content containing more than 10 μg/g (other 19 patients, 1.1 5 ± 0.3 μg/g), no relationship was found between amylin content or amyloid protein and pancreas insulin contents. However, in the one patient with the highest amylin amounts and much amyloid protein deposit, the pancreas insulin content was low (5).

In this study, we did not determine the extent to which the observed amyloid deposits or fibrils are in contact with β-cells, nor did we measure local concentrations of free amylin. One patient with a very high level of amylin had large amyloid deposits, and a low pancreatic insulin content might indicate cytotoxicity or inhibition of insulin biosynthesis. The overall lack of any strong correlation among these parameters, however, would argue that other more important factors may influence insulin secretory capacity and/or β-cell survival in type 2 diabetes. Clinically, the presence or absence of amyloid deposition seems to be relatively unimportant.

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Leptin in Children and Adolescents With Type 1 Diabetes

A 2-year longitudinal study

In vitro studies have shown that insulin stimulates production of leptin by human adipocytes (1). Two recent clinical studies on type 1 diabetic patients report opposite results: Kiess et al. (2) observed low levels of serum leptin before insulin treatment that increased during treatment, while Verrotti et al. (3) found levels of serum leptin in type 1 diabetic patients similar to those in a control group.

We measured leptin (radioimmunoassay; Linco, St. Louis, MO) in serum from 24 type 1 diabetic patients (19 boys and

5 girls aged 2.5–19.4 years) at onset of type 1 diabetes and after 12 (14 cases) and 24 (22 cases) months. There were 12 patients who were studied after both 12 and 24 months. The following parameters were collected for each patient: height, weight, BMI, ideal BMI percentage, pubertal stage, HbA_{1c} at onset, annual mean HbA_{1c}, and insulin requirement.

Leptin, log transformed and adjusted for BMI and sex, was, on average, lower at onset than after 12 and 24 months of insulin treatment. Paired *t* testing, however, showed statistical significance only for values at 24 months (onset: 0.235 ± 0.247 ng/ml, 24 months: 0.503 ± 0.241 ng/ml; $n = 22$, $P < 0.005$); whereas, when comparing the overall results by analysis of variance, we found statistically significant higher leptin after both 12 and 24 months of the disease compared with that at onset (onset: 0.210 ± 0.251 ng/ml vs. 12 months: 0.393 ± 0.266 ng/ml, $P < 0.05$; vs. 24 months: 0.503 ± 0.241 ng/ml, $P < 0.001$). We found no correlation between leptin HbA_{1c}, insulin requirement, and weight excess. Unadjusted leptin, compared with reference values, related to BMI, and grouped for sex and pubertal stage (4), resulted in a majority of patients between the 5th and the 95th percentile, except for 6 cases at onset, 5 after 12 months, and 11 after 24 months of disease who showed leptin levels above the 95th percentile ($\chi^2 = 3.1$; $P > 0.05$). In six patients, hyperleptinemia was already present at onset of the disease, whereas five became hyperleptinemic during treatment. In each case, the patients were boys, eight prepubertal and three pubertal. Moreover, leptin at onset of type 1 diabetes was significantly correlated with leptin during insulin treatment (12 months: $r = 0.67$, $P < 0.01$; 24 months: $r = 0.69$, $P < 0.001$). Although our results confirm that prolonged insulin treatment significantly increases levels of leptin, the correlation between leptin at type 1 diabetes onset and during treatment suggests that genetic disposition plays a more relevant role in determining hyperleptinemia.

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Wegener's Granulomatosis Presenting With Life-Threatening Pulmonary Hemorrhage in a Boy With Type 1 Diabetes

Type 1 diabetes (1) is strongly associated with other organ-specific autoimmune conditions (2,3), but rarely occurs in conjunction with systemic autoimmune disorders, particularly in the pediatric age group.

Wegener's granulomatosis (WG) is an idiopathic systemic disease characterized by necrotizing granulomatous inflammation of the upper and lower respiratory tract in combination with vasculitis and focal crescent glomerulonephritis (4,5). Pulmonary symptoms are found in 60–80% of patients with WG and include cough, dyspnea, hemoptysis, and chest pain. Catastrophic pulmonary hemorrhage is rare, but is associated with an adverse short-term prognosis (4). Anti-neutrophil cytoplasmic antibody (ANCA) detection, specifically with cytoplasmic pattern of staining (c-ANCA), strongly supports the diagnosis.

Our patient, brother of a girl with type 1 diabetes, developed clinical diabetes at the age of 7 years. At that time, anti-islet cell antibodies were detected, while other organ and non–organ-specific antibodies were absent. HLA typing was A 2,9 (24); CX,W7; B 18,21 (49); DR 3,3; DQ 2,2, and molecular analysis of the HLA-DQ region showed four susceptible heterodimers. At 7 years after the onset of diabetes, he was admitted with a 1-month history of fever, fatigue, arthralgias, nasal stuffiness, and dry cough with blood-tinged sputum. Physical examination showed deep pallor, severe respiratory distress with shortness of breath, chest pain, and extreme weakness. Cardiac failure and enlargement of liver, spleen, or lymph nodes were absent. Blood pressure was 150/90 mmHg. The hemoglobin concentration was 4.4 g/dl, and a chest roentgenogram showed diffuse alveolar infiltrates consistent with pulmonary hemorrhage (Fig. 1). Laboratory investigation disclosed acute renal failure, hypoproteidemia, elevated parameters of systemic inflammation, and hyperglycemia. Urinalysis showed glycosuria, proteinuria, and 4+ microhematuria. Antinuclear, anti-DNA, anti-phospholipid, and anti-glomerular basement membrane antibodies and rheumatoid factor were absent, whereas c-ANCA were detected (titer 1:160). The boy was given intravenous pulse methylprednisolone, 1 g/day for 3 days, 2 mg · kg^{-1} · day^{-1} intravenous cyclophosphamide, and several units of packed red blood cells. Clinical conditions improved 4 days later, with disappearance of respiratory distress and increase in hemoglobin concentration. The patient was maintained on oral prednisone and cyclophosphamide and anti-hypertensive therapy; a course of intensive plasma-exchange therapy was started. At 6 days after admission, anterior rhinoendoscopy revealed diffuse crusting of the nose. Removal of the crusts showed a friable mucosal surface underneath and a large easily bleeding perforation of the nasal septum, confirmed by high-resolution computed tomography scan. Nasal mucosa biopsy showed vasculitis, necrosis, and granulomatous inflammation. At 3 weeks after admission, chest roentgenogram was

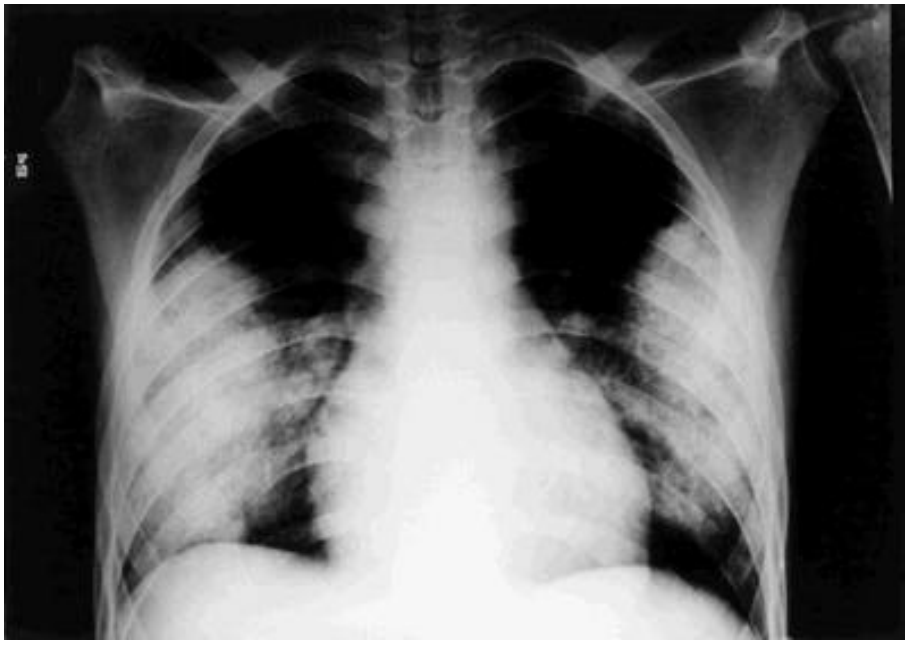

Figure 1—*Chest roentgenogram showing bibasilar infiltrates consistent with pulmonary hemorrhage.*

normal. The boy was in good clinical condition 2 months later, but still had slight hypertension. c-ANCAs were absent.

Although organ- and non–organ-specific autoantibodies are frequently detected in newly diagnosed and in long-standing type 1 diabetic patients (6), systemic autoimmune disorders are exceedingly rare. A survey of 25 Italian pediatric centers caring for 3,736 children with type 1 diabetes reported only 9 patients with systemic inflammatory diseases (7 with juvenile chronic arthritis, 1 with systemic sclerosis, and 1, the present case, with WG) (7). To our knowledge, only one previous instance of WG and type 1 diabetes in the pediatric age has been described. Sugimoto et al. (8) reported a 14-year-old girl with newly diagnosed type 1 diabetes and WG, presenting in a limited form with maxillary and sphenoidal sinuses and central nervous system granulomas. The authors speculated that WG-triggered immunological abnormalities leading to insulitis may have led to the development of diabetes. In our patient, however, WG occurred 7 years after the onset of diabetes and developed in a diffuse form, with renal and respiratory tract involvement.

Our case presented as a clinical emergency with severe pulmonary hemorrhage and acute anemia. Clues for the diagnosis of WG were the association of pulmonary and renal disease with the presence of c-ANCAs, the history of persistent nasal discharge, and the finding of necrotizing vasculitic granulomas in the biopsy of the nasal mucosa. Early diagnosis of WG and prompt institution of therapy are essential to prevent irreversible organ damage. The drug of choice has been demonstrated to be cyclophosphamide, which is usually associated with high-dose corticosteroids (5).

We conclude that awareness of the possible association of type 1 diabetes and WG is important because prompt recognition of the vasculitic disease can lead to early intervention with immunosuppressive treatment.

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Blood Volumes and Pain Following Capillary Punctures in Children and Adolescents With Diabetes

Pain has been mentioned as a restricting factor in the daily use of self-monitoring of blood glucose in children (1). Pain perception is dependent on the neurodevelopmental and psychosocial development of an individual (2,3). The aims of the present study were to evaluate

Table 1—*Effects of age and weather conditions on the frequency of insufficient blood volumes*

		Blood volumes obtained (μl)		Frequency of insufficient blood volumes (μl)		
	n	Normal	Shallow	<7.5	<5	<3
Total group	118	11.6 ± 0.8	8.6 ± 0.9	36	22	14
Age-group (years)*						
8–11	34	9.9 ± 2.2	6.0 ± 1.4	62	47	32
11–13	32	9.3 ± 1.2	7.4 ± 1.1	44	22	13
13–16	38	12.4 ± 1.0	9.7 ± 1.1	18	8	3
>16	14	16.3 ± 0.8	19.0 ± 5.8	0	0	0
Weather conditions						
Cool	30	6.1 ± 1.0	5.5 ± 1.2	70	50	33
Warm	88	13.4 ± 0.9	9.7 ± 1.1	24	13	7

Data are means ± SD and %. Cool weather conditions: 21–25°C; warm: 26–31°C. *$P < 0.001$ for each level of blood volume.

in older children with diabetes whether a shallower capillary puncture could yield enough blood for an adequate measurement and be less painful.

All children attending a summer camp for children with diabetes in the Eastern Laurentians (Camp Carowonis) were invited to participate. Information on age, sex, duration of diabetes, hand dominance, and frequency of home blood glucose monitoring was collected. The ambient temperature was noted. Softtouch finger pricking devices were prepared either as recommended by the manufacturers or with the cap unscrewed three-fourths of a turn to give a shallower puncture. The dimensions of the lancets used were 3.15 × 0.8 mm, and the evaluated regular depth of the penetration was 1.63 mm. Pairs of finger pricking devices were prepared to give either two regular punctures, a shallower puncture on the right hand, or a shallower puncture on the left hand. Both subjects and investigators were blinded for the depth of the punctures by covering the junction point of the device. A mechanical colored analogue pain scale (4) was used. The use of visual analogue scales has been validated for use in children starting from age 5 (5,6). The back of the scale is numbered from 0 to 10, allowing the investigators to grade the pain indicated by the child. Capillary tubes were used to measure the amount of blood produced by the punctures.

At the time of a regular blood test, participating children were asked to first prick one finger of their choice on the left hand and to obtain enough blood for a test. This puncture was arbitrarily set at 5 on the numeric pain scale, to allow for increasing or decreasing intensity of pain of the second puncture compared with the first. The blood was collected in the capillary tube and measured. The child was then asked to prick the corresponding finger of the right hand, to show how painful this puncture was compared with the first one (measure of pain difference), and obtain enough blood for a test. Again, blood was collected in the capillary tube and measured. Data was analyzed using the Statistical Program for Social Sciences (SPSS for Windows; SPSS, Chicago). Significance levels were set at $P < 0.05$.

There were 59 children and adolescents (aged 12.8 ± 0.4 years [8.2–20.1], duration of diabetes 5.4 ± 0.5 years) who participated in the study. Weather conditions varied from 21°C (71.6°F) and dry to 30°C (87.8°F) and humid. All subjects were asymptomatic and had a blood glucose >3 mmol/l (average 10.4 ± 0.8 mmol/l). Of these, 13 subjects received identical punctures, 24 received a shallower puncture on the right, and 22 on the left.

The mean blood volume obtained for all types of punctures was 10.4 ± 0.6 μl. As shown in Table 1, the amounts of blood obtained increased with age ($P < 0.001$). The shallower punctures produced smaller blood volumes ($P = 0.03$). Blood volumes were also found to be linked to the weather conditions: warmer conditions produced greater blood volumes than cooler conditions ($r = 0.3$, $P = 0.004$). Frequency of home blood glucose testing and hand dominance were not found to influence results.

Based on the manufacturers' recommendations of using a minimum of 3–7.5 μl (depending on the meter) for an adequate test, samples were categorized as sufficient or insufficient (Table 1). The proportion of insufficient volumes increased with younger age ($P < 0.001$) and with cooler weather conditions ($P < 0.001$). Insufficient blood samples were associated with less pain ($P = 0.04$).

Independent factors found to influence pain perception on multiple regression analysis ($P < 0.01$) were the order of the test, the blood volume obtained, and the weather conditions. The first puncture (left) was perceived as more painful independently of the puncture depth ($P < 0.001$). This order effect decreased with age. Higher pain was found in the presence of higher blood volumes ($r = 0.3$, $P = 0.04$). Pain was found to be independent from depth of puncture, hand dominance, frequency of home blood glucose testing, sex, duration of diabetes, and blood glucose reading.

In summary, shallow punctures were not perceived to be less painful, and often yielded insufficient blood volumes for an adequate meter glucose reading. Environmental factors seem to have more influence on pain in children than in adults (5,6). Higher volumes seemed to generate higher pain, but higher volumes were also obtained by older subjects. Older subjects were less influenced by the order effect and were more likely not to find a difference between the two punctures.

Our findings on pain and blood volumes differ from those of Fruhstorfer et al. (7). In their study, finger pricking devices with a greater penetration depth were more painful and generally provided too much blood. Pain and blood volumes were linearly related to depth, and a penetration depth of 1.0 mm provided sufficient blood for testing (>20 μl). They found no correlation between blood volumes and pain. The fact that these studies were done in adult subjects without diabetes may explain the discrepancies.

We conclude that a shallower puncture does not necessarily reduce pain and is often associated with insufficient blood volumes for adequate measurements of blood glucose. In children <13 years of age, minimum blood volume requirements for an adequate blood glucose reading should be considered in the choice of a home blood glucose meter.

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Significance of Parental History of Type 2 Diabetes on Insulin Sensitivity and Glucose Effectiveness in Obese Nondiabetic Offspring of African-American Patients

Previous studies have demonstrated that offspring of mothers with type 2 diabetes are more obese, glucose intolerant, and hyperinsulinemic than offspring of fathers with type 2 diabetes (1–3). These studies suggest significant impact of the intrauterine environment on glucose regulation and insulin action in adult offspring of mothers with type 2 diabetes (1–3). It has been suggested that reduced insulin sensitivity (S_I) and lower glucose effectiveness (S_G) could be predictors of future type 2 diabetes (4). We and others have previously demonstrated that African-Americans with and without type 2 diabetes are more insulin resistant than their white counterparts (5–7). However, whether parental history of type 2 diabetes has distinct effects on serum glucose, insulin secretion, and S_I and S_G in offspring of African-Americans with mothers with type 2 diabetes, compared with those with fathers with type 2 diabetes, remains unknown.

To examine the impact of parental history of type 2 diabetes on β-cell secretion and the insulin action in nondiabetic obese offspring of African-American parents with type 2 diabetes, we studied 227 African-Americans with parental history of type 2 diabetes residing in Franklin County, OH. The subjects were offspring of type 2 diabetic patients whose mothers (group 1, n = 116), fathers (group 2, n = 68), or both parents (group 3, n = 28) had type 2 diabetes and individuals without family history of type 2 diabetes (group 4, n = 15) and were tested using the standard oral glucose tolerance test (OGTT) and the frequently sampled intravenous glucose tolerance test (Bergman's minimal model method).

As shown in Table 1, mean age and body compositional variables such as BMI, waist-to-hip circumference ratio (WHR), and lean body mass were not significantly different among the three relative subgroups. However, mean age and obesity indices were significantly greater in the relatives when compared with the reference control group. Mean systolic and diastolic blood pressures were similar in those with mothers with type 2 diabetes when compared with the other three groups. The control group was younger, and less obese than those with a family history of diabetes. The mean fasting and postprandial serum glucose levels were not different in group 1 when compared with groups 2 and 3. The serum glucose levels at fasting and after glucose challenge were greater in the family members than in the healthy control subjects, irrespective of parental history. In addition, mean fasting and postprandial serum insulin levels tended to be greater in those with family history of diabetes than in healthy control subjects. In contrast, corresponding serum C-peptide concentrations at basal and after both oral and intravenous glucose stimulation were not different among the four groups. As shown in Table 1, there was a tendency for S_I to be lower in the group 1, 2, and 3 subjects with parents with type 2 diabetes than in group 4 subjects. The S_I was lower, but not significantly different, in those with both parents with type 2 diabetes compared with that in those with only one parent with type 2 diabetes. The S_G was not significantly different in group 1 patients compared with those in groups 2, 3, and 4.

It is well established that nondiabetic offspring and first-degree relatives of patients with type 2 diabetes are more insulin resistant and hyperinsulinemic than those without family history of type 2 diabetes (4,6). Furthermore, ethnic and racial populations with higher propensity and predilection for type 2 diabetes manifest S_I and hyperinsulinemia (4–7). While this is partly genetic, there is a tremendous environmental component to the risk of type 2 diabetes. In both adults and adolescents in the Western world, this environmental component has been described as obesity, poor physical fitness, and sedentary lifestyle. However, there is increasing evidence that the intrauterine environment experienced by the offspring may also be important for future development of type 2 diabetes and insulin resistance and that maternal history of diabetes confers further risks for type 2 diabetes (1–3). We found that clinical and metabolic characteristics were similar in offspring of African-American mothers and fathers with type 2 diabetes. We found no differences in serum insulin and C-peptide responses or S_I in the offspring of mothers with type 2 diabetes compared with those with fathers with type 2 diabetes, and these levels were significantly lower than those in the healthy control subjects. Most importantly, individuals with both parents having type 2 diabetes tended to have a lower, but not

Table 1—*Clinical and biochemical characteristics of nondiabetic first-degree relatives of African-American patients with type 2 diabetes and healthy control subjects*

	Father	Mother	Both	Control subjects	*P* value
n	68	116	28	15	—
Age (years)	42.0 ± 1.04*	43.5 ± 0.79*	39.9 ± 0.6*	34.1 ± 1.7	0.001
BMI (kg/m^2)	34.5 ± 1.00	31.87 ± 0.79	31.25 ± 1.6	34.1 ± 1.7	NS
Waist-to-hip ratio	0.88 ± 0.01	0.89 ± 0.75	0.89 ± 0.02	—	NS
Body fat mass (%)	42.22 ± 1.20*	39.42 ± 0.92*	40.73 ± 2.0*	30.12 ± 1.67	NS
Serum glucose (mmol/ml)					
0 min	4.79 ± 0.15	4.79 ± 0.12	4.92 ± 0.24	4.43 ± 0.0	NS
120 min	6.65 ± 0.34	6.91 ± 0.26†	6.74 ± 0.56	6.41 ± 0.04	0.04
Serum insulin (mU/l)					
0 min	16.2 ± 1.6	15.6 ± 1.2	15.2 ± 2.5	12.1 ± 0.9	NS
120 min	83.6 ± 8.5	86.6 ± 6.5	80.4 ± 13.6	71.1 ± 6.9	NS
Serum C-peptide (nmol/l)					
0 min	0.97 ± 0.06	0.93 ± 0.13	0.86 ± 0.09	0.89 ± 0.04	NS
120 min	3.21 ± 0.48	3.27 ± 0.12	3.10 ± 0.25	3.29 ± 0.15	NS
Minimal model parameters					
S_I	1.49 ± 0.30*	1.23 ± 0.29*	0.83 ± 0.62*	3.00 ± 0.27	0.001
S_G	2.34 ± 0.31	1.94 ± 0.24	1.62 ± 0.50	2.77 ± 0.27	NS

Data are means ± SEM. *$P < 0.001$, relatives vs. control subjects; †$P < 0.04$, mother vs. healthy control subjects; S_I, $\times 10^{-4}$ per minute per (microunit per milliliter); S_G, $\times 10^{-2}$ per minute.

significantly different, S_I compared with those with mothers alone or fathers alone with type 2 diabetes. Thus, unlike Pima Indians (1) and Caucasians (2,3), offspring of African-American mothers with type 2 diabetes did not manifest lower S_I compared with nondiabetic offspring of fathers with type 2 diabetes. To the best of our knowledge, this is the first report to describe the absence of any significant impact of paternal and maternal history of type 2 diabetes on the risk factors for type 2 diabetes in nondiabetic African-Americans.

The in vivo glucose disposal is determined not only by insulin secretion and sensitivity, but by non-insulin-dependent glucose disposal (i.e., S_G) in humans (8,9). Previous studies have shown that S_G is reduced in patients of diverse ethnicity and race with impaired glucose tolerance or type 2 diabetes and could be a predictor of type 2 diabetes in offspring of patients with type 2 diabetes (4). The impact of parental history of type 2 diabetes on S_G was not examined in these previous studies. We found that S_G was not significantly different among the healthy first-degree relatives of African-American patients with type 2 diabetes when compared with healthy control subjects without family history of type 2 diabetes. In the present study, there was also a tendency for a lower S_G in those offspring with two conjugal parents with type 2 diabetes, but the mean differences were not statistically significant compared with those offspring with either a mother alone or a father alone with type 2 diabetes. Thus, in high-risk African-Americans, maternal history of type 2 diabetes did not confer significant alterations in S_G compared with that in patients with fathers or siblings with type 2 diabetes. Note that the obesity indices were similar in all of the subgroups of relatives. Thus, these anthropometric variables cannot explain the lack of differences in the metabolic profiles examined in the present study. Further studies using more sophisticated methodologies, such as computed axial tomography scans and magnetic resonance imaging, to measure visceral abdominal fat content, will be necessary to define the impact of parental history of diabetes on these various metabolic parameters in the obese offspring of African-American parents with type 2 diabetes (10).

Our present study demonstrates that nondiabetic African-American offspring of mothers with type 2 diabetes manifest similar anthropometric parameters, β-cell function, S_I, and glucose effectiveness to those of fathers with type 2 diabetes. We conclude that in young nondiabetic offspring of African-American parents with type 2 diabetes, maternal history of type 2 diabetes per se does not appear to exert any deleterious effects on β-cell function and S_I or glucose-dependent glucose disposal when compared with paternal history of the disease.

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Serum Fructosamine and Obesity

In an ongoing epidemiological study of older inner-city African Americans (1,2), we measured a large number of serum fructosamine tests using the "second-generation" fructosamine test described by Cefalu et al. (3). We had previously reported the test to be of great value in determining overall glycemic control in older diabetic patients (4) and have subsequently routinely used this test to guide diabetic patient therapy. In the literature, there are two documented studies (5,6) claiming an inverse relationship between obesity and fructosamine concentrations. Because of our satisfaction with fructosamine tests in managing both obese and nonobese patients, we set about to review those publications and to perform an independent study of this claim. We obtained blood samples from 95 nondiabetic patients with a BMI ranging from 16.5 to 44.1 and measured their serum fructosamine concentration. The mean age for the patients in this study was 79.8 (range 70–95). As shown in Fig. 1, contrary to published reports, we observed no significant relationship in fructosamine values in patients with BMIs ranging from 16.5 to 44.1 ($r = -0.077$, $P = 0.453$).

We noted that in the article by Skrha and Svacina (6), the fructosamine values reported for both obese and nonobese patients were substantially below the range of fructosamine values for normal patients reported with the older fructosamine method (7,8) used by these investigators. The normal range for nondiabetic subjects published in the original publications for their method was 1.69 ± 0.23 mmol/l (7,8), while Skrha and Svacina observed mean values of only 0.74 ± 0.13 and 0.95 ± 0.10 mmol/l for their obese and nonobese subjects, respectively. The values reported by Broussolle et al. (5) were 1.78 ± 0.16 and 2.06 ± 0.18 mmol/l for their obese and nonobese nondiabetic subjects, respectively; $P < 0.01$. Because the distribution of BMI for this analysis is unknown, it is unclear whether the differences are due to a small number of discrepant values.

Broussolle et al. (5) also performed an analysis of a comparison between fructosamine and HbA_{1c} in obese and nonobese patients with diabetes. Their analysis indicated that while good correlation was observed with all patients, the obese patients appeared to have a correlation with a lower slope. Interestingly, 8 of the 19 obese patients had values that fell on the nonobese correlation line. Because BMI for the patients in this study are not shown, it is unclear whether the obese patients with fructosamine below the correlation line were mildly, moderately, or severely obese. In addition, because fructosamine and HbA_{1c} measure different time windows of glycemic control, it is possible that some of the obese patients with lower fructosamine values compared with HbA_{1c} had been in a recent period of improved glycemic control. It is well established that fructosamine is a more sensitive indicator of recent improvements in improved glycemic control than is HbA_{1c} (9).

We believe that the clinical utility of fructosamine measurements in diabetes management is well established (10). We have been unable to substantiate the observations of Skrha and Svacina (6) and Broussolle et al. (5), suggesting a possible inverse relationship between fructosamine and obesity. Our laboratory uses the second-generation fructosamine test (3), which has several enhancements over the method used by these investigators. Regardless of the reason for the discrepancy, we believe that the fructosamine test remains a valuable tool for managing diabetes in all patients.

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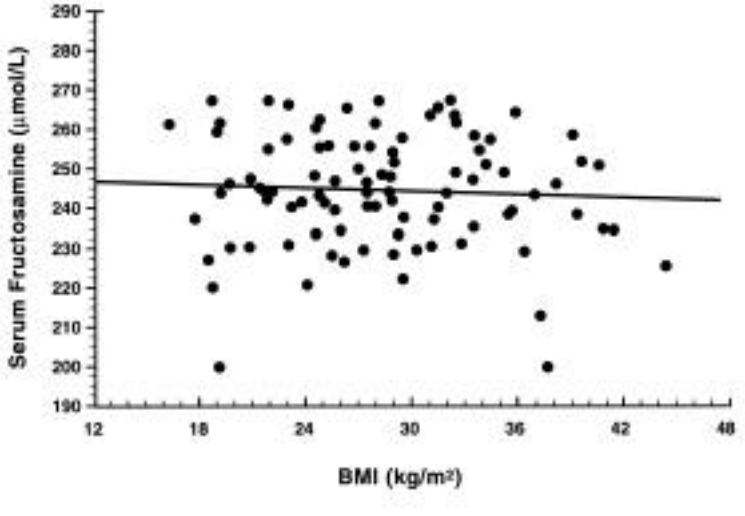

Figure 1—*BMI versus serum fructosamine.*

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Prediction of Albumin Excretion Rate From Albumin-to-Creatinine Ratio

Albumin-to-creatinine ratio (ACR) is recommended for diabetic nephropathy screening (1–4). Thus, the relationship between ACR and values of the albumin excretion rate (AER) indicative of microalbuminuria and established nephropathy is important. Simple least-square regression of log-transformed AER and ACR has been used to study the relationship, but calculation of confidence intervals around values of the predictor variable (ACR) is problematic. The aim of this study was to determine with 95% CIs the values of ACR that predict AER of 20 and 200 µg/min by a mathematically rigorous method, determine the effect of sex, and compare the reproducibility of ACR with AER. The results were compared with current guidelines.

This analysis is based on 415 timed overnight urine collections obtained, with Ethics Committee approval and informed patient consent, from 147 (93 male, 54 female) diabetic patients. Of these, 72 male and 42 female patients provided three collections. All collections were confirmed to be sterile. Samples were rejected if there was clear collection error, based on creatinine excretion rate. Log(AER) (micrograms per minute) was taken as the dependent and log(ACR) (milligrams per millimole) as the independent variable. A bootstrapping technique was used to determine values of ACR that predict AER values of 20 and 200 µg/min (5). The bootstrap sampling reflected the structure of the data without oversampling patients who provided more samples. We compared ACR and AER measurements made on the same sample, thereby eliminating within-subject variation. To compare within-patient variability in AER and ACR, we considered the paired differences (Wilcoxon) of coefficient of variation (CV)(ACR) – CV(AER) in patients who had provided three collections.

The values of ACR (95% CI) corresponding to an AER of 20 µg/min were 2.4 (2.2–2.7) in male and 4.0 (3.5–4.7) mg/mmol in female subjects. Using these ACR values, the sensitivity and specificity of the prediction of microalbuminuria in male subjects were 94 and 98%, and in female subjects, 96 and 93%, respectively. The values of ACR corresponding to AER 200 µg/min were 28.0 (23.1–33.9) in male and 44.0 (32.1–60.2) mg/mmol in female subjects. The overnight creatinine excretion rate was (mean ± SD) 8.8 ± 3.0 µmol/min in male and 5.5 ± 1.9 µmol/min in female subjects ($P < 0.001$). Combining data for male and female subjects, mean CV(ACR) was 27% and CV(AER) was 31% ($P = 0.035$).

There are theoretical objections to the use of standard regression techniques in this situation. Some studies of the relationship between AER and ACR have relied on receiver-operator characteristics (sensitivity and specificity); however, the distinction between normal and abnormal based on ACR values then becomes arbitrary (6,7). If ACR is to be widely used, an agreed calculated figure to distinguish the abnormal would be preferable. Bootstrapping is a computationally intensive nonparametric technique using large numbers of repetitive computations to estimate the distribution of predicted cutoff values rather than utilizing strong distributional assumptions and analytic formulas (5). The CIs around the predictive values of ACR are larger than those found with least-square regression because measurement error in the independent variable (ACR) is included. Others suggest that the relationship between ACR and AER is different in nondiabetic subjects, probably as a result of different creatinine excretion (6).

We found that ACR had less variability than AER. Others did not find this difference, but they studied smaller numbers with greater within-patient variability (8,9). Early studies show considerable variation in ACR values said to predict microalbuminuria, probably because they did not take into account sex, some used small patient populations, and both early morning and random urine samples were used (10). The relationship between AER and ACR is different between the sexes because of lower creatinine excretion in women. The predictive values of ACR that we obtained in diabetic patients were similar to those obtained by Connell et al. (6), but differed from those of Mangili et al. (11), owing to greater creatinine excretion in the Italian population.

Long-term follow-up of Pima Indians showed that an ACR of 30 mg/g (3.4 mg/mmol) predicts progression to overt

nephropathy (12). If our results are applied to their predominantly female study population, a similar figure (3.5 mg/mmol) is obtained. Current American Diabetes Association guidelines and a United States National Kidney Foundation expert panel recommend an annual ACR measurement using the 30 mg/g value to diagnose microalbuminuria (2,4). The St. Vincent Task Force and others have recommended diagnostic values of 2.5 mg/mmol in men and 3.5 mg/mmol in women (1,3). These values seem to be based on data that give sensitivity and specificity similar to ours, but that contain only small numbers of microalbuminuric patients (13). Thus, clarification of the definition of a normal ACR is needed. Current U.S. recommendations do not take sex into account, and St. Vincent recommendations, while achieving acceptable sensitivity and specificity, are not derived by direct calculation from published data or from outcome measurement.

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Insulin Lispro

The ideal pump insulin for patients with severe hypoglycemic unawareness?

Insulin lispro is more rapidly absorbed than conventional short-acting insulin and can achieve better glycemic control with lower postprandial excursions and a reduced risk of hypoglycemia (1). Several studies suggest that insulin lispro may be the ideal insulin for continuous subcutaneous insulin infusion (CSII) and found lower glucose values, with no increase in the rates of hypoglycemia, when patients using conventional insulin CSII pumps were switched to insulin lispro (2,3). Schmauss et al. (2) recorded no episodes of severe hypoglycemia, but Melki et al. (3) detected a reduction in the rate of very low blood glucose (<2 mmol/l), although their study excluded patients with hypoglycemic unawareness.

We, therefore, assessed the use of insulin lispro in a 58-year-old man with type 1 diabetes for 45 years who was subject to severe recurrent hypoglycemia during CSII treatment with conventional insulin. He had hypoglycemic unawareness, but was keen on maintaining strict glycemic control. In the 2 years before starting CSII (in March 1995), he had 53 emergency hospital admissions with profound hypoglycemia. CSII (Minimed; Minimed Technologies, Sylmar, CA) with conventional soluble insulin (Human Actrapid; Novo Nordisk, Crawley, U.K.) was started to reduce the frequency of recurrent severe hypoglycemic events. In early 1998, the basal infusion rate was 1.2 U/h from 0730 to 1730, 1.6 U/h from 1730 to 2230, and 0.4 U/h from 2230 to 0730 with a bolus of 2 U before his main meal around 1800. He suffered hypoglycemia every 2–3 weeks, but episodes were generally less severe and dealt with effectively by friends and family; he was hospitalized only once between February and April 1998.

In May 1998, the pump insulin was changed to insulin lispro (Humalog; Eli Lilly, Basingstoke, U.K.) with the aim of reducing further the frequency of hypoglycemic events. The basal infusion rate was reduced initially and then gradually increased to the regime described above because his blood glucose measurements rose to levels (frequently >10 mmol/l) that he considered unacceptable.

The patient had measured his blood glucose (One Touch; LifeScan, High Wycombe, U.K.) at least four times daily since starting CSII, allowing us to make a detailed comparison of his blood glucose profile while on soluble insulin and insulin lispro. In the 76 days before switching to insulin lispro, 311 blood sugar measurements were recorded, with a mean value of 7.0 mmol/l (range 1.8–24.3) and an *M* value (Schlicktkrull et al. [4]) of 11.9 (with 5.0 mmol/l chosen as the standard euglycemic value). While on Humalog (68 days), 479 blood sugar measurements were recorded, with a mean of 6.3 mmol/l (range 0.8–28.3 mmol/l) and an *M* value of 19.0. In the

10 weeks that insulin lispro was used, the patient experienced hypoglycemic events once every 2–3 days and required seven hospital admissions.

At the patient's request, the pump insulin was then changed back to soluble insulin at the previous basal infusion rate. The number of hypoglycemic events decreased, with only two episodes (both requiring admission) over a period of 87 days. Mean blood glucose during this period (n = 521) was 6.4 mmol/l (range 2.4–21.3), with an M value of 10.3.

This case suggests that in certain individuals who have poor hypoglycemic awareness and who achieve extremely tight metabolic control, use of insulin lispro in CSII may increase the frequency of hypoglycemia and destabilize glycemic control. Presumably, the analog's more rapid diffusion and absorption from subcutaneous tissue is responsible. This situation, in patients at particularly high risk of hypoglycemia, appears to be different from that in well-controlled patients who are reported to have more stable glycemic control and suffer fewer episodes of hypo- or hyperglycemia when treated with insulin lispro by injection (1) or CSII (2,3).

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COMMENTS AND RESPONSES

Screening for Diabetic Nephropathy: Is Measurement of Urinary Albumin-to-Creatinine Ratio Worthwhile?

Proposal for a simple algorithm

We read with much interest the recently published article by Bakker (1). We appreciate the fact that Bakker found that a urinary albumin concentration (UAC) of 16 mg/l corresponds to a urinary albumin excretion rate (UAER) of 20 µg/min. This is very similar to the value we reported (16.9 mg/l) in a study regarding the measurement of UAC in a diurnal random urine specimen for diabetic nephropathy (DN) screening (2). Differently from us, however, Bakker concludes that urinary albumin-to-creatinine ratio (UACR) is a better method for detecting microalbuminuria than UAC. Since cost and ease of application are also relevant for screening tests, we would like to comment on three aspects of Bakker's article.

Bakker's conclusion is based on a comparison of the sensitivity and sensibility for UACR and UAC in relation to the reference standard (UAER). The same timed overnight urine was used for all measurements, and therefore these data cannot be extrapolated to spot urine samples; the measurement of urinary albumin (and probably creatinine) in a random urine sample could be subject to the effect of dilution and other factors (protein intake) (3). Thus, Bakker's finding should be confirmed using spot urine samples. Random urine collection is easier and more practical for DN screening than timed urine collection because it can be carried out in office settings. If spot urine samples are used, the number of diabetic patients screened for DN may increase; in some clinics, less than 50% of type 2 diabetic patients are regularly screened for DN, probably because timed urine collection is time-consuming and cumbersome (4), as Bakker himself points out.

Secondly, the measurement of creatinine increases the cost of screening. At our institution, the cost (in U.S. dollars) per test is $0.78 for UAC and $0.93 for UACR. Considering that the projected number of diabetic patients in our country is 5 million, the cost of annual screening for DN would have an increase of U.S. $750,000 if UACR were used.

Finally, Bakker observed that expressing the results as UACR has a better sensitivity (94.4%) than expressing them as UAC (90.4%). This difference is very small in practical terms. Based exclusively on these data, and considering a 20% population-based prevalence of DN (5), UACR and UAC will detect 18.8 and 18.04 patients, respectively, for each 100 diabetic patients screened.

Taking these facts into account, as well as our recent observation (6) that measuring total protein in random urine samples is cheap ($0.17) and accurate for diagnosing overt DN (430 mg/l = 100% sensitivity for diagnosing macroalbuminuria), we propose the following algorithm for DN screening:

1) Quantitative measurement of total protein using a spot urine sample collected during the office visit. If the urinary protein concentration is >430 mg/l, the diagnosis of clinical proteinuria should be confirmed by total proteinuria measurements using 24-h urine; if the urinary protein concentration is <430 mg/l, then albumin concentration is measured in the same spot urine sample. *2*) If albumin concentration is <17 mg/l, the patient is considered normoalbuminuric, but if the value is >17 mg/l, albumin should be measured in a timed urine.

In conclusion, considering the small difference in sensitivity between the two screening methods UACR and UAC (<1 patient for every 100 patients screened) as reported by Bakker and the higher cost of measuring UACR in comparison with the cost of measuring total protein or albumin, we believe that random sample protein and albumin concentration measurements may be a more efficacious method for DN screening, especially in developing countries, in times of economic restraint.

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Response to Gross et al.

Like Gross et al. (1), I think that a random urine specimen is preferable in screening for diabetic nephropathy. However, no prospective studies have yet been published comparing the effectiveness of random urinary albumin concentration (UAC) and urinary albumin-to-creatinine ratio (UACR) in screening for diabetic nephropathy. Therefore, one can only speculate which of these screening procedures is the most efficient.

Since urinary creatinine excretion throughout the day is relatively constant, and very cheap to analyze, creatinine can be used to correct for variability of urinary concentration differences. Because first morning urine specimens usually show less concentration variability, I compared the effectiveness of both screening procedures in timed overnight urine specimens (procedure: discard the urine voided before going to bed; collect all urine including the first morning urine; record the voiding times at starting and ending of collection). In the comparison presented, UACR was shown to be better than UAC. Because concentration differences in daytime urine specimens vary to a greater extent, it will be expected that the difference between UACR and UAC is more pronounced in daytime urine, compared with nighttime urine. Therefore, I think that correction for concentration differences will be necessary.

Based on the sensitivity data presented in my article, Gross and co-workers calculated the additional patients for whom albumin should be measured in a timed overnight urine. However, they overlooked the fact that based on the differences for specificity, a number of patients would also collect a timed urine unnecessarily. The age-related cutoff values for UACR presented in my article can help to restrict the amount of patients selected for follow-up with timed urine.

Because the measurement of urinary albumin and creatinine in my institution are performed on the same analyzer, and because the cost of reagents for the creatinine assay is only $0.02 per test, I decided to use the UACR in screening for diabetic nephropathy. Depending on the local situation, however, others may decide differently.

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