OBSERVATIONS

Hemoglobinopathies and HbA_{1c} Measurement

The measurement of glycosylated hemoglobin (HbA_{1c}) is one of the cornerstones of management of diabetes. Most physicians use HbA_{1c} values in the assessment of a patient's control of their blood glucose levels and as a reality check for home glucose-monitoring results. A target value of 7.0% is widely regarded as excellent glycemic control (1). Good glycemic control is associated with lower rates of microvascular complications from diabetes in both type 1 (1) and type 2 (2) diabetic patients.

Changes in therapy are often based on HbA_{1c} values. Some patients attending outpatient clinics for diabetes management were noted to have HbA_{1c} values that differed from what was expected based on home blood–glucose monitoring (hBGL) results. We have previously reported Hb Hamadan in one of our patients with an unexpectedly low HbA_{1c} value (3). The hypothesis was that a proportion of patients with an unexpected HbA_{1c} result would have a hemoglobinopathy. Hb electrophoresis (HbEPG) was performed on patients in whom the HbA_{1c} result differed from the expected value.

The study was a prospectively collected cross-sectional study of 30 consecutive patients whose HbA_{1c} values differed significantly from the expected results. The decision to perform HbEPG was made clinically by the investigators, on the basis of comparison of HbA_{1c} and hBGL results. Of the patients included in the study, 29 had HbA_{1c} values lower than expected, and 1 had a value higher than expected. Clinically, it is recognized that some patients underreport hBGL results. Thus, there was a bias toward testing unexpectedly low HbA_{1c} values.

The study started in May 1998 and concluded in November 1999. The computerized investigation report system used at our institution makes it possible to access every HbEPG performed by the investigators during the time of the study, thus eliminating recall bias. Subjects were classified as Caucasian or non-Caucasian according to their countries of birth.

Table 1—*Patient characteristics and results*

	Overall	Normal	Hemoglobinopathy
n	30	23	7
Type 1 diabetic patients	2	2	0
Type 2 diabetic patients	14	12	2
Patients with gestational diabetes	14	9	5
Age (years)	47 ± 17	48 ± 18	41 ± 11
HbA_{1c} (%)	6.1 ± 2.4	6.5 ± 2.4	4.6 ± 1.8*
Hb (g/l)	128 ± 23	128 ± 23	128 ± 26
MCV (fl)	85 ± 10	87 ± 10	81 ± 12
LDH (mmol/l)	184 ± 59	195 ± 63	147 ± 25†
Bilirubin (mmol/l)	9 ± 3	9 ± 4	9 ± 2
HbA_2 (%)	2.9 ± 0.5	2.8 ± 0.2	3.0 ± 1.0
HbF (%)	1.1 ± 2.2	0.5 ± 0.3	2.8 ± 4.1‡

Data are *n* or means ± 2SD. *P = 0.059; †P = 0.069; ‡P = 0.003.

Patient characteristics are shown in Table 1. The mean age of the subjects was 47 ± 17 years. Two of the patients had type 1 diabetes, 14 patients had type 2 diabetes, and 14 women had gestational diabetes. HbA_{1c} was measured by ion exchange high-performance liquid chromatography (HPLC) using the method of Jeppsson et al. (4). Of the patients, 27 had their full blood count, lactate dehydrogenase (LDH), and serum bilirubin measured. Results for HbA_{1c}, fetal Hb, and LDH measurements were not normally distributed.

Patient results are shown in Table 1. The proportion of pregnant subjects did not differ significantly between groups. Patients with abnormal HbEPG had higher fetal Hb than patients with normal Hb (2.8 ± 4.1 vs. 0.5 ± 0.3%, respectively; P = 0.003). There was a trend toward higher LDH in subjects with a hemoglobinopathy (P = 0.06). The mean corpuscular volume correlated with the total Hb ($P < 0.01$).

The patient with an HbA_{1c} higher than expected did not have a hemoglobinopathy. The 7 patients with abnormal HbEPG had lower than expected HbA_{1c} results. The abnormalities were HbE in 2 patients, hereditary persistence of fetal Hb (HPFH) in 2 patients, and Hb Hamadan, β-thalassemia, and HbS in one patient each. The first abnormality was detected in the subject with Hb Hamadan, as previously reported (3).

Of the 23 subjects with normal HbEPG, 10 (43.5%) were non-Caucasian, and of the patients with abnormal HbEPG, 3 of 7 had a hemoglobinopathy (42.9%) (NS). Considered by ethnicity, 4 of 17 Caucasian subjects (23.5%) and 3 of 13 non-Caucasian subjects (23.1%) had a hemoglobinopathy.

Pregnant women had lower HbA_{1c} values than nonpregnant subjects 4.5 ± 1.3 vs. 7.6 ± 2.4% ($P < 0.001$), respectively.

When only pregnant subjects were considered (15 subjects), the HbA_{1c} value in those with a hemoglobinopathy was 4.0 ± 1.7 vs. 4.9 ± 1.0% in those with abnormal Hb. When nonpregnant subjects were considered (15 subjects), the HbA_{1c} value in those with normal Hb was 6.3 ± 0.8 vs. 7.9 ± 2.5% in those with abnormal Hb.

Pregnancy is associated with lower blood glucose and higher LDH levels. Thus, the trend toward lower HbA_{1c} and higher LDH in the subjects with hemoglobinopathies may be related to the proportion of pregnant women. However, the difference in the proportion of pregnant women in each group was not significant. There is a trend toward lower HbA_{1c} values with hemoglobinopathy when pregnant women are considered separately and when nonpregnant subjects are considered separately, but the difference is not significant. A larger number of subjects may clarify this issue.

Hemoglobinopathies are known to affect HPLC measurement of HbA_{1c} (3,5,6). There are at least 2 methods by which abnormal Hb may affect HbA_{1c} values. One is the presence of an abnormal peak on chromatography, making the estimation of the fraction of HbA_{1c} unreliable. Second, some abnormal forms of Hb (e.g., β-thalassemia and sickle cell trait) make red blood cells more susceptible to hemolysis. Increased hemolysis corresponds with decreased red cell lifespan. This decreases the time available for glycosylation of Hb chains. The 2 effects may coexist.

Specific effects, which have been described, include decreased HbA_{1c} results

with homozygous or heterozygous HbS, HbC, HbG, and Hb Hamadan (3,5). Variably decreased or increased results are found with HbE and increased quantities of HbF, including HPFH.

Of the subjects, 43% were non-Caucasian. There was no difference in frequency of hemoglobinopathy between Caucasians and non-Caucasians. At this institution, only women with an abnormal glucose tolerance test during pregnancy or with pregestational diabetes have HbA_{1c} measurements performed during pregnancy. For women with abnormal glucose tolerance, figures for 1998 show that 41% were non-Caucasian.

Because of the importance placed on HbA_{1c} in the management of diabetes, it is important to consider hemoglobinopathy in patients when the HbA_{1c} value does not correlate with clinical expectations. If the value is artificially low, these patients may be at higher risk for complications of diabetes than the HbA_{1c} result would suggest, and they may require alterations in therapy.

It is well recognized that subjects with diabetes may underreport hBGL. However, it seems unlikely that they would report levels higher than they find during home monitoring. Thus, if the HbA_{1c} value is lower than expected, based on the results of hBGL, HbEPG should be performed. In subjects with a hemoglobinopathy, use of fructosamine to monitor diabetes may be more reliable.

It is reasonable to expect that otherwise clinically silent hemoglobinopathies may be present with greater frequency than currently realized. If discrepant results are found on an HbA_{1c} assay (either higher or lower than expected), hemoglobinopathy should be considered as a possible cause.

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Improvement of Glycemic Control After Treatment With Mosapride for Diabetic Gastropathy

Upper gastrointestinal symptoms, such as postprandial nausea, vomiting, bloating, early satiety, fullness, and abdominal discomfort, are commonly found in patients with either type 1 or type 2 diabetes (1,2). Diabetic gastropathy has been found in ~50% of patients with type 1 diabetes and in ~30% of patients with type 2 diabetes (2). In addition to problems concerning quality-of-life issues (3), diabetic gastropathy may cause erratic and unpredictable blood glucose levels by reducing the effectiveness of dietary regimen and the absorption of oral medications, thereby causing difficulties in timing insulin peak with meals (3–6). However, no study has reported the effects of treatment for diabetic gastropathy on glycemic control, except for a preliminary observation of 8 Japanese subjects (6).

Various prokinetic agents, including the dopamine D2 antagonists metoclopramide and domperidone (3,4), the motilin agonist erythromycin (5), and a cholinergic mimetic cisapride (2) have been used to treat diabetic gastropathy. In the present study, we examined the effect of mosapride, a new prokinetic drug (a selective serotonin 5-HT4 receptor agonist) (7), on glycemic control in patients with type 2 diabetes presenting with upper gastrointestinal symptoms typical of diabetic gastropathy. A total of 21 Japanese subjects (6 men and 15 women, mean age 68.8 ± 5.6 years) with type 2 diabetes participated in the study. After a mean of 100.7 days of mosapride treatment (15 mg/day), gastrointestinal symptoms disappeared in all subjects. In 21 subjects, 14 showed a decrease in HbA_{1c}, although HbA_{1c} was increased or unchanged in 5 and 2 of them, respectively. HbA_{1c} changes showed a statistically significant decrease (7.6 ± 0.3 to 7.0 ± 0.3%, $P < 0.05$). Furthermore, there was a significant negative correlation between the HbA_{1c} change and the duration of mosapride treatment ($r = 0.789$, $P < 0.0001$).

This preliminary result suggests a possibility that treatment of diabetic gastropathy with mosapride results in better glycemic control and disappearance of gastrointestinal symptoms in patients with type 2 diabetes. Although the present study is limited because it was not a controlled study, it seems likely that better glycemic control may be attributable to an improvement of gastrointestinal activity, which is considered to result in better timing of the insulin peak with an increase in postprandial glucose, as proposed by other investigators (4,5). Prospective controlled trials may be justified in order to investigate whether mosapride treatment may improve glycemic control.

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Response to Training in Blood Glucose Awareness Is Related to Absence of Previous Hypoglycemic Coma

Cox et al. (1,2) extensively reported about their Blood Glucose Awareness Training (BGAT) Program. We translated the BGAT into Dutch, adapted it to local standards and practices (3), and added a chapter about self-regulation (4). We evaluated this so-called BINGO program with regard to feasibility, compliance, and satisfaction of the participants; overall glycemic control (HbA_{1c}); and fear of hypoglycemia. Its efficacy in improving blood glucose estimation accuracy was compared in patients with and without a recent history of hypoglycemic coma. Two groups of 12 type 1 diabetic patients, who were taking at least 3 daily insulin injections and were familiar with self-monitoring of blood glucose levels (SMBG) were enrolled.

Their assessments before and after BINGO included the Accuracy Index (AI) (by means of Error Grid Analysis), Hypoglycemia Fear Survey Worry Scale (5,6), and HbA_{1c}. Data of 20 compliant patients (defined as having attended at least 4 of 6 evening classes) are presented (Tables 1 and 2). Responders were defined as participants with an increase in AI of >1 SD (≥12%).

Overall, AI increased from 18 ± 11 to 29 ± 19% ($P = 0.01$); the number of hypoglycemic blood glucose (BG) readings (<3.9 mmol/l) decreased from 10 ± 11 to 7 ± 7 per 2 weeks ($P = 0.03$), but the proportion of hypoglycemic readings did not change. The frequency of SMBG (during the assessments) decreased from 4.5 ± 1.2 before to 3.8 ± 1.4 times daily after ($P = 0.01$). Nonresponding was related to a history of hypoglycemic coma in the previous year ($P < 0.05$, adjusted for decrease in SMBG). However, we observed a larger decrease in the proportion of hypoglycemic (<3.9 mmol/l) SMBG readings in participants with a history of coma as compared with patients without coma (8 ± 7 vs. 0 ± 5%, $P = 0.02$, adjusted for decrease in SMBG). Average HbA_{1c} levels before and after the course were similar. The course was awarded with a mean score of 7.7 ± 0.9 points on a 10 point-scale by compliant participants. Hypoglycemia-related anxiety decreased overall ($P = 0.006$); decreases in worry level correlated with baseline levels ($r = 0.72$, $P = 0.001$).

We conclude that it is feasible to apply BGAT after translation into a foreign language and adaptation to local standards, with preservation of an improvement in overall BG estimation accuracy comparable with previous reports (1,2), and we observed a modest decrease in the number of hypoglycemic readings. A recent history of hypoglycemic coma markedly decreases chances of responding with a significant increase in AI, but equally results in a reduction in hypoglycemia-related distress.

Table 1—*Baseline characteristics of responders and nonresponders*

Characteristics	Responders	Nonresponders
n	10	10
Sex (M/F)	5/5	3/7
Age (years)	36 ± 11	44 ± 11
Duration of diabetes (years)	13 ± 6	19 ± 10
Coma in previous year	11%	60%*

Data are means ± SD, unless otherwise indicated. *$P < 0.05$ vs. responders.

Table 2—*End-point results of intervention with BINGO in responders and nonresponders*

	Responders		Nonresponders	
	Before	After	Before	After
AI (%)	17 ± 13	41 ± 12	18 ± 10	16 ± 15
2-week SMBG	59 ± 18	55 ± 21	67 ± 17	50 ± 18*
SMBG < 3.9 mmol/l	6 ± 6	6 ± 4	14 ± 14	9 ± 10*
Detection (%) BG <3.9 mmol/l	47 ± 23	56 ± 38	36 ± 20	33 ± 32*
HbA_{1c} (%)	8.2 ± 0.9	7.8 ± 1.1	8.1 ± 1.8	7.8 ± 1.8

Data are means ± SD. *$P < 0.05$ vs. before intervention.

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Small-Bowel Bacterial Overgrowth in Diabetic Subjects Is Associated With Cardiovascular Autonomic Neuropathy

Gastrointestinal symptoms are present in 50–70% of patients with diabetes. Delayed gastric emptying, and disturbance of intestinal motility are frequent findings (1,2). Impaired intestinal motility is often followed by small-bowel bacterial overgrowth (SBBO), which can possibly lead to deconjugation of bile acids, diarrhea, steatorrhea, malabsorption of vitamin, and/or micronutrients and weight loss, as well as mucosal injury, bacterial translocation, and worsening of small-bowel motility (3). However, patients in whom bacterial overgrowth is found may also be asymptomatic (4).

Up until now, little attention has been devoted to the relationship among autonomic neuropathy, impaired intestinal motility, and SBBO in diabetic patients (3,5). The aim of our study was to evaluate the prevalence of bacterial overgrowth and its association with autonomic neuropathy in 50 diabetic outpatients with previously unknown diabetes-related gastrointestinal disorders (20 type 1 and 30 type 2 diabetic patients, mean age 47.3 ± 2.2 years, duration of diabetes 14.4 ± 1.3 years, HbA_{1c} 8.4 ± 0.3%). Exclusion criteria consisted of a history of gastric or pancreatic surgery, celiac disease, inflammatory bowel disease, lactose intolerance, scleroderma, hypothyroidism, liver cirrhosis, and colonoscopy within the last 4 weeks. All of these conditions, as well as administration of antibacterial medication within the last 4 weeks, are known to influence intestinal motility or small-bowel bacterial growth. Patients using β-blockers, H_2 blockers, proton pump inhibitors, corticosteroids, or other immunosuppressants, antidepressants, opioids, and metoclopramid were also excluded. All patients gave their informed consent for study participation. Testing for SBBO was performed at 8:00 A.M. with 80 g glucose dissolved in 200 ml of water. Samples of end-expiratory breath (20 ml) were taken at 0, 10, 20, 30, 40, 50, 60, 80, 100, and 120 min. H_2 breath concentration was measured by gas chromatography with thermal conductivity (GMI-Exhaled Hydrogen Monitor Medical; Stimotron, Wendelstein, Germany). An increase in breath H_2 concentration (H_2 exhalation) >20 parts per million was defined as indicative of SBBO. Cardiovascular autonomic nervous function was assessed with the following standardized tests: variation coefficient of 150 heart beat intervals in supine position, expiration-inspiration difference (heart rate variation during 6 deep breaths/min), the Valsalva ratio (maintaining a pressure of 40 mmHg for 15 s when blowing into the mouthpiece of a manometer), lying-to-standing ratio (heart rate response to standing up measured at the 15th and 30th heart beat), and orthostatic systolic blood pressure fall (systolic response to standing). The diagnosis of overall cardiovascular autonomic neuropathy was made if 2 or more of the 5 tests were abnormal. In a questionnaire addressing intestinal symptoms, patients were asked about diarrhea, flatulence, constipation, abdominal pain, and food intolerance. In addition, patients were asked to mark the leading symptom from which they suffered.

In 17 of 50 diabetic patients, a pathological H_2 exhalation was found (indicating $SBBO^+$), whereas H_2 exhalation was normal in 33 $SBBO^-$ patients. Diabetic patients with and without SBBO were comparable according to age, sex, duration of diabetes, BMI, HbA_{1c}, and blood pressure. Only cardiovascular autonomic neuropathy was significantly found more often in $SBBO^+$ as compared with $SBBO^-$ (41.2 vs. 9.1%; $P < 0.01$), while frequencies of retinopathy, nephropathy, peripheral neuropathy, angiopathy, hyperlipidemia, and hypertension were comparable in both subgroups. There was no correlation between the presence of cardiovascular autonomic neuropathy and duration of diabetes. Patients with SBBO reported suffering more frequently from intestinal symptoms as compared with patients with normal glucose H_2 breath tests (92.9 vs. 60.7%, $P < 0.05$). Flatulence and diarrhea were shown to occur more often in $SBBO^+$ in comparison with $SBBO^-$ patients, whereas constipation, food intolerance, and abdominal pain were equally distributed in both groups.

Scarpello et al. (6) described a pathological ^{14}C-glycocholate test, which is also considered indicative of SBBO in 4 of 7 diabetic patients suffering from diarrhea and other symptoms of autonomic neuropathy. SBBO was found in 43% of diabetic patients suffering from chronic diarrhea (3). To our knowledge, there are few other studies on animals or human that have focused on SBBO in diabetes (7).

Bacterial cultures of small intestinal aspirates are considered the "gold standard" in the diagnosis of SBBO (8). However, this procedure is invasive and requires specialized equipment. Therefore, noninvasive techniques are preferable in clinical practice. The glucose H_2-breath test is reported to have a sensitivity of 62–91% and a specificity of 75–100%, both of which are comparable with those of other non-invasive tests (3,9). Dysfunction of intestinal motility has been shown to be the leading cause of small intestinal bacterial overgrowth in other conditions, such as progressive systemic sclerosis (10). Most studies have focused on the impairment of gastric emptying and rarely on the disturbance in intestinal motility in diabetic patients (11). Impairment in frequency and amplitude of motor-migrating complex in diabetic patients with symptoms of gastroparesis was shown by Björnsson et al. (12) and could also be demonstrated by intestinal manometry. In contrast to other studies, we found a significant association between SBBO and autonomic neuropathy diagnosed by pathological cardiovascular reflex tests (3). We believe that the association of SBBO and cardiovascular autonomic neuropathy is probably because patients with cardiovascular neuropathy are likely to suffer also from gastrointestinal neuropathy. Thus, SBBO may reflect intestinal dysmotility in patients with cardiovascular autonomic dysfunction. Although the pathogenesis of small-bowel motility dysfunction is not completely understood, it has been suggested that hyperglycemia, hyperinsulinemia, and autonomic neu-

ropathy may be involved. The presence of these conditions would lead to decreased concentrations of pancreatic polypeptide and motilin (11,12). Gastrointestinal symptoms were found to be only weakly associated with the grade of intestinal motility dysfunction in previous studies (2). In our study, patients with bacterial overgrowth suffered more often from gastrointestinal symptoms like flatulence as compared with patients without SBBO.

Taken together, we found SBBO in approximately one-third of patients with diabetes associated with cardiovascular autonomic neuropathy. Therefore, in diabetic patients suffering from unspecific gastrointestinal symptoms, bacterial overgrowth should be taken into diagnostic and therapeutic considerations.

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Thyroid Autoimmunity Starting During the Course of Type 1 Diabetes Denotes a Subgroup of Children With More Severe Diabetes

Thyroid autoimmunity (TAI) is the most prevalent immunological process affecting children and adolescents with type 1 diabetes (1–5). The susceptibility to develop multiple autoimmune diseases could be associated with disease-specific determinants. Several cross-sectional studies focused on clinical, genetic, and immunological differences that could distinguish patients with and without thyroid dysfunction, but no significant difference was found in either adult or pediatric studies (5–7).

Heterogeneity has been described in the natural history of TAI in type 1 diabetes: TAI may be diagnosed either at the onset of diabetes or during the follow-up, but no comparison has been made between these 2 populations.

In our longitudinal study, we analyzed 270 consecutive patients attending the Department of Pediatrics of the University Federico II of Naples from 1992 to 1998. The mean age was 13.1 ± 4.3 years (range 1–18). Thyroid screening (TT3, TT4, thyroid-stimulating hormone, thyroglobulin, and thyroperoxidase antibodies) was performed at the end of the first admission and then yearly. Diagnosis of TAI was based on the presence of persistent elevated serum levels of thyroid autoantibodies and was confirmed by ultrasound images.

Prevalence of TAI in our diabetic population was 18.1% (49 of 270 patients), and the female-to-male ratio was ~2:1 (32 females, 17 males). At the time of TAI diagnosis, 42 patients were euthyroid and 7 were hypothyroid (overt or subclinical). After a mean follow-up of 6.2 ± 3.8 years, a progression toward hypothyroidism was observed in 1 male subject and hyperthyroidism in 2 female subjects. Therefore, among TAI patients, the prevalence of hypothyroidism was 16% and that of hyperthyroidism was 4%. A family history of thyroid disorders was more prevalent among diabetic patients with TAI than among patients without TAI (33 vs. 9.4%, $P < 0.0001$).

Among diabetic patients with TAI, subjects with thyroid dysfunction presented a higher prevalence of a third autoimmune condition (celiac disease or chronic arthritis) than euthyroid patients and the diabetic control population (33 vs. 7.7 and 7.6%, respectively).

In 27 of 49 (55%) patients, TAI was diagnosed at the onset of diabetes (group A), whereas in the remaining 22 it was diagnosed after a mean duration of diabetes of 7 years (range 1.16–8.8 years) (group B). The remaining 221 diabetic patients, who were TAI negative, were the control group (group C). The age at diabetes onset was significantly higher in group A (9.9 ± 3.8 years) than in groups B and C (6.0 ± 3.6 and 7.6 ± 3.8 years, respectively; $P = 0.001$, analysis of variance [ANOVA]). Moreover, the mean age of group A at TAI diagnosis (9.9 ± 3.8 years) was lower than that of group B (13.1 ± 3.3 years, $P = 0.0001$). Pubertal stage was assessed at TAI diagnosis. In group A, 12 of 27 (44.4%) were prepubertal, 11 of 27 (40%) were pubescent, and 4 of 27 (14.6%) were postpubertal. In group B, 3 of 22 (13.6%) were prepubertal, 10 of 22 (45.5%) were pubescent, and 9 of 22 (40.9%) were postpubertal. Interestingly, group B patients presented a more severe form of diabetes, which was characterized by a higher prevalence of ketoacidosis at

diabetes onset (50 vs. 26 in group A and 33% in group C), a higher daily insulin dose (1.1 ± 0.1 vs. 0.7 ± 0.3 in group A and 0.8 ± 0.3 U · kg^{-1} · day^{-1} in group C; $P = 0.004$, ANOVA), and worse metabolic control assessed in the last year of the follow-up (HbA_{lc} [mean of the last 3 values], 8.3 ± 1.1 vs. 7.3 ± 1.2 in group A and 7.5 ± 1.1% in group C; $P = 0.003$, ANOVA).

Our study on children and adolescents with type 1 diabetes supports previous studies in terms of TAI prevalence, female predominance, and presence of family history of thyroid diseases. As previously reported (4), a higher prevalence of another autoimmune disease was found in patients with thyroid dysfunction.

By dividing patients according to the time of TAI diagnosis, it was possible to identify 2 subgroups with different clinical expressions of diabetes. In particular, patients with contemporary diagnoses of both diseases presented at an unusual age for diagnosis of both diabetes and TAI. In these patients, compared with our local diabetic population, presentation of diabetes was slightly delayed, but TAI was diagnosed earlier than that reported by Maenpaa et al. (8) in the general population (12.2 ± 0.58). On the contrary, TAI diagnosed during the course of diabetes seems to be the result of 2 serial hits: the first one is diabetes at prepubertal age and with more severe characteristics and the second one is TAI in the years of late puberty, when the physiological pubertal changes seem to play a triggering role.

Therefore, we recommend that if the initial thyroid screening is negative, future tests should be performed in type 1 diabetic patients, especially during pubertal ages, even in the absence of clinical signs.

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Diabetic Ketoacidosis

A complication of type 2 diabetes in Canadian aboriginal youth

Diabetic ketoacidosis (DKA) is characterized by hyperketonemia, metabolic acidosis, and hyperglycemia (1). It is usually considered a complication of type 1 diabetes and can cause severe morbidity and mortality if not recognized and treated in a judicious manner. DKA is precipitated by an absolute or relative lack of insulin in combination with an increase in the catabolic hormones, which leads to an increased production of ketone bodies and glucose by the liver (1).

There have been several recent reports of DKA in adults with type 2 diabetes (2–6). Pinhas-Hamiel et al. (7) have reported its occurrence among obese African-American youth with typical insulin-resistant type 2 diabetes. There are several reports that described the increasing problem of type 2 diabetes in youth; these studies have also reported DKA at diagnosis in some of these youth. These reports do not, however, define DKA and/or include pH in their criteria for DKA (8–10). We present our experience with DKA in Canadian aboriginal children and youth with type 2 diabetes

We reviewed the charts of all individuals diagnosed with type 2 diabetes at the Winnipeg Children's Hospital (Winnipeg, Manitoba, Canada) for the 14-year period between January 1986 and December 1999 inclusive. All patients were 18 years of age or younger and resided in Manitoba or Northwestern Ontario. These regions are serviced by a single tertiary care pediatric center (Winnipeg Children's Hospital). It is possible that mild cases of DKA were treated in peripheral hospitals and were not referred to the Children's Hospital. Thus, this report generates a minimal prevalence for DKA in youth with type 2 diabetes in these regions.

Diabetes was diagnosed according to the guidelines of the Canadian Diabetes Association (11). Type 2 diabetes was diagnosed in individuals who were able to be maintained without exogenous insulin for >6 months and who had clinical features typical of type 2 diabetes. These included a positive family history, obesity, acanthosis nigricans, and absence of any medication or underlying illness that might predispose to secondary diabetes. We have recently reported that the First Nation youth with diabetes seen at our institute lack evidence of autoimmunity (12). Two of the subjects reported here (subjects 11 and 12) were included in that report and were negative for islet cell antibodies, GAD antibodies, and insulin autoantibodies.

DKA was defined as pH ≤7.35 and HCO_3 ≤15 mEq/l in the presence of hyperglycemia. Total glycosylated hemoglobin was measured by an affinity chromatography method (Isolab) from 1986 to 1996 and by the Abbott Imx Analyzer from 1996 and thereafter. Results are reported as calculated HbA_{1c} values (normal range 4.4–6.4%).

Between 1986 and 1999, 120 type 2 diabetic children and adolescents 6–18 years of age were seen at our center. Of these children, 118 (98%) were of self-declared aboriginal origin, 90 (75%) were girls, and 13 (10.8%) experienced episodes of DKA. All 13 episodes were experienced by children of aboriginal descent; 5 (38.5%) of

Table 1—*Clinical presentation of DKA*

Case	Sex	Age at diagnosis (years)	Age at DKA (years)	BMI (kg/m^2) at DKA* (percentile)	pH	HCO_3 (mmol/l)	BHOB (normal 0.0–0.3 mmol/l)	Blood glucose (mmol/l)	HbA_{1c} (%)
1	F	9	12	24 (>95th)	7.35	13.0	1.9	27.0	12.6–15.3†
2	F	12	14	28 (>95th)	6.90	NA	NA	32	10.9–12.2†
3	F	11	14	23 (>75th)	7.10	NA	NA	22.2	16.2
4	F	16	16	36 (>95th)	7.02	NA	NA	NA	NA
5	F	14	17	35 (>95th)	7.25	7.7	6.1	22.5	14.6
6	F	15	15	35 (>95th)	7.10	15.0	6.2	32.6	9.5
7	F	11	13	22 (>75th)	7.00	2.7	15.0	31.0	14.3
8	F	13	15	28 (>95th)	7.00	1.0	8.0	16.8	18.6
9	F	15	15	27 (>95th)	7.31	14.7	6.9	28.8	NA
10	F	12	12	29 (>95th)	7.17	3.0	8.3	37.7	NA
11	M	12	12	26 (>95th)	7.28	9.9	8.9	58.2	13.8
12	M	13	13	34 (>95th)	7.09	5.8	5.4	54.9	NA
13	F	10	17	27 (>90th)	7.22	7.8	8.8	24.1	12.7

Cases 1–3 were observed between 1986 and 1990. Cases 4–9 were observed between 1991 and 1995. Cases 10–13 were observed between 1996 and 1999. *BMI percentiles are listed in the article by Hammer (17); †because HbA_{1c} values were unavailable at the time of DKA, they were obtained 6 months before the episode of DKA. BDHB, betahydroxybutyrate; NA, not available.

these episodes occurred at the time of type 2 diabetes diagnosis. Thus, DKA occurred in 4.2% (5 of 120) of all presentations of type 2 diabetes seen at our institute. A female predominance was seen (11 of 13 [84.6%]) as a slight overrepresentation compared with the sex distribution within our clinic. Mean age at DKA was 14.2 ± 1.8 years. This is similar to the mean age of our current caseload with type 2 diabetes (14.9 ± 2.1 years). As a group, the subjects were obese, having a mean BMI of 28.8 (± 5.0 kg/m^2).

Obvious precipitants for the episode of DKA were found in 3 individuals (pneumonia, gonoccoccal septicemia, and a severe culture-negative systemic illness resembling sepsis). One young woman was pregnant at the time of DKA and subsequently had a spontaneous miscarriage. Glycemic control at the time of DKA was uniformly poor in all patients in whom an HbA_{1c} was available (mean HbA_{1c} 13.9 ± 2.6%). Currently, ~50% of the youths with type 2 diabetes seen in our center maintain an HbA_{1c} value <7.0%. There were 5 of 13 (38.5%) individuals (all girls) who had a second documented episode of DKA.

A positive family history of type 2 diabetes was found in all of the subjects. Of 13 patients, 11 had an affected first-degree relative; all 13 subjects had many affected second-degree relatives. This is typical of the population seen at our institute with type 2 diabetes. Details of their clinical presentation are shown in Table 1.

The prevalence of type 2 diabetes is increasing in the children and adolescents of Canada's aboriginal people (13,14). In another Native North American population, there is evidence that the prevalence, and not just the detection of this problem, is increasing (15). In our institute, the majority of cases with type 2 diabetes are in youth of aboriginal origin. The diagnosis of type 1 diabetes is very rare in this group and occurs in young children of mixed ancestry.

The distinction between type 1 and type 2 diabetes can be difficult in the pediatric population, particularly when DKA is the presenting feature. However, this distinction is important because of differing education and long-term treatment strategies. The implications for family members for the risk of diabetes also differ. Those young people with type 2 diabetes may well be able to discontinue insulin once their condition has stabilized; therefore, they may not have to contend with injections and the side effects of insulin e.g., weight gain, and hypoglycemia.

DKA has been previously reported in type 2 diabetes, predominantly in adults (2–6). Many of the previous reports demonstrate a predominance of males (2,4,5,16). A lower prevalence of obesity has been noted in some reports (3–5). In our population, females predominate and the majority of BMIs were in the obese range (>85th percentile for age and sex).

Pinhas-Hamiel et al. (7) reported the occurrence of DKA among obese African-American youth with typical insulin-resistant type 2 diabetes. Our population is also obese and had their episode of DKA at a mean age of 14.0 years, similar to the African-American adolescents. The sex distribution in our population, compared with that reported by Pinhas-Hamiel, is more skewed, having a greater female predominance. Four older adolescents (aged 15–17 years) with type 2 diabetes presenting in DKA have been reported from Japan, all of whom were obese males with a history of exceptionally large intakes of sugared drinks (16).

A precipitating illness was found in the minority (3 of 13) of our population, contrary to other reports (5,6,16). This is similar to the population reported by Pinhas-Hamiel et al. (7), who found an acute illness in only 4 of 12 episodes of DKA in their series. Glycemic control in our population was uniformly poor (mean HbA_{1c} 13.79 ± 2.6%) and is likely a contributing factor to DKA.

Five of the subjects in this report had at least 1 documented repeat episode of DKA. Despite this, we remain confident that they have type 2 diabetes on the basis of clinical criteria and the significant periods of time without insulin therapy, weight loss, symptoms of hyperglycemia, or acute metabolic decompensation. Continued poor long-term glycemic control was the factor common to all these cases.

The occurrence of DKA in type 2 diabetes in aboriginal youth emphasizes the importance of screening youth at risk for diabetes (e.g., aboriginal origin, positive family history, or obesity). In this article, 38.5% of patients who had an episode of

DKA had DKA at presentation of diabetes. Screening at-risk populations may prevent presentation of individuals in DKA and thus prevent a potentially fatal complication of diabetes. Screening will also provide for earlier diagnosis, thereby allowing introduction of education and treatment at an earlier stage and potentially decreasing the chronic complications of diabetes.

In summary, DKA occurs in aboriginal children and youth with type 2 diabetes and represents a potentially life-threatening complication of this disorder. DKA may occur at the presentation of the disease or during the disease course. Thus, the presence of an episode of DKA cannot be used to support the diagnosis of type 1 diabetes in this population or, alternatively, as evidence against the diagnosis of type 2 diabetes.

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Interaction of Gliclazide and Rifampicin

We describe a patient with type 2 diabetes who required an increase in daily dosage of gliclazide after rifampicin administration. To our knowledge, this is the first report of the interaction between gliclazide and rifampicin.

A 65-year-old man with type 2 diabetes had been treated with diet (30 kcal/kg) and gliclazide (80 mg/day) without problems for 2 years. In mid-February 1998, he was diagnosed with atypical mycobacteriosis caused by *Mycobacterium gordonae* and was treated with rifampicin, isoniazid, ethambutol, and clarithromycin (450, 400, 750, and 400 mg/day, respectively). The fasting plasma glucose (FPG) concentration was 6.4 mmol/l; HbA_{1c} was 5.4%; and 1,5-anhydroglucitol was 17.9 μg/ml before the commencement of treatment for atypical mycobacteriosis. FPG was found to be increased 11 days later, and after treatment on day 17 it was further elevated up to 11.3 mmol/l. Although the dose of gliclazide was increased to 120 mg/day on day 20, FPG was still >9 mmol/l. Finally, the dose was increased up to 160 mg/day on day 32. The plasma concentration of gliclazide 2 h after an oral dose of 80 mg gliclazide was 1.4 μg/ml on day 75, but it increased up to 4.7 μg/ml after discontinuation of 7 months of rifampicin treatment. Therefore, the dose of gliclazide was reduced to 80 mg/day, and HbA_{1c} diminished to 5.4–5.6%.

This case strongly suggests an interaction between rifampicin and gliclazide. Rifampicin has been reported to interact with several drugs, such as oral anticoagulants, glucocorticoids, digitoxin, quinidine, ketoconazole, and verapamil (1). Some oral hypoglycemic agents have also been reported to interact with rifampicin. For example, the half-life and serum concentration of tolbutamide were decreased after rifampicin treatment in both healthy volunteers and patients with tuberculosis (2,3). In patients receiving treatment other than rifampicin for tuberculosis, no significant changes in serum levels of tolbutamide were observed (2). Self and Morris (3) reported a diabetic patient who required higher doses of chlorpropamide when treatment with rifampicin was initiated. The serum chlorpropamide concentration diminished during rifampicin therapy, but rose dramatically on discontinuation of the antibiotic with a decrease in blood glucose level (3). In patients with diabetes treated with glibenclamide, plasma glucose levels increased after administration of rifampicin (4,5), and dose modification of glibenclamide was required because of poor control of diabetes (4,5). Plasma glucose concentration in these patients returned to the normal range by day 6 after discontinuation of rifampicin therapy (4).

Cytochrome P-450 (CYP), which is the most important enzyme in the liver concerned with drug metabolism, plays a part in the interaction between rifampicin and oral hypoglycemic agents (6). Rifampicin is a potent inducer of CYP2C9 (6), which metabolizes tolbutamide and glibenclamide (7). Gliclazide is also metabolized by CYP2C9 (8). In the present case, the concentration of gliclazide during treatment with rifampicin was lower than the effective concentration, and the concentration of gliclazide increased after discontinuation of rifampicin. This case suggests that treatment with rifampicin increases the clearance of gliclazide eliminated by CYP2C9 and reduces the concentration of gliclazide.

Isoniazid, rather than rifampicin, may have affected the metabolism of gliclazide in this case. In 1959, Segarra et al. (9) reported that simultaneous administration of both tolbutamide and isoniazid slightly reduced the plasma glucose level, compared with that of tolbutamide alone. There is only one prior report on the interaction between isoniazid and an oral hypoglycemic agent, and the mechanism of this interaction has not been entirely elucidated. Isoniazid could hardly have exerted an influence on the metabolism of gliclazide in our case.

Our case demonstrates the clinical importance of adverse pharmacokinetic interactions between gliclazide and rifampicin. Caution should be exercised during concurrent use of these 2 agents.

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No Inverse Relationship Between Total IgE Levels and Islet Autoimmunity in Children of Parents With Type 1 Diabetes

Type 1 diabetes is considered a Th1-mediated autoimmune disease (1), and it is suggested that its development is negatively associated to that of Th2-mediated allergy (2,3). In particular, a recent study reported that patients with type 1 diabetes had fewer allergic episodes than control subjects, and interestingly, the frequency of episodes in the first-degree relatives of the patients was intermediate between that of patients and control subjects. This suggests that there may be a genetic and/or environmental basis to the negative association (3). Because allergy is accompanied by high levels of IgE, it might be expected that total IgE levels would be lower in subjects who are at risk of developing type 1 diabetes. We have prospectively examined the IgE levels of 114 children of parents with type 1 diabetes at birth, 9 months, 2 years, and 5 years of age. This group included 30 children with persistently positive islet autoantibodies (11 of whom subsequently developed type 1 diabetes and 16 who had the high diabetes risk HLA-DR3/4 or HLA-DR4/4 genotypes) and 84 islet antibody–negative children (42 with the high-risk genotypes) from the BABYDIAB Study (4,5). IgE levels in the total cohort increased from a median of 1 kIU/l at birth to 4, 8, and 15 kIU/l at 9 months, 2 years, and 5 years, respectively. No differences were found between children when analyzed by either islet autoantibody status or diabetes-associated HLA genotypes: medians at birth, 9 months, 2 years, and 5 years were 1, 5, 8, and 17 kIU/l in children with islet autoantibodies and high-risk genotypes; 1, 4, 6, and 11 kIU/l in children with islet autoantibodies, but without high-risk genotypes; 1, 3, 9, and 17 kIU/l in children without islet autoantibodies but with high-risk genotypes; and 1, 4, 9, and 14 kIU/l in children without islet autoantibodies and without high-risk genotypes. IgE levels associated with allergy (>150 kIU/l) were found in 4 (13%) islet autoantibody–positive children (1 has subsequently developed type 1 diabetes) and 3 (4%) islet autoantibody–negative children ($P = 0.08$). Increases in IgE levels were found concomitant with autoantibody appearance in 2 children and after islet antibody appearance in the other 2 children. Decreases in IgE levels at the time when islet autoantibodies appeared were not seen. These data fail to show an inverse relationship between IgE levels as a marker of allergy and islet autoimmunity within relatives of patients with type 1 diabetes.

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COMMENTS AND RESPONSES

Status of American Diabetes Association–Funded Research

After much hard work on the part of members of the Professional Section, volunteers, and staff, the most recent Five-Year Plan of the American Diabetes Association (ADA) contained a research funding goal of allotting 1 in 3 dollars of total public support to research awards and grants. A model presented to the Board of Directors a few years ago proposed that this goal might be reached with gradual increases during the first 3 years and more steep increases during the final 2 years. In my presidential address in June 1998 (1), I asked that members of the Professional Section not only hold the ADA accountable, but work with the ADA to reach these research funding goals.

This letter is to apprise members of the Professional Section and other interested parties of our progress. During fiscal year 1998, the year before the current Five-Year Plan started, total public support was $90.8 million, $15.5 million of which was devoted to research awards and grants. Total public support for fiscal year 1999 was $101.5 million, of which $18.2 million was slated for research awards and grants.

Although the ADA did follow its established research funding policies this first year of the plan, goals for subsequent years will be significantly more challenging to meet. A quick calculation of the amounts raised and the proportion devoted to research awards and grants in fiscal years 1998 and 1999 reveals the distance we have to go to meet the goal of 1 in 3 dollars for research in fiscal year 2003. To help meet this challenge, members of the Professional Section should not only remind ADA representatives of what still needs to be accomplished, but more importantly, devote some time and effort to help raise funds. This is especially important for the Research Foundation, where at least 80% of the monies go directly to research. Some of you see patients who have the means to help the ADA research mission; please consider engaging these individuals in that mission.

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GHb (HbA_{1c}) Is More Sensitive Than Fasting Blood Glucose as a Screening Test for Diabetes

In a recent article, Rohlfing et al. (1) proposed the use of HbA_{1c} as a highly specific and convenient alternative to fasting plasma glucose (FPG) for diabetes screening. These results are issued from the Third National Health and Nutrition Examination Survey (NHANES III), which was performed in a representative sample of the U.S. population. The limit proposed by the authors is an HbA_{1c} value $>6.1\%$. The corresponding relative sensitivity was estimated at 63.2%, and the relative specificity was estimated at 97.4%.

This analysis raises several questions. The validation of HbA_{1c} relies on the diagnosis of diabetes with FPG $\geq$126 mg/dl as the "gold standard" according to the American Diabetes Association (ADA) criteria (2). However, it has been demonstrated in the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe study, which pooled epidemiologic data from 8 European countries, that 52% of the subjects having a 2-h plasma glucose level (2-h PG) $\geq$200 mg/dl are not detected when using only FPG $\geq$126 mg/dl (3). According to the ADA Expert Committee (2), in NHANES III, the corresponding percentage is at least 31%. Thus, FPG alone is not sensitive enough to screen for diabetes screening.

In addition, we wonder why the cutoff of 6.1% was chosen by the authors; a lower value would have resulted in a sensitivity better than 63.2%.

Our experience with diabetes screening, though in a smaller sample, is at variance with these results. We are conducting a diabetes prevalence survey in the Island of La Réunion, a French overseas department. Fasting capillary blood glucose (FCBG) (LifeScan One Touch II; Ortho Diagnostics, Milpitas, CA) and HbA_{1c} (DCA 2000; Ames, Bayer Diagnostics, Basingstoke, U.K.) were systematically measured at home in a representative sample of 1,580 subjects 30–69 years of age. Informed written consent was obtained from all participants. A second examination was performed at the study center on 258 subjects not previously diagnosed with diabetes. All of the subjects underwent a 2-h oral glucose tolerance test (4). Plasma glucose was measured by the glucose oxidase method.

There were 54 subjects classified as diabetic (according to the ADA criteria) because they had an FPG $\geq$126 mg/dl (3) and/or a 2-h PG $\geq$200 mg/dl. Results show that, among the 54 subjects classified as having diabetes, only 4 had HbA_{1c} $<6.0\%$, whereas 25 had FCBG $<$126 mg/dl. Thus, HbA_{1c} $\geq 6.0\%$ seems to be a relevant limit. However, among the 103 subjects with HbA_{1c} $\geq 6.0\%$, only 50 were classified as diabetic. Consequently, HbA_{1c} considered alone appeared highly sensitive (93%) but moderately specific (74%). We did not obtain a better performance with FCBG alone or in combination with HbA_{1c}.

Finally, we agree with the recommendations of Rohlfing et al. (1) for the use of HbA_{1c} for diabetes screening, but we pro-

pose a limit corresponding to a high sensitivity, estimated at HbA_{1c} ≥6.0% in our survey. In opposition to the findings of Rohling et al., use of this value resulted in a high sensitivity (93%) and a moderate specificity (74%). These results, as compared with those using FCPG alone, contributed to the overall effectiveness of using HbA_{1c} to screen for diabetes.

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Use of GHb (HbA_{1c}) to Screen for Undiagnosed Diabetes in the U.S. Population

Rohlfing et al. (1) used data from the Third National Health and Nutrition Examination Survey (NHANES III) to evaluate the use of glycohemoglobin (GHb) as a screening test for undiagnosed diabetes. There are 3 issues that need to be considered when interpreting their results.

First, the authors chose to evaluate GHb as a screening test for undiagnosed diabetes based on fasting plasma glucose (FPG) ≥7.0 mmol/l alone. Reliance on FPG for the diagnosis of diabetes differentially misses substantial numbers of subjects with isolated post-challenge hyperglycemia who have rates of microvascular complications (particularly diabetic retinopathy) and mortality similar to those of other diabetic subjects (2–4). Of the 6,615 subjects in the NHANES III data set with all 3 glucose measures, 1,272 had diabetes based on either an FPG ≥7.0 mmol/l or a 2-h (75-g oral glucose load) plasma glucose (2-h PG) ≥11.1 mmol/l. Of the individuals with diabetes, 485 were diagnosed on the basis of both FPG and 2-h PG, 82 on the basis of FPG alone, and 705 on the basis of 2-h PG alone. Thus, 705 (55%) patients would not have been identified if only the FPG criterion had been used. If GHb is compared with FPG as the gold standard, a cutoff value of GHb ≥6.0% provides sensitivity of 0.862 and specificity of 0.850. However, if GHb is compared with 2-h PG ≥11.1 mmol/l as the gold standard, GHb ≥6.0% is associated with sensitivity of 0.627 and specificity of 0.880. If GHb is compared with FPG ≥7.0 mmol/l or 2-h PG ≥11.1 mmol/l, GHb ≥6.0% is associated with sensitivity of 0.613 and specificity of 0.885. Thus, GHb does not perform as well in predicting diabetes based on FPG and 2-h PG criteria.

Secondly, studies have demonstrated that GHb does not perform as well as 2-h PG or FPG in diagnosing diabetes. We have previously demonstrated that in the Egyptian population, 2-h PG and FPG both perform better than GHb in minimizing the overlap of the components of the bimodal distributions (5). Using receiver-operating characteristic analyses, we also demonstrated that both 2-h PG and FPG perform significantly better than GHb in predicting the prevalence of diabetic retinopathy (5).

Lastly, GHb may be unsuitable as a screening test for other reasons. GHb tends to be more expensive than other glucose measures. The lack of widely used laboratory standard reference materials and variation in the reference method remain a limitation; however, as the authors note (and in a large part, due to their efforts), many advances have been made in this area. Finally, a study in a small number of normoglycemic individuals failed to find a relationship between fasting venous glucose and HbA_{1c} values (6). Others have found that only 2–30% of the variance in GHb in nondiabetic individuals can be explained by fasting or postload glucose; the remainder is presumably related to factors independent of glycemia, such as differences in the rate of glycation and in red cell survival (7,8).

In summary, the performance of GHb for the diagnosis of diabetes based on a gold standard that includes FPG and 2-h PG criteria is substantially less sensitive than reported. A number of factors further limit the suitability of GHb as a screening test.

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Response to Herman et al. and Papoz et al.

We appreciate the interest of Herman et al. (1) and Papoz et al. (2) in our study of the use of glycohemoglobin (GHb) as a screening test for diabetes (3). Our purpose was not to debate the validity of the current American Diabetes Association criteria for diabetes diagnosis, which will undoubtedly be a topic of discussion for some time. Our data simply show that GHb is both sensitive and specific in detecting diabetes when compared with fasting plasma glucose (FPG).

As noted in our report, some cross-sectional studies comparing GHb with FPG and/or the oral glucose tolerance test have concluded that GHb is a useful screening test, while others, including the study cited by Herman et al. (4), have suggested the opposite. However, prospective studies have shown a high correlation between GHb and the presence of microvascular complications (5–7).

Regarding the issue of cost, it has been noted that because GHb does not require special patient preparation, it may actually be more cost effective than FPG in some screening situations (8). With respect to the issue of GHb standardization, we agree that considerable progress has been made in this area. Since 1996, the National Glycohemoglobin Standardization Program (NGSP) has certified many GHb assay methods that have passed a rigorous precision- and bias-testing protocol comparable with the Diabetes Control and Complications Trial. Proficiency-testing data from the College of American Pathologists have documented excellent comparability of results between laboratories when NGSP-certified methods were used (9). With respect to the issue of interindividual variation of GHb, we are unaware of any data suggesting that normoglycemic individuals are at significant risk for development of diabetic complications as long as GHb levels remain within the nondiabetic range. Moreover, numerous studies have shown a strong correlation between GHb and plasma glucose levels in individuals with diabetes (10–12).

Interestingly, Papoz et al. found higher sensitivity and lower specificity than we did for detecting diabetes at a GHb cutoff of 6.0% (our cutoff was 6.1%). Different GHb cutoff levels can be selected for screening based on the sensitivity/specificity desired, but this in turn depends on the assay method used and the characteristics of the population being screened; as we showed, there are differences in sensitivity and specificity between ethnic groups. Based on our assay method and study population, we chose a cutoff of 2 standard deviations above the normal mean, which resulted in moderate sensitivity but very high specificity. Given that GHb levels $<7.0\%$ confer low risk for complications, we believe this cutoff would identify almost all individuals at significant risk for complications, while resulting in very few false positives.

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Transcutaneous Glucose Measurements Using Near-Infrared Spectroscopy

Validation of statistical calibration models

A recent article on a noninvasive transcutaneous assay for blood glucose using near-infrared spectroscopy was published by Gabriely et al. (1). The authors reported on mean absolute pre-

diction errors for blood glucose concentrations as low as 2.6 mg/dl (0.14 mmol/l). This approach would provide a splendid analytical performance for the hypoglycemic range, which has never been achieved, even with far less complex in vitro samples using near-infrared spectroscopy. Unfortunately, their results based on statistical partial least-squares (PLS) calibrations are extremely questionable.

An important and sensitive issue in statistical calibrations is the validation of calibration models. Problems related to such measurements were recently discussed by Arnold et al. (2), elucidating the pitfalls of statistical calibrations using tissue phantoms without glucose being present. Their conclusion, which we support, was that more rigorous testing strategies have to be applied to prove the applicability of such calibration models.

Details on the calibration and validation design are essential for judging the scientific value of the calibration models used. Such rules were not followed in the article by Gabriely et al. (1). The authors omitted any information concerning spectral quality, range, resolution, and the number of spectral variables used for their calibrations. Most results were from the calibration fit itself, which is known to give better results for sensitive linear equation systems compared with independent predictions. For such a validation, the authors picked 6–10 masked data pairs from each of their individual calibration populations. However, it is not clear whether these data were left out one at a time (similar to leave-one-out crossvalidation) or as a complete package. Furthermore, the calibration experiments were made up from 2 glucose concentration profiles of nearly constant slope, prone to run parallel to other drift effects. Without more sophisticated validation strategies, their results cannot be accepted. We calculated from their results (Fig. 3*C*) a standard error of prediction (SEP) of 5.4 mg/dl (0.3 mmol/l) (mean absolute error 3.7 mg/dl) for the pooled masked values (n = 75, SD 17 mg/dl, mean reference concentration 76 mg/dl).

For comparison, the illustrative results presented below were obtained within our previous feasibility studies from in vivo data as measured during oral glucose tolerance testing (3). Different PLS calibration models, based on a selected spectral interval, were considered. For validation, different methods, such as crossvalidation with leaving 1 or 10 samples out, as well as using day-to-day testing were applied in our case (H.M.H., P.L., unpublished observations). The results demonstrate the dangers of overfitting when too many variables are taken into account for modeling. For calculating robust calibration models, the parsimony principle with respect to the number of spectral variables is of great importance. We have seen an improvement in prediction performance with a reduction of spectral variables (3). Our best result with a mean absolute error of 30 mg/dl (1.7 mmol/l) (SEP 37 mg/dl, SD [reference data] 168 mg/dl) was obtained with leave-one-out crossvalidation for our complete 2-day series. However, we also tested the robustness with respect to transferability of the calibration models to data of other separate days (H.M.H., P.L., unpublished observations).

Another test demonstrated that any simple artificial glucose concentration profile can be fitted with good precision, using the same validation tools as applied by Gabriely et al. Instead of using the actual blood glucose profiles, we calculated a PLS regression against a running spectrum number (equivalent to a straight line through the origin) during our 2-day test (SD [reference data] 38.2, mean value 66.5 [dimensionless]). For example, using 115 spectral variables, a splendid fit was obtained, leading to an SEP value of 7.1 and 8.2 by crossvalidation with leave-one-out and leave-ten-out strategies, respectively. With calibration models calculated from data of 1 day only, the predictions using the spectral measurements of the other day failed completely and were therefore in opposition with the results obtained from measuring blood glucose concentration profiles.

In regard to the work of Gabriely et al. (1), it is essential to know if the calibrations calculated from measurements with decreasing blood glucose, successfully predict the concentrations observed on the increasing blood glucose range and vice versa. To acquire such knowledge, more day-to-day tests must be conducted. To avoid chance correlations and overfitting with many spectral variables, more sophisticated calibration design and validation experiments than previously applied in many investigations are essential.

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Transcutaneous Glucose Measurement Using Near-Infrared Spectroscopy During Hypoglycemia

We appreciate the opportunity to respond to the issues raised in this issue by Heise and Lampen (1) concerning our article "Transcutaneous Glucose Measurements Using Near-Infrared Spectroscopy: Validation of Statistical Calibration Models" (2).

First, we should emphasize that differences in the accuracy of glucose prediction using near-infrared spectroscopy depend on both the hardware used and spectral data processing to construct calibration models. The goal of achieving improved prediction and accuracy by using this technology will ultimately need optimization of both components to develop the biological models that reflect relevant physiology in humans.

More specifically, Heise and Lampen misinterpreted our data and thus reached some erroneous conclusions. Their assumption that "most results were from the calibration fit itself" is incorrect; all of the results given, other than those for the "masked" values, were obtained by leave-one-out crossvalidation, the same technique used by Heise et al. (3). In addition

the "masked" values we reported were not included in the calibrations and thereby formed an independent validation set. Information on calibration and validation experimental design was provided, and we believe that selection of spectral variables is only one of several strategies used to optimize the calibration and to avoid overfitting (4).

Heise and Lampen also failed to appreciate the basis for using an in vivo experimental model with a glucose profile involving hypoglycemia and recovery. To clarify, such a profile minimizes the potentially spurious correlation between plasma glucose values and any components within the data that vary linearly. For example, a sometimes unappreciated source of linear variation results from the process of drawing blood samples for reference analysis and infusing saline to maintain the integrity of the catheterization, both of which may lower hemoglobin concentrations in a linear fashion. Although the dual-beam instrument used in this study was continually corrected for reference energy and dark offset, which thereby minimized instrument drift, the hypoglycemia protocol also rejected any residual linear drift. Heise and Lampen's suggestion that we should calibrate on measurements with declining blood glucose and predict the concentrations from observations on the increasing blood glucose, and vice versa, fails to break the correlation between linear-drift components and the glucose values. Consequently, the advantages of our experimental design would be eliminated.

Heise and Lampen also misconstrued our data concerning the "mean absolute errors for blood glucose concentrations [being as low as] 2.6 mg/dl." This calculation of the difference of mean values for each of the reported 10-mg/dl ranges is a measure of bias between results derived from using the Beckman analyzer and the corresponding near-infrared spectral data. This calculation is a different statistic than the mean absolute error, the standard error of prediction, or the root mean square difference (RMSD). Bias-corrected standard error of prediction is usually used to describe the variability of the errors as distinct from bias, whereas RMSD is used to include the effect of bias.

Finally, we are well aware of the published work of Arnold et al. (5) as referenced in our article. We support their conclusion that rigorous testing strategies have to be applied to validate calibration models. We stated in our article that challenges remain before we can clinically apply such a noninvasive technique. Studies designed to broaden the applicability of near-infrared spectroscopy are under way. The prevention and treatment of hypoglycemia remain primary goals of our research program.

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"Real-Life" Driving Behavior While Hypoglycemic?

As a researcher who examines the psychological aspects of diabetes and as a diabetic patient, I was compelled to critique the study by Cox et al. (1) concerning hypoglycemia's impact on driving. I am a longstanding diabetic patient (diabetes duration = 29 years) who has hypoglycemia unawareness, so I check my blood glucose levels (BGL) before I drive and approximately every 2 h while driving (including stop overs for shopping, work, etc.). I hope this is the practice of diabetic individuals who are also in my position. Cox et al., Marrero et al. (2), and Frier (3) emphasized the need for practitioners to help people with diabetes understand how to identify and correct hypoglycemia, especially in the context of driving, and the need to check BGL before driving. I wholeheartedly agree with the latter recommendation; the former is unrealistic. In my personal experience, I have never been told by someone who does not have diabetes how to monitor for hypoglycemia. Furthermore, if they had done so, I would have dismissed their advice. A practitioner simply cannot tell me how I react or how "I feel" when my BGL is low. Yes, there are certain signs to watch for, but diabetic patients will react differently. (For example, a sibling of mine also has type 1 diabetes, but our hypoglycemic symptoms are totally different.)

Diabetic patients believe that they are at risk for losing their driving privileges because of their disease. This perceived risk may prevent the diabetic patient from speaking openly about BGLs with his or her healthcare provider. An approach that should be taken by practitioners is simply emphasizing the importance of immediate attention to hypoglycemia as well as the need to check, check, check BGLs! Self-monitoring should always be stressed. Our main objective, as diabetic individuals, is to maintain normal sugar levels. My own instructions have been to try to keep my BGL between 4.0 and 8.0 mmol/l. Thus, I would not treat myself for hypoglycemia when my blood glucose levels are between 4 and 5 mmol/l, as suggested by Cox et al. (1). Because individual responses to hypoglycemia are idiosyncratic, it is not reasonable to assert general rules of practice. Each diabetic patient will know (or learn) what is right for her/himself.

There are also concerns about the methodology of the study by Cox et al. The research was designed to reflect a more real-life situation. So, why not have instructions to the diabetic participant that read, "We are going to examine the effects of high and low BGLs on brain activity and driving behavior. Respond to your symptoms as you normally would"? On the night before testing, the participants were told to drink some soda (actually diet soda) or pull off of the road if they thought their BGL was low. There is no indication

that they were told to do so during the test duration, and perhaps it was unclear to the 26 diabetic subjects who did not stop (to correct hypoglycemia) that this was a viable option. I would need to know my BGL to know what the appropriate response would be (i.e., how much soda to drink), but this was also not an option. In a safe simulator, if someone told me that they wanted to know the effects of BGL on driving, I would have kept driving. In real life, I have different options available. Also, in the event that one of the participants did drink some soda, they may have been under the false impression that their BGL would rise, which would have prompted them to continue to drive. This emphasizes that the real objective of the research was to find out what happens to driving skills at low glucose levels, not what the reactions of diabetic subjects would be when experiencing low BGL, while driving.

Future research could replicate this study with some different objectives. First, the researchers did not want practice effects to interfere with data collection (i.e., the number of driving errors). It is important to know if errors are reduced at low BGL because of familiarity. How many of us take the same route to work each day? Is there a greater potential for danger for diabetic drivers because automization is interfering with recognizing low BGL? Secondly, at what point did driving become severely impaired for diabetic individuals? These questions were not answered because impairment seemed to be idiosyncratic. These results would be extremely beneficial for diabetic patients, especially when comparing those who are aware with those who are unaware of hypoglycemia. Other extraneous variables unaccounted for include the following: age of diagnosis, duration of disease, and driving experience. Thirdly, Cox et al. indicated that participants reported experiences of not remembering drives or other interventions when they drove. Important information would be gained by asking the following: *1*) How many times have you forgotten a driving experience? *2*) How many times did someone else help you while driving? *3*) How many times have you treated yourself for hypoglycemia while driving? *4*) How many times have you stopped driving to treat yourself for hypoglycemia? *5*) How often do you check your BGL before driving? *6*) How often do you check BGL while driving for long periods of time? and *7*) How often do you feel your driving skills have deteriorated while behind the wheel? These questions would provide much more useful information to diabetic patients and their health care providers that could possibly lead to rectifying these types of situations.

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Response to Barry-Bianchi

We strongly agree with several of the points raised in the letter by Dr. Barry-Bianchi (1) concerning our recent article on hypoglycemia and driving (2). We concur that drivers should measure their blood glucose levels before and during long drives, especially if they have either lost symptoms of low blood glucose or have a history of driving mishaps. We applaud Dr. Barry-Bianchi's diligent use of self-testing to ensure that she does not drive during hypoglycemia; however, the unfortunate reality is that not all people with type 1 diabetes follow such a stringent regimen. We also agree that health care providers cannot tell a person with diabetes what their personal symptoms of hypoglycemia are. All of our research on Blood Glucose Awareness Training (BGAT) (3,4) and hypoglycemic symptoms (5) is consistent with her opinion that symptoms are quite idiosyncratic. For this reason, BGAT encourages each person to experiment and record their symptom experiences to identify their own most sensitive and specific cues of hypoglycemia. Like Dr. Barry-Bianchi, we would strongly encourage further research to increase our understanding of the problem of hypoglycemia and driving. Her suggestions for the types of questions that need to be addressed are excellent (e.g., how often drivers cannot remember driving, have been assisted by others while driving, and have measured and/or treated low blood glucose before and while driving). Only by understanding such issues will we be better able to avoid driving mishaps while hypoglycemic.

In response to the methodological concerns raised by Dr. Barry-Bianchi, we need to clarify that subjects were given the same instructions concerning pulling off the road or treating themselves immediately if they suspected their blood glucose was too low before each driving trial. If it is true, as Dr. Barry-Bianchi suggests, that many people with diabetes hesitate to discuss driving issues with practitioners, this is indeed unfortunate. We feel strongly that practitioners should discuss with their patients how to identify and care for hypoglycemia. Individuals should be instructed about how to identify their own most reliable cues of hypoglycemia (6). Further, practitioners cannot (and should not) assume that their patients know how to optimally treat low blood glucose. The dangers of this assumption were illustrated by the case of a nurse who was found unconscious in her car with a bag of candy corn in her lap after running into a tree. She had recognized she was hypoglycemic before she got into her car and had taken and consumed fast-acting carbohydrates, but did not understand/appreciate that these carbohydrates might require 15–20 min to raise her blood glucose to a normal level. Despite being an intelligent person who recognized the danger hypoglycemia presented, and even though she initially took the correct steps to self-treat, she made the nearly fatal error of not allowing enough time for the carbohydrates to raise her blood glucose. If she had been instructed by health care practitioners about the risk of driving before certain recovery from hypoglycemia, this accident might not have happened. Even though this individual ultimately did "learn what was right for herself," this experiential learning came at a dear price.

Our hope is that future research will focus on this important area to find ways to help people with diabetes reduce their

risk of placing themselves in potential danger. There exists some experimental data that BGAT reduces such risks (7,8).

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