Severe Hypoglycemia in Children With IDDM

A prospective population study, 1992–1994

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OBJECTIVE — Is an increased incidence of severe hypoglycemia an unavoidable effect of improved metabolic control? And, if so, to what extent?

RESEARCH DESIGN AND METHODS — In 1992–1994, severe hypoglycemia was prospectively registered in our intensively treated IDDM population, 146 children 1–18 years of age with >90% of the patients on ≥4 insulin injections per day. The two categories, "severe hypoglycemia with unconsciousness" (U hypoglycemia) and "severe hypoglycemia without unconsciousness but needing the assistance of another person" (NU hypoglycemia), were analyzed in relation to yearly mean HbA$_{1c}$ levels, insulin doses and proportion of short-acting insulin, age at onset, duration of diabetes, age, sex, and weight-to-height ratio.

RESULTS — Yearly mean HbA$_{1c}$ levels improved from 8.1 ± 1.6% in 1992 to 6.9 ± 1.3% in 1994. The yearly incidence of U hypoglycemia was 0.15–0.19 events per patient-year, seen in 10–16% of patients, showing no significant increase from 1992–1994. For NU hypoglycemia, slightly increasing figures from 1.01 to 1.26 events per patient-year, seen in 27–38% of patients yearly, were reported. There was no significant correlation between severe (U or NU) hypoglycemia and HbA$_{1c}$, but still an association was seen in certain calculations. In multiple regression analysis, U hypoglycemia was not related to any factor, but the square root of the rate of NU hypoglycemia was related to lower HbA$_{1c}$ levels ($P = 0.0003$), higher insulin doses (IU · kg^{-1} · 24 h^{-1}) ($P = 0.0024$), and a lower proportion of short-acting insulin out of the total daily insulin dose ($P = 0.031$).

CONCLUSIONS — Multiple-dose insulin therapy with rather low yearly mean HbA$_{1c}$ values causes a slight increase of NU hypoglycemia but no increase of U hypoglycemia in our population of children with IDDM. Near physiological HbA$_{1c}$ levels may be achieved without any pronounced risk of increasing the incidence of severe hypoglycemia when multiple-injection insulin therapy is combined with adequate self-control based on psychosocial support and active education.

Active multiple-dose insulin therapy with near physiological HbA$_{1c}$ levels has been clearly shown to prevent, delay, or slow the progression of the long-term complications of IDDM, as aimed for in the 1989 St. Vincent (Italy) Declaration (1). Significant improvements in the time of onset and the rate of progression of microvascular complications were found with multiple insulin-injection therapy in the Diabetes Control and Complications Trial (DCCT) (2). In a 25-year population-based follow-up of 213 IDDM patients, Bojestig et al. (3) in 1994 reported substantially decreased cumulative incidence of diabetic nephropathy, probably related to improved metabolic control.

On the other hand, a higher incidence of severe hypoglycemia has been noted in relation to low HbA$_{1c}$ levels. Some authors, such as Egger et al. (4), relate increasing numbers of hypoglycemic coma to improved metabolic control. In the Diabetes Control and Complications Trial (DCCT) (5–7), an approximately threefold greater incidence of severe hypoglycemia (requiring the assistance of another person) was found in the intensively treated group.

If so, this is serious, as a number of authors (8–11) have described persistent electroencephalographic (EEG) abnormalities related to a history of severe hypoglycemia among children with IDDM. In 1989, Soltész and Acsádi (12) reported EEG abnormalities in 49% of 70 children with IDDM, compared with 24% of 70 healthy control subjects. EEG abnormalities were found in 80% of 27 children with a history of severe hypoglycemia, compared with 30% of 43 children with no history of severe hypoglycemia. No correlation was found with duration of diabetes, insulin dose, or HbA$_{1c}$ level, but the abnormal EEGs were found more often among the younger children with an earlier onset of diabetes. Earlier workers (13,14) pointed out the risk for permanent brain damage and neurophysiological impairment caused by prolonged and recurrent severe hypoglycemia in children. Later authors, such as Ryan et al. (15,16), found significantly more frequent impaired neurophysiological function among the diabetic children with early onset, possibly related to a larger number of severe hypoglycemic episodes at a vulnerable age.

Is an increased incidence of hypoglycemia an unavoidable effect of improved metabolic control? And, if so, to what extent? Although treatments should aim to prevent or minimize the frequency of all degrees of hypoglycemia, we decided to analyze our own material with regard to the incidence of the severe hypoglycemia, the easiest to define and recall, in relation to yearly mean HbA$_{1c}$ levels and other data.

The study was approved by the Ethics Committee of the Medical Faculty at Linköping University, Linköping, Sweden.

RESEARCH DESIGN AND METHODS

Study population
The study population consisted of the 146

Table 1—*Clinical characteristics of subjects with IDDM (69 girls and 77 boys), 1992–1994*

	Range	Mean ± SD	Median
Age (years)	1.8–18.6	12.7 ± 4.2	13.9
Age at onset of diabetes (years)	1.0–17.5	7.9 ± 4.2	7.5
Duration of diabetes (years)	0.1–16.6	4.9 ± 4.0	3.7
Insulin (IU · kg^{-1} · 24 h^{-1})	0.2–2.0	0.89 ± 0.3	0.91
HbA$_{1c}$ (%)	4.0–12.7	7.5 ± 1.5	7.4

Data were obtained yearly.

children with IDDM who were <19 years of age in our catchment area during the years 1992–1994. According to our health care system, all IDDM patients aged 1–18 years within the catchment area are treated at our clinic. Thus, we can be quite sure that we have studied an unselected patient population.

The clinical characteristics of the studied population are shown in Table 1, referring to all patient-years. The patients were treated with ≥4 daily doses of insulin during 94% of the patient-years. Age and duration of diabetes, expressed as yearly means ± SD, are shown in Table 2. The number of patients with mean insulin dose <0.5 IU · kg^{-1} · 24 h^{-1} was 6 in 1992, 16 in 1993, and 11 patients in 1994. The number of patients with a duration of diabetes <1 year was 18 in 1992, 24 in 1993, and 17 patients in 1994. The number of patients with a duration of diabetes ≥1 and <2 years was 11 in 1992, 12 in 1993, and 23 patients in 1994.

Details of treatment regimens

The patients were seen during their regular visits to the outpatient pediatric clinic of the University Hospital in Linköping, Sweden, scheduled at 3-month intervals and, if necessary, more often. In exceptional cases, a visit was delayed up to 5 months. Of the patients, 70% were seen three times a year or more and 23% were seen four times or more, with a mean of 3.6 yearly visits (in 1994).

At each visit, they met with their diabetes nurse and a pediatric diabetologist. At least yearly, and whenever needed, they also met with their dietitian. After each visit, every patient and his or her treatment was discussed with our diabetes team, including also a psychologist and a social worker. Group education, camps, evening lectures for parents and teenagers, and individual psychosocial support were important additional elements of the treatment. The patients were educated and encouraged to perform the following self-control regimen. Daily · urine tests for glucosuria and ketonuria should be performed, at least in the morning to give information about suspected hypoglycemia during night (ketonuria without glucosuria) or insulin deficiency (ketonuria plus glucosuria). Glucosuria alone should not be used to adjust insulin doses but rather to indicate the need to perform blood glucose tests. Adjustments of insulin should be based on self-control of blood glucose levels. The patients were told how to make 24-h blood glucose profiles, determinations of blood glucose just before and 1–1.5 h after every meal and in the evening and during the night around 2:00 A.M. The random blood glucose values, on an average of two per day, should be registered in diagrams in the patient's diary together with the profile curves to validate the profiles. Insulin adjustments should not be made on the basis of actual single blood glucose values, but should aim at prevent-

ing fluctuations of blood glucose. Acute insulin adjustments can be made before a foreseen change of meal size or heavy exercise, but the general policy to facilitate metabolic balance is planning meals that are regular in time and content (i.e., energy and the proportions of carbohydrate, fat, protein, and fiber).

In general, it was considered important to meet and support the individual patient and his or her family in each unique life situation with whatever special habits and needs. This attitude influences the whole treatment, from the insulin types and doses to the education and psychosocial support.

Study design and criteria of severe hypoglycemia

The patients and/or parents were asked to register every severe hypoglycemia prospectively in 1992–1994. Questionnaires were distributed to patients and/or parents at every visit in the outpatient clinic, and they were expected to deliver the questionnaire at the next visit.

The number and severity of severe hypoglycemic reactions since last visit were asked for, as well as the actual insulin doses. With special emphasis and questions, severe hypoglycemia was split into two categories: "severe hypoglycemia with unconsciousness" (U hypoglycemia) and "severe hypoglycemia without unconsciousness but needing the assistance of another person" (NU hypoglycemia), as reported by the families. No further criteria were added. The questionnaire included other questions of importance for treatment, some of which had immediate benefit for the patient such as "I need to get prescribed . . ." and "I want to discuss/learn more about . . .".

Before meeting the physician, the questionnaire was checked by our diabetes nurse who had good knowledge of the family. The yearly accumulated numbers of episodes of U and NU hypoglycemia were used for incidence calculations. The indi-

Table 2—*Yearly clinical data and incidences of severe hypoglycemia*

Year	Patients (*n*)	Age (years)	Duration of diabetes (years)	Insulin injections ≥4/day (%)	Insulin pump (%)	HbA$_{1c}$ (%)	Events of NU/ patient-year	Percentage with NU	Events of U/ patient-year	Percentage with U	Events of U + NU/ patient-year	Percentage with U + NU
1992	102	13.1 ± 3.9	4.9 ± 3.9	87	6	8.1 ± 1.6	1.01	27	0.15	10	1.17	31
1993	115	12.4 ± 4.2	4.8 ± 4.0	87	3	7.7 ± 1.5	0.98	38	0.19	13	1.17	46
1994	126	12.7 ± 4.3	4.8 ± 4.0	95	3	6.9 ± 1.3	1.26	34	0.17	16	1.43	42

Data are means ± SD, unless otherwise indicated. HbA$_{1c}$ differences were significant: 1992–1993, $P < 0.03$ (Mann-Whitney U test); 1993–1994, $P < 0.0001$; and 1992–1994, $P < 0.0001$.
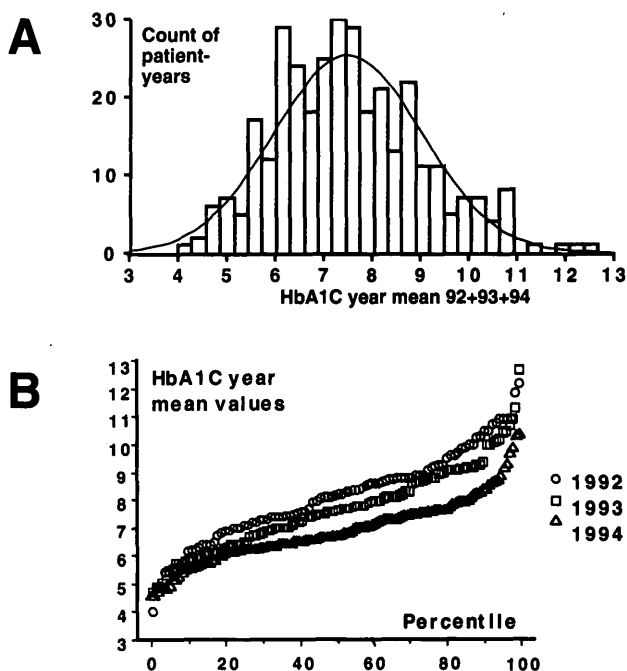
Figure 1—*Distribution of yearly mean HbA$_{1c}$ values, 1992–1994 (A), with yearly percentile distribution (B).*

vidual numbers of yearly events of severe hypoglycemia were analyzed in relation to HbA$_{1c}$ level, insulin doses and the proportion of short-acting insulin to the total daily insulin dose, age at onset of diabetes, duration of diabetes, age, sex, and weight-to-height ratio.

The yearly number and distribution of visits varied due to individual needs. Therefore, the method of yearly mean calculations has been used for HbA$_{1c}$ levels as well as other data. This means that a subject may appear three times in a figure, since data were collected on a yearly basis and then presented together for 1992–1994.

The HbA$_{1c}$ methods used were high-performance liquid chromatography (HPLC) or DCA 2000 adjusted to give values corresponding to HPLC. DCA 2000 was the main method used during the study period and has been used routinely in our outpatient department since August 1992. The HPLC method was used only when patients visited the laboratory for other reasons (e.g., a hospital stay).

The normal range of HbA$_{1c}$ for the DCA 2000 method was 4.1–5.7% (mean ± 2 SD, 4.9 ± 0.8%), determined in five healthy children for each year of age up to 20 years and five adults of every 10 years more of age. The HPLC normal range was 3.2–6.0% (mean ± 2 SD, 4.6 ± 1.4%), determined from a normal material of 85

healthy blood donors.

A total of 32 parallel samples showed very good correlation between DCA 2000 and HPLC ($r = 0.98$, $P < 0.0001$), giving the formula DCA 2000 = 1.18 × HPLC. This formula has been used to adjust our DCA 2000 values into values corresponding with HPLC.

There was a yearly 10–15% change of patients in the material (mixed longitudinal study). This was due to the exits from the study at 19 years of age, as well as the new cases entering.

Two cases of very high numbers of NU hypoglycemia in preschool children in 1992 and 1993 were excluded due to a misunderstanding of the assistance criteria, reporting every hypoglycemia as severe, even though they meant mild symptoms.

We received for 1992 57%, for 1993 61%, and for 1994 78% of the expected questionnaires. The yearly incidence figures of severe hypoglycemia were corrected by dividing by these percentages. Other methods for correcting were considered, with possible deviations in both directions. The simple method chosen includes the risk of the overestimation of hypoglycemia, as patients were more frequently seen and thus more often reporting during periods of unstable metabolic control.

Of the patients, 93% returned at least some questionnaires (in 1992 86%, in

1993 93%, and in 1994 98%). Therefore, there is only a very little chance that patients less adherent to the treatment regimen are excluded.

Statistical analysis

Statview 4.02 software was used in a Power Macintosh 7100/66 for diagrams, incidence calculations, population means and SD values, median values, correlations with Fisher's r to z test, multiple regression analysis, and Mann-Whitney U test. As a complement, the square roots of the rates of U plus NU hypoglycemia and NU hypoglycemia were calculated to reduce possible bias caused by the statistical variance in the reported numbers of events. All results that were significant at $P < 0.05$ are indicated.

RESULTS

HbA$_{1c}$ distributions

The yearly mean HbA$_{1c}$ distributions for the 146 patients during the study period 1992–1994 are shown in Figs. 1A and B. A gradual improvement in metabolic control took place, from a population yearly mean HbA$_{1c}$ of 8.1 ± 1.6% in the 102 patients 1992 to 6.9 ± 1.3% in the 126 patients in 1994 ($P < 0.0001$, Mann-Whitney U test) (Table 2; Fig. 1B).

The HbA$_{1c}$ distributions for the groups with and without severe hypoglycemia (U and NU hypoglycemia), shown in Fig. 2, were significantly lower for those with severe hypoglycemia in Mann-Whitney U test ($P = 0.0047$). The range of HbA$_{1c}$ values of the patients without severe hypoglycemia overlaps the range of the patients with severe hypoglycemia. Some patients with yearly mean HbA$_{1c}$ levels up to 9–11% had events of severe hypoglycemia.
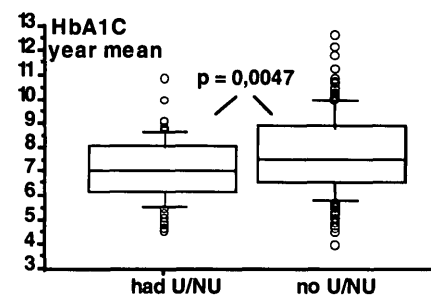

Figure 2—*Percentile box plot comparing yearly mean HbA$_{1c}$ distributions 1992–1994 in the two groups with and without events of severe hypoglycemia. Inside box are 50% of values; rings represent the 10% outliers at each end.*
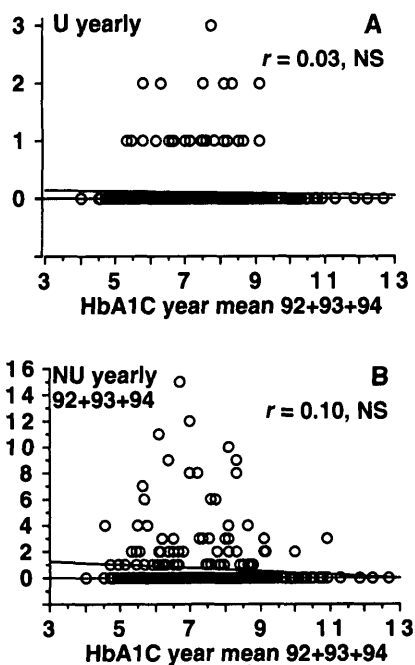
Figure 3—*Yearly individual numbers of U and NU hypoglycemia in relation to yearly mean HbA_{1c} levels of the same individual in the same year, 1992–1994.*

The distributions of HbA_{1c} related to U and NU hypoglycemia are shown in the Figs. 3A and B.

Incidences
The yearly incidences of U, NU, and U plus NU hypoglycemia, with the corresponding yearly number of patients with mean age, duration of diabetes, HbA_{1c} level, and percentage of patients on ≥ 4 doses insulin daily, are shown in Table 2.

Single correlations
The NU hypoglycemic events were weakly correlated to a lower age ($r = 0.12$, $P = 0.027$) and to a lower proportion of short-acting insulin to the total daily insulin dose ($r = 0.12$, $P = 0.028$), but not significantly correlated to yearly mean HbA_{1c} levels or any other factor.

The U hypoglycemic events were weakly correlated to a lower age at onset of diabetes ($r = 0.13$, $P = 0.016$) and simultaneously to a longer duration of diabetes ($r = 0.15$, $P = 0.0075$), but not significantly correlated to yearly mean HbA_{1c} levels or any other factor. No events of U hypoglycemia were reported for ages 1–7 years or for any patients with yearly mean HbA_{1c} levels >9.1% (Fig. 3A).

For all severe hypoglycemic events (U plus NU hypoglycemia), a weak correlation

was found to a lower proportion of short-acting insulin ($r = 0.11$, $P = 0.047$), but there was no significant correlation to yearly mean HbA_{1c} levels or any other factor.

Relative risk
The relative risk for events of U plus NU hypoglycemia when yearly mean HbA_{1c} levels were <7.0% was 1.24, and for NU hypoglycemia alone the relative risk was 1.29.

Multiple regression analysis
In multiple regression analysis, U plus NU hypoglycemia were related to lower HbA_{1c} levels ($P = 0.0060$), a higher insulin dose (IU · kg^{-1} · 24 h^{-1}) ($P = 0.019$), and a lower proportion of short-acting insulin to the total daily insulin dose ($P = 0.024$). None of the factors was significant for U hypoglycemia alone, but NU hypoglycemia showed a relation to lower HbA_{1c} levels ($P = 0.014$), a higher insulin dose (IU · kg^{-1} · 24 h^{-1}) ($P = 0.0038$), a shorter duration of diabetes ($P = 0.010$), and a lower age at onset of diabetes ($P = 0.035$).

The square root of U plus NU hypoglycemia was calculated as a complement, since the yearly numbers of NU hypoglycemia varied from 0 to 15 (Fig. 3B). It was related to lower HbA_{1c} levels ($P < 0.0001$), a higher insulin dose (IU · kg^{-1} · 24 h^{-1}) ($P = 0.0060$), and a lower age at onset of diabetes ($P = 0.040$).

The square root of the rate of NU hypoglycemia, finally, was related to lower

HbA_{1c} levels ($P = 0.0003$), a higher insulin dose (IU · kg^{-1} · 24 h^{-1}) ($P = 0.0024$), and a lower proportion of short-acting insulin ($P = 0.031$).

CONCLUSIONS

HbA_{1c}
As others have shown (18), we too find lower HbA_{1c} values in the patients who had severe hypoglycemia. However, HbA_{1c} does not seem to be a strong predictor for the population as a whole. There is a large overlap in yearly mean HbA_{1c} level, and there is no safe zone for clinical use (Fig. 2), as patients with HbA_{1c} levels up to 9–11% still had occasions of severe hypoglycemia.

In 1994, 98% of the patients were on ≥ 4 injections daily, and the mean HbA_{1c} level was 6.9 ± 1.3% (Table 2). Compared with 1992–1993, with HbA_{1c} levels from 8.1 ± 1.6 to 7.7 ± 1.5%, this improvement in metabolic control caused only a slight increase in the incidence of severe hypoglycemia without unconsciousness (NU hypoglycemia) and no increase of severe hypoglycemia with unconsciousness (U hypoglycemia). In addition, there was no significant correlation between U hypoglycemia and yearly mean HbA_{1c} levels.

Previous reports
In Table 3, we have tried to summarize previous reports on severe hypoglycemia in children with IDDM. To make these reports

Table 3—*Severe hypoglycemia with unconsciousness and/or seizures in diabetic children*

No. of episodes per patient-year	Percentage of patients yearly	Mean HbA_1 or HbA_{1c} and normal range (%)		Reference
0.16*	16*	HbA_1:	12.0 (5.3–8.8)	Macfarlane et al. (27), 1989
0.12	7.4	HbA_1:	11.4 (5.4–7.4)	Bhatia and Wolfsdorf (18), 1991
0.12	8.8*	HbA_1:	11.3*	Soltész and Acsádi (12), 1989
0.063*	6.0*	HbA_1:	11.2* (4.8–8.8)	Bergada et al. (28), 1989
—	17	HbA_{1c}:	10.9 (4.5–6.5)	Åman et al. (20), 1989
0.13*	6.5	HbA_1:	9.7* (5.1–7.8)	Egger et al. (4), 1991
0.01*	1*	HbA_{1c}:	9.3 (4.7–6.1)	Goldstein et al. (29), 1981
0.17	7.8	$HbA1$:	9.2 (5.1–7.8)	Zuppinger et al. (30), 1989
3.6	—	HbA_{1c}:	9.0	Brambilla et al. (31), 1987
0.16	16	HbA_{1c}:	8.7*	Daneman et al. (19), 1989
0.42	27	HbA_{1c}:	8.3 (4.1–5.7)	Limbert et al. (22), 1993
0.27	—	HbA_{1c}:	8.1 (4.05–6.05)	DCCT adolescents (25), 1994
0.22*	17		—	Barkai et al. (32), 1991
—	6.5		—	Pinkney et al. (33), 1994
0.17	13	HbA_{1c}:	7.5 (3.2–6.0)	This study

HbA_1 and HbA_{1c} are population mean values, determined with various methods and different normal ranges. Studies varied from 14 weeks to 8 years and ranged from 0.01–3.6 (median, 0.16) episodes per patient-year, or 1–27% (median, 8.8%) of patients yearly. *Extracted and/or calculated from the author's data.

comparable, we defined severe hypoglycemia as unconsciousness and/or seizures. To interpret such a summary is difficult. In some cases, extrapolations or extractions from the given data have been necessary. The methods of determining glycated hemoglobin and other methods in the studies may differ. The need for standardization of HbA$_{1c}$ assays is obvious. In several reports, the registration of hypoglycemia has not been done prospectively or quite regularly. We believe that the number of severe hypoglycemia episodes is underestimated in those studies. In spite of this, our incidence numbers for U hypoglycemia, 0.15–0.19 events per patient-year and 10–16% of the patients yearly, does not seem to be higher than in the previous reports of 0.1–0.2 episodes per patient-year (17) or 1–27% of the patients yearly (Table 3). Our mean HbA$_{1c}$ level of 6.9% in 1994 is reasonably lower than in previous studies of children with IDDM, even when different methods are considered.

For example, in 1986–1987, Bhatia and Wolfsdorf (18) found in 196 patients with a mean HbA$_1$ of 11.4 ± 1.9% (normal range, 5.4–7.4%) an incidence of 0.12 episodes per patient-year. In 1986, Daneman (19) studied 311 children with a mean HbA$_{1c}$ level of 8.7% and found 16% having had hypoglycemic coma or convulsion. In 1986, Åman et al. (20) studied 92 children 7–18 years with a mean HbA$_{1c}$ level of 10.9 ± 2.1% (normal range, 4.5–6.5%) and found that 17% reported unconsciousness. Egger et al. (4) in an 8-year study of 155 children found fewer episodes of U hypoglycemia, but they used stricter inclusion criteria, such as unconsciousness with documented low blood glucose and/or immediate response to glucose or glucagon. The frequency of patients with U hypoglycemia then increased from 4.4% of patients at the mean HbA$_1$ level of 9.86 ± 1.3% (normal range, 5.1–7.8%) to 7.4% of patients at the mean HbA$_1$ level of 9.48 ± 1.6%. Their number of U hypoglycemic events per patient-year was 0.13 for the whole period. They did calculate an odds ratio of 4.5 for U hypoglycemia at an HbA$_1$ level of <8.5% compared with HbA$_1$ values >10.0%. However, their patients were treated with only one or two doses of insulin daily during >90% of the patient-years. In other studies, attempts to lower HbA$_1$ or HbA$_{1c}$ with maintained conventional treatment has also resulted in increases in the rates of severe hypoglycemia (21). More recently, Limbert et al. (22) retrospectively found

27% having U hypoglycemia, or 0.42 U hypoglycemic episodes per patient-year, in 1990. The HbA$_{1c}$ was 8.3 ± 1.5% (normal range, 4.1–5.7%), and 51 out of their 74 study patients were treated with only two insulin doses daily. Dorchy (23) compared two- or three-dose treatments (with an HbA$_{1c}$ level of 6.8 ± 1.3% [normal range, 4.4–6.0%]) with a four-dose treatment (HbA$_{1c}$ level, 7.1 ± 1.7%). The two groups had been given the same intensive education. The reported incidences of patients hospitalized or receiving intravenous glucose because of severe hypoglycemia were 6% of the two- or three-dose patients and 20% of the four-dose patients. For all severe hypoglycemia, he found 10% (respectively 31%) without relationship to HbA$_{1c}$ levels. The four-dose group, however, had a higher mean age (15.1 vs. 22.5 years) and duration of diabetes (7.5 vs. 13.7 years). Unlike ourselves, none of the previous authors studied a mainly intensively treated pediatric population.

Problem-based diabetes education and psychosocial support are important elements for successful glycemic control in young patients (24). Multiple-dose insulin therapy without such intensive continuous education and support might even cause increased instability and adverse events.

Comparison with the DCCT

In the DCCT (6), the incidences of severe hypoglycemia among the intensively treated patients were analyzed.

The five clinics with the highest median HbA$_{1c}$ concentrations, all ≥7.3%, reported an average of 0.52 events per patient-year. This was similar to the five clinics with the lowest median HbA$_{1c}$ levels, all ≤6.8%, who had an average of 0.51 events per patient-year. These incidences were also similar to the study group as a whole. This does not suggest any strong relation between population mean HbA$_{1c}$ levels and incidences of severe hypoglycemia in patients with multiple insulin therapy.

In the DCCT adolescent cohort (25), the rates of severe hypoglycemia were even higher than in the adult group, and the mean HbA$_{1c}$ was higher as well. The ages of these selected patients were 13–17 years at entry, and they were then included for 4–9 years. A comparison between laboratories (26) has indicated that the HbA$_{1c}$ values from our laboratory were on average 1% lower than the values of the same samples analyzed in the DCCT lab. Therefore, our

population in 1994 and the intensively treated DCCT adolescents should be comparable in terms of mean HbA$_{1c}$ values.

One may wonder why we do not see as high an increase of severe hypoglycemia as did most of the clinics participating in the DCCT (6). The DCCT subjects had been asked for data about adverse advents by a standard form at quarterly visits (5). In contrast to our study, they had also been instructed to report immediately when severe hypoglycemia occurred, and in addition the intensively treated DCCT patients were seen in the clinic monthly. The first possibility to be regarded is that we may have underestimated the incidences in our study. This explanation cannot be excluded, but is less probable regarding the attacks of severe hypoglycemia with unconsciousness, which are normally not forgotten and in general reported quite rapidly by the parents. We have corrected for missing questionnaires in a way that, if anything, tends to overestimate the number of hypoglycemic episodes. Another factor that contributes to our low incidence of hypoglycemia may be that some of our patients had a short duration of diabetes, but the proportion of patients with a low insulin requirement, suggesting a good residual insulin secretion, was small (<10%).

Another explanation for the difference from the DCCT could be that in the DCCT a prompt and sudden change of therapy was introduced in many patients when they were randomized to this type of treatment. As far as we understand, this also was a rather new regimen for the diabetes teams at some clinics. We have been using this type of policy for a long time. This might, however, only count for differences between our study and the initial years of the DCCT. We believe that a more plausible explanation is that our patients were educated in this type of treatment and living with diabetes from the very onset of the disease. It is certainly difficult to reeducate patients who are used to a certain regimen. Furthermore, our policy of using self-control to prevent fluctuations, instead of adjusting insulin on the basis of actual blood glucose values or using sliding scales, etc., may also be of importance.

The fact that the DCCT patients were selected, highly motivated, and 13–39 years of age, could be expected to give a lower incidence of acute complications. We studied an unselected pediatric population, including patients from broken homes, with serious psychosocial problems, etc., but

they were all treated with a pediatric view of developmental psychology, family dynamics, and psychosocial care. We believe that a flexible use of such knowledge may help to adjust treatment to the life of the individual patient and thereby help to prevent and minimize severe hypoglycemia.

Finally, we have noted a pronounced difference in rates of severe hypoglycemia among centers in the DCCT (6). Except for the one clinic reporting no case of severe hypoglycemia, the relative risk between intensive and conventional treatment varied from 1, that is, no increased risk, to 11. This cannot be fully explained by different insulin regimens and heterogeneous materials, but may be explained by differing levels of experience and competence in handling intensive treatment.

It certainly would be desirable to be able to predict individuals at increased risk for severe hypoglycemia. In the DCCT (7), the useful predictors seem to be repeated previous episodes of severe hypoglycemia and the absence of hypoglycemia warning symptoms. We cannot from our study see any clear characteristics of those who will get severe hypoglycemia. We believe that the main method to prevent severe hypoglycemia is to educate the patient and family how to manage IDDM, with or without multiple-injection insulin therapy, and to make the diabetes team competent for the treatment recommended. The risk of severe hypoglycemia is rarely a reason to give up the important aim of good metabolic control.

Summary
In our experience and with our methods, multiple-dose insulin therapy with rather low yearly mean HbA$_{1c}$ values causes a slight increase in severe hypoglycemia without unconsciousness, but no increase of severe hypoglycemia with unconsciousness. In an IDDM population treated with multiple-dose insulin therapy, combined with adequate self-control based on psychosocial support and active education, the improvement in metabolic control to near physiological HbA$_{1c}$ levels may be achieved gradually over months without any pronounced risk of increasing the incidence of severe hypoglycemia.

References
1. World Health Organization/International Diabetes Federation (European region): Diabetes Care and Research in Europe: the Saint Vincent Declaration. *Diabet Med* 7:360, 1990
2. The DCCT Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–986, 1993
3. Bojestig M, Arnqvist H, Hermansson G, Karlberg B, Ludvigsson J: Declining incidence of nephropathy in insulin-dependent diabetes mellitus. *N Engl J Med* 330:15–18, 1994
4. Egger M, Gschwend S, Smith GD, Zuppinger K: Increasing incidence of hypoglycemic coma in children with IDDM. *Diabetes Care* 14:1001–1005, 1991
5. The DCCT Research Group: Epidemiology of severe hypoglycemia in the Diabetes Control and Complications Trial. *Am J Med* 90:450–459, 1991
6. The DCCT Research Group: Implementation of treatment protocols in the Diabetes Control and Complications Trial. *Diabetes Care* 18:361–376, 1995
7. The DCCT Research Group: Adverse events and their association with treatment regimens in the Diabetes Control and Complications Trial. *Diabetes Care* 18:1415–1427, 1995
8. Eeg-Olofsson O, Petersen I: Childhood diabetic neuropathy: a clinical and neurophysiological study. *Acta Paediatr Scand* 55:163–176, 1966
9. Schlank H, Palm D, Jochnus J: Der Einfluss rezidivierender Hypoglykämien auf des EEG des diabetischen Kindes. *Monatsschr Kinderheilkd* 117:251–252, 1969
10. Gilhaus KH, Daweke H, Lülsdorf HG, Sachee B: EEG-Veränderungen bei diabetischen Kindern. *Dtsch Med Wochenschr* 98:1449–1454, 1973
11. Haumont D, Dorchy H, Pelc S: EEG abnormalities in diabetic children: influence of hypoglycaemia and vascular complications. *Clin Pediatr* 18:750–753, 1979
12. Soltész G, Acsádi G: Association between diabetes, severe hypoglycaemia, and electroencephalographic abnormalities. *Arch Dis Child* 64:992–996, 1989
13. Ack M, Miller I, Weil WB: Intelligence of children with diabetes mellitus. *Pediatrics* 28:764–770, 1961
14. Haworth JC, Coodin FJ: Idiopathic spontaneous hypoglycaemia in children: report of seven cases and review of the literature. *Pediatrics* 25:748–765, 1960
15. Ryan C, Vega A, Drash A: Cognitive deficits in adolescents who developed diabetes early in life. *Pediatrics* 75:921–927, 1985
16. Ryan CM, Aitchison J, Puczynski S, Puczynski M, Arslanian S, Becker D: Mild hypoglycaemia associated with deterioration of mental efficiency in children with insulin-dependent diabetes mellitus. *J Pediatr* 117:32–38, 1990
17. Soltész G: Hypoglycaemia in the diabetic child. *Baillieres Clin Endocrinol Metab* 3:741–755, 1993
18. Bhatia V, Wolfsdorf JI: Severe hypoglycemia in youth with insulin-dependent diabetes mellitus: frequency and causative factors. *Pediatrics* 88:1187–1193, 1991
19. Daneman D, Frank M, Perlman K, Tamm J, Ehrlich R: Severe hypoglycaemia in children with insulin-dependent diabetes mellitus: frequency and predisposing factors. *J Pediatr* 115:681–685, 1989
20. Åman J, Karlsson I, Wranne L: Symptomatic hypoglycaemia in childhood diabetes: a population-based questionnaire study. *Diabet Med* 6:257–261, 1989
21. Dahl-Jørgensen K: Near normoglycaemia and late diabetic complications: the Oslo study. *Acta Endocrinol* 115 (Suppl. 284):1–38, 1981
22. Limbert C, Schwingshandl J, Haas J, Roth R, Borkenstein M: Severe hypoglycemia in children and adolescents with IDDM: frequency and associated factors. *J Diabet Complications* 7:216–220, 1993
23. Dorchy H: Quel contrôle glycémique peut être obtenu chez dez jeunes diabétiques sans sécrétion résiduelle d'insuline endogène? Quelle est la fréquence des hypoglycémies sévères et des complications subcliniques? *Arch Pédiatr* 1:970–981, 1994
24. Ludvigsson J: Successful glycemic control in diabetic adolescents. In *Diabetes*. Rifkin H, Colwell JA, Taylor SI, Eds. Amsterdam, Elsevier, 1991, p. 822–827
25. The DCCT Research Group: Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. *J Pediatr* 125:177–188, 1994
26. Cullberg CE, Bergström A, Dinesen B, Larsson L, Little RR, Goldstein DE, Arnqvist HJ: Comparisons of studies on diabetic complications hampered by differences in GHb measurements. *Diabetes Care* 19:726–729, 1996
27. Macfarlane PI, Walters M, Stutchfield P, Smith CS: A prospective study of symptomatic hypoglycaemia in childhood diabetes. *Diabet Med* 6:627–630, 1989
28. Bergada I, Suissa S, Dufresne J, Schiffrin A: Severe hypoglycemia in IDDM children. *Diabetes Care* 12:239–244, 1989
29. Goldstein DE, England JD, Hess R, Rawlings SS, Walker B: A prospective study of symptomatic hypoglycemia in young diabetic patients. *Diabetes Care* 4:601–605, 1981

30. Zuppinger K, Egger M, Aebi C, Schoenle E, Gschwend-Eigenmann S, Mullis P: Hypoglykämien bei Kindern mit Diabetes unter humanem oder porcinem Insulin. *Schweiz Med Wochenschr* 119:532–535, 1989

31. Brambilla P, Bougneres PF, Santiago JV, Chaussain JL, Pouplard A, Castano L: Glu-cose counterregulation in pre-school-age diabetic children with recurrent hypoglycemia during conventional treatment. *Diabetes* 36:300–304, 1987

32. Barkai L, Madácsy L, Vámosi I: Autonomic dysfunction and severe hypoglycaemia in insulin dependent diabetes mellitus. *Arch Dis Child* 66:1438–1441, 1991

33. Pinkney JH, Bingley PJ, Sawtell PA, Dunger DB, Gale EAM, The Bart's-Oxford Study Group: Presentation and progress of childhood diabetes mellitus: a prospective population-based study. *Diabetologia* 37:70–74, 1994