0.001). There was no significant difference in the frequency of mild hypoglycemia during CT (20.46 per patient-year), MIT (18.06 per patient-year), and CSII (16.07 per patient-year), respectively. Although a decrease in the rate of severe hypoglycemia was noticed after the change from CT (1.71 per patient-year) to MIT (0.57 per patient-year) or CSII (0.80 per patient-year), those differences were not significant. The frequency of hypoglycemic comas was similar during MIT (0.17 per patient-year) and CSII (0.23 per patient-year) using human insulin in comparison with that during CT (0.23 per patient-year) using animal insulin during the previous year (retrospective analysis).

There was no significant difference in the frequency of hypoglycemia between MIT and CSII, in spite of significantly lower levels of HbA_{1c} achieved during the pump therapy. The change from CT to CSII or MIT in general does not increase the risk of hypoglycemia in patients trained in hypoglycemia awareness and strict prevention of hypoglycemia. Even a further decrease in frequency of hypoglycemia could be expected during both kinds of intensive therapy as a result of better and more stable metabolic control, strict prevention of hypoglycemia, and acquired patient experience. We are performing a larger study to confirm these results.

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U.K. Prospective Diabetes Study

In *Diabetes Care*, a conference report (1) mistakenly stated that the U.K. Prospective Diabetes Study (UKPDS) primary endpoint was glycemic regulation and that there was loss of separation of glucose control between conventional and intensive groups so that the study may not be able to address the question as to whether improved glycemic control decreases the incidence of cardiovascular disease. We wish to state the following:

1. The primary endpoint of UKPDS has always been prevention of clinical complications (2). To determine whether clinical complications can be delayed by improved diabetes control, newly diagnosed type II diabetic patients were allocated either to a conventional treatment policy, primarily with diet, or to an intensive policy with sulfonylurea, insulin, or metformin therapy. By 7.8 years (median) from the randomization dates, 33% of the 4,108 randomized patients had a clinical endpoint; 22% had a cardiovascular endpoint.
2. The study has maintained separation of glycemic control between the two allocated policies over 9 years (see Fig. 1), with a median difference of 1.7 mmol/l fasting plasma glucose and 0.8% HbA_{1c}.

The glycemic increase with time is an inevitable feature of type II diabetes given the progressive impairment of β-cell function (3). Nevertheless, this does not prevent the study from determining whether the improved blood glucose control that can be obtained with current therapies will be clinically beneficial. The study, which is planned to report in 1998, has an 81% power of determining, at the 1% level of significance, whether improved blood glucose control for a median of 11 years decreases or increases the incidence of clinical complications.

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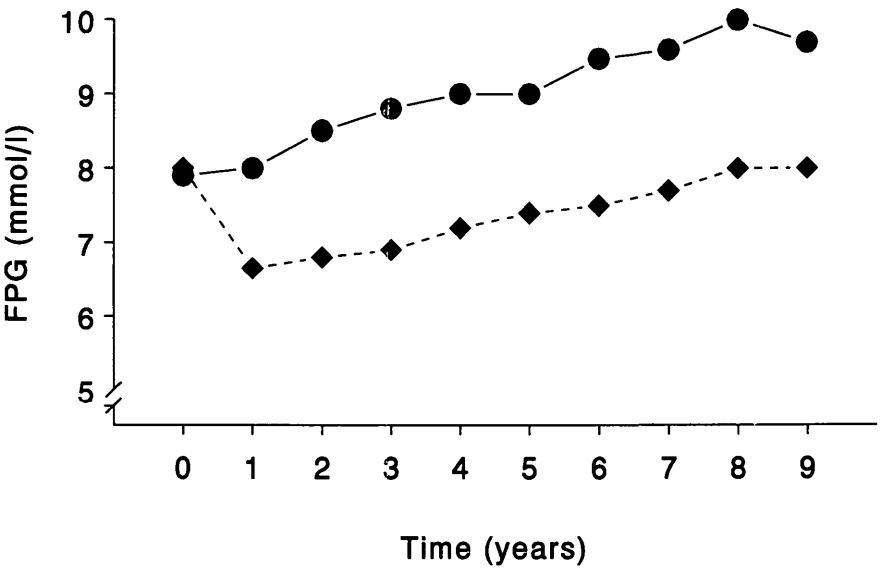

Figure 1—*Median fasting plasma glucose in subjects studied over 9 years in those allocated to conventional policy and those allocated to intensive policy with sulfonylurea or insulin therapy.* ●, *conventional, n = 378;* ◆, *intensive, n = 965.*

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Threshold of HbA_{1c} for the Effect of Hyperglycemia on the Risk of Diabetic Microangiopathy

We previously reported the results of the Berlin Retinopathy Study, demonstrating a significant increase in the rate of background retinopathy from 1.64 to 4.31 per 100 patient-years around an HbA_{1c} of 9.0%, indicating a nonlinear relationship between the degree of hyperglycemia and retinal complications (1). Similarly, Krolewski et al. (2) reported recently that the relationship between glycemic control and microalbuminuria may follow a threshold model, showing a steep increase beyond an HbA_{1c} of 8.1%.

Practicing physicians are faced with the problem of applying these results to the long-term glycemic control seen in their patients. Current recommendations based on results of the Diabetes Control and Complications Trial (3) emphasize the aim of achieving HbA_{1c} values of ≤7%, and action should be taken when levels are >8.0% (high-performance liquid chromatography [HPLC], normal range 5.0 ± 0.5%) (4). The European IDDM policy group (5) defines the following targets: HbA_{1c} values <3 SD above the mean of healthy individuals indicate good control, 3–5 SD fair control, and >5 SD poor control.

To investigate whether the reference to the values of healthy control subjects is a useful tool to extrapolate the risk for complications, we conducted parallel determinations of HbA_{1c} in Berlin and at the Steno Diabetes Center of 225 children with IDDM who are part of the ongoing Berlin Retinopathy Study. Although, using similar assay procedures (HPLC, Biorad Diamat [Berlin] and Biorad Variant [Steno]), comparable normal ranges ($\bar{x}$ ± 2 SD; Berlin: 4.0–6.0%; Steno: 4.1–6.4%) and excellent correlation between results were obtained (r = 0.984; Fig. 1), the estimation of the percentage of patients in fair and poor control varied considerably. This was caused by a minor slope in the regression line, apparently due to slight variations in the assay conditions, which are relevant in particular in the higher readings obtained in patients with diabetes.

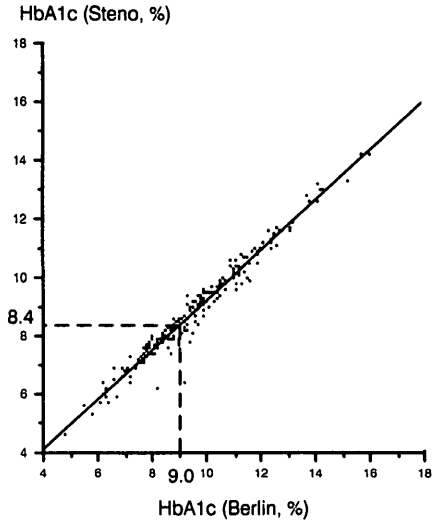

Figure 1—*Correlation between the HbA_{1c} values determined at Steno Diabetes Center and at the Berlin Children's Hospital indicating systematic discrepancies between centers despite similar HbA_{1c} methods and comparable normal ranges. The suspected threshold at an HbA_{1c} of 9.0% in Berlin corresponds to 8.4% at Steno.*

In these unselected children, satisfactory control (≤5 SD of normal) was reached by only 15% according to the Berlin results compared with 37% according to Steno. Interestingly, the threshold for retinopathy calculated from the long-term Berlin results of 9.0% would correspond to an HbA_{1c} of 8.4% at Steno (Fig. 1). This is close to the described threshold of 8.1% in the Joslin study, supporting the notion that a similar threshold may exist for microalbuminuria and retinopathy (6). In fact, the goal of an HbA_{1c} below the suspected threshold (9.0 or 8.4%, respectively) was reached by 46% of the patients in the Berlin Retinopathy Study.

Such comparative studies have proven to be necessary to compare the clinical outcomes of patient care in different institutions as a measure of quality control. In contrast, the exclusive calibration of HbA_{1c} values to the standard deviation range of control values may lead to clinically relevant wrong conclusions regarding the risk for microangiopathy.

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