Two-Year Experience with Continuous Subcutaneous Insulin Infusion in Relation to Retinopathy and Neuropathy

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SUMMARY

Thirty patients with insulin-dependent diabetes mellitus (IDDM) who had advanced background retinopathy were randomized to unchanged conventional treatment (UCT) or to continuous subcutaneous insulin infusion (CSII). They were followed prospectively for 2 yr. The mean blood glucose and hemoglobin A_{1c} (HbA_{1c}) were significantly lower in the CSII group than in the UCT group. The mean blood glucose and HbA_{1c} did not change from the first to the second year in either of the treatment groups in spite of less frequent home-monitoring of blood glucose and less frequent outpatient visits during the second year. Four patients in the CSII group and five in the UCT group developed proliferative retinopathy. However, a marginally significant trend was found toward more frequent improvement of retinal morphology in the CSII group (47%) than in the UCT group (13%). Beat-to-beat variation was found to deteriorate significantly with UCT compared with a nonsignificant improvement with CSII therapy. Vibration sense was unchanged in both treatment groups. It is concluded that near-normal blood glucose levels can be maintained with CSII therapy in spite of less frequent home-monitoring of blood glucose and outpatient visits. Furthermore, established background retinopathy may progress to proliferative retinopathy in spite of 2 yr of near-normal blood glucose levels. However, a marginally significant trend toward more frequent improvement of retinal morphology was found among CSII-treated patients compared with conventionally treated patients. Large-scale, prospective, randomized studies are needed to confirm these results.

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The relationship between metabolic control and the development of microvascular disease is crucial to the understanding and clinical management of diabetes. The issue remains unresolved despite many previous studies,[1] mainly because long-term normalization or even near-normalization of blood glucose has not been possible in larger groups of insulin-dependent diabetic patients. However, introduction of home-sampling and -monitoring of blood glucose, glycosylated hemoglobin (HbA_{1c}) assessment, and the introduction of continuous subcutaneous insulin infusion (CSII) now enables near-normal metabolic control.

The aim of the present study was to evaluate the effect of near-normal blood glucose levels on retinopathy in patients with insulin-dependent diabetes mellitus (IDDM) with established background retinopathy. The patients were randomized to 1 yr of treatment with either unchanged conventional therapy (UCT) or CSII. After 1 yr of study, we concluded that treatment with CSII could not prevent the development of proliferative retinopathy in some patients with background retinopathy.[2] We felt, however, that longer periods of treatment might be beneficial.[2] Therefore, we extended our study. The results of a 2-yr follow-up are presented below.

PATIENTS AND METHODS

The patients had to fulfill the following criteria to participate in the study: (1) background retinopathy; (2) postprandial C-peptide ≤0.2 nmol/L; (3) serum creatinine ≤150 μmol/L; (4) age 18–51 yr; (5) diabetes onset before age 30; and (6) diabetes duration <35 yr.

A search through the clinic records identified 40 consecutive patients fulfilling the above-mentioned criteria. Three were found unsuitable for psychosocial reasons. The remaining patients were invited for an interview and reexamination of the eyes. Two were now found to have proliferative retinopathy, and three were unwilling to participate. The 32 remaining patients were allocated at random to UCT with two daily injections of mixtures of intermediate- and short-acting insulins, or to CSII using the portable Mill Hill 1001HM insulin infusion pump (Muirhead Medical Products Ltd., London, England). One patient in the UCT group was excluded be-

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TABLE 1
Patient data at baseline (0 mo) (median and range)

	UCT	CSII
Number and sex	6 W, 9 M	8 W, 7 M
Age (yr)	32 (24–26)	36 (21–51)
Duration of IDDM (yr)	19 (9–27)	19 (11–23)
Body weight (% of ideal)	100 (79–123)	106 (84–123)
Color fundus photographs*	3.5 (1–5)	3.7 (2–5)
Fluorescein angiogram†	2.5 (1–3)	2.6 (2–3)
Retinal Morphology Index (arbitrary units)	3.0 (1–4)	3.2 (2–4)
Macular recovery time (arbitrary units)	597 (155–1700)	414 (135–1023)
Oscillatory potential (μV)	209 (30–315)	183 (13–335)
Posterior vitreous fluorophotometry‡	16.3 (5.5–32.0)	20.0 (6.5–34.5)

CSII, continuous subcutaneous insulin infusion; UCT, unchanged conventional therapy.
*Ranking values—see Table 2.
†Ranking values—see Table 3.
‡ $\times 10^{-8}$ g/ml.

cause of emigration, and one patient in the CSII group was excluded after 6 mo because an evaluation of the initial fundus photos revealed proliferative retinopathy. After 1 yr one patient changed from UCT to CSII. Therefore, this patient was excluded from the second-year evaluation. One patient in the CSII group had well-regulated hypertension treated with 25 mg hydroflumethizide daily. No other patients took any medication other than insulin.

Details of the patients are given in Table 1. Patients in the CSII group had the following occupations: 1 storekeeper, 1 sacristan, 5 clerks, 2 housewives, 1 plumber, 1 nurse, 1 student, 1 engineer, 1 director, 1 banker. An equally wide range of occupations was represented in the UCT group.

Blood glucose monitoring. During the first year, every patient collected a seven-sample blood glucose profile for 1 day every second week. During the second year, a similar blood glucose profile was collected every fourth week. Blood samples were taken from the fingertip into 10-μl end-to-end capillary tubes and mailed to hospital for analysis.[3] Samples were taken before and 90 min after each main meal, and at bedtime. Patients in the CSII group were allowed free use of "Haemo Glucotest, 1-44 strips" (Boehringer Mannheim, Mannheim, FRG) for self-monitoring of blood glucose.

During the first year, all patients were seen at monthly intervals in the outpatient clinic; during the second year they were seen at 3-mo intervals. At these visits, the results of blood glucose and HbA_{1c} (measured as the stable fraction

TABLE 2
Classification of color fundus photographs

	Ranking numbers
≤10 Microaneurysms	1
>10 Microaneurysms + hemorrhages	2
>10 Microaneurysms + hemorrhages + hard exudates	3
>10 Microaneurysms + hemorrhages + cotton-wool exudates*	4
>10 Microaneurysms + hemorrhages + hard and cotton-wool exudates	5
Proliferative retinopathy	6

*Cotton-wool exudates (i.e., retinal infarcts, soft exudates).

TABLE 3
Classification of fluorescein angiograms

	Ranking numbers
≤10 Microaneurysms + ≤3 hemorrhages	1
>10 Microaneurysms ± hemorrhages, no capillary free areas, no leakage	2
>10 Microaneurysms ± hemorrhages, capillary free areas, and/or leakage	3
Proliferative retinopathy	4

expressed as a percentage of total hemoglobin)[4] samples were presented and discussed with each patient in both treatment groups, and the treatment was adjusted according to the following aims. In the UCT group the aim was postprandial blood glucose values <15 mmol/L, 24-h urinary glucose excretion <20 g, no ketonuria, and no hypoglycemic episodes. The aim in the CSII group was postprandial blood glucose <9 mmol/L and no glucosuria.

Retinal morphology. Color fundus photographs and fluorescein angiography were carried out as described earlier.[2] Photographs were taken at 0, 6, 12, and 24 mo. A ranked classification of the initial color fundus photographs and fluorescein angiograms were made according to the worse eye of each patient (Tables 2 and 3). All photographs were assessed "blindly." To characterize the retinal status by one figure for each individual, a Retinal Morphology Index was constructed as the mean of the rank numbers of the corresponding classification of fundus photographs and fluorescein angiograms.

After 2 yr of treatment, the two ophthalmologists made a joint "blind" evaluation of the change in morphology from 0 to 2 yr.

The following scoring system was used: Each specific lesion [microaneurysms, retinal hemorrhages, hard exudates, cotton-wool exudates (retinal infarcts, soft exudates), areas of capillary nonperfusion, and leakages] were assigned −1, 0, or +1 for increased numbers of lesions, unchanged numbers, or decreased numbers, respectively. Progression into proliferative retinopathy was assigned −3. An overall score was designed before the final evaluation was done. If proliferative retinopathy developed, the overall score was −3; if proliferative retinopathy did not develop, all specific scores were added, but the score for microaneurysms and retinal hemorrhages were only weighted by half their value.*

Functional retinal parameters. Macular recovery time was measured by nyctometry (normal range 336–1089 arbitrary units)[5] and the oscillatory potential with electroretinography (normal range 223–317 μV).[6] These tests, together with posterior vitreous fluorophotometry (normal range $<10 \times 10^{-8}$ g/ml)[7] were carried out at time 0, 6, 12, and 24 mo. Mean value for the two eyes was used to characterize each patient, since changes in the two eyes are not independent.

Beat-to-beat variation and vibration sense. Beat-to-beat variation was evaluated as the mean difference between the minimal and maximal heart frequency registered on electrocardiograms during five consecutive deep inspirations and expirations. Inspirations and expirations were held for 5 s.

*Alternative methods of classification of patient retinopathy levels and assignment of change scores are discussed in the article by Davis et al., pages 42–49, this supplement.

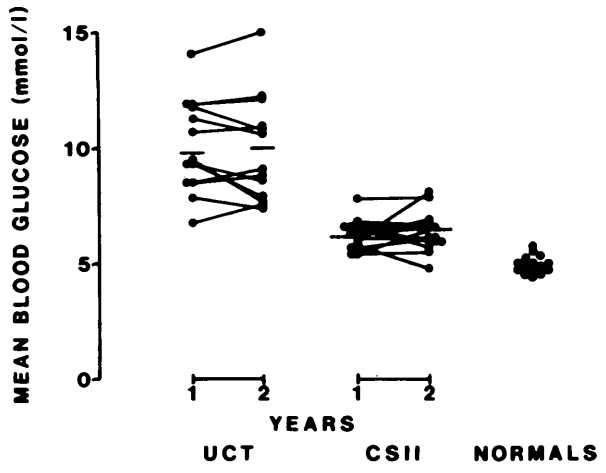

FIGURE 1. Mean blood glucose by outpatient self-sampling during the first and second years for unchanged conventional treatment (UCT) patients, and patients treated with continuous subcutaneous insulin infusion (CSII) compared with mean blood glucose in normal subjects. There is no significant difference between mean blood glucose during the first and the second years in either treatment group, whereas the difference between treatment groups at 2 yr is significant ($P < 0.01$).

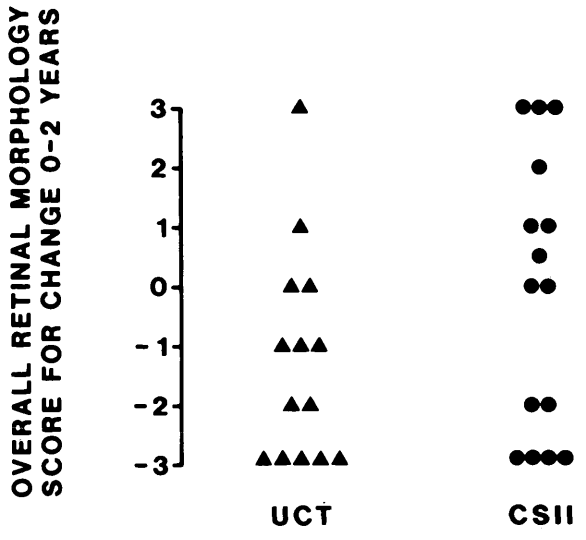

FIGURE 3. Distribution of overall score for change in retinal morphology in the unchanged conventional treatment (UCT) group and the continuous subcutaneous insulin infusion (CSII) group ($P = 0.1$).

Vibration sense at the first phalanges of hands and feet plus the medial malleoli of the legs was measured by biotensiometer.[8] The means of the hands, feet, and malleoli, respectively, were used to characterize each patient. Beat-to-beat variation and vibration sense were evaluated at 0, 6, 12, and 24 mo.

Statistical analyses. Results are given as mean ± 1 SEM or median (range). Where not otherwise specified, the Mann-Whitney test and *t*-test were used for unpaired data and the Wilcoxon test for paired data. Significant levels were 0.05 (two-tailed).[9]

RESULTS

Metabolic control. Figure 1 shows the mean blood glucose for each patient during the first year (195 samples per patient) and during the second year (85 samples per patient). Figure 2 shows mean HbA_{1c} for each patient during the first and second years (12 samples as compared with 4 samples per patient). The overall mean blood glucose and HbA_{1c} were significantly lower in the CSII group than the UCT group ($P < 0.01$ and $P < 0.01$, respectively). In spite of the less frequent visits in the outpatient clinic during the second year, the overall mean blood glucose and HbA_{1c} did not change in either of the treatment groups (Figures 1 and 2).

During the first year, the frequency of blood glucose values <2.5 mmol/L in the CSII group and UCT group were 4% (1–15%) and 2% (0–16%), respectively (no significant difference, NS). During the second year, the frequencies were 1% (0–6%) and 0% (0–21%), respectively (NS). The frequency of blood glucose values <2.5 mmol/L fell significantly ($P < 0.01$) from the first to the second year in the CSII group.

Retinal morphology. Retinal morphology at the start of the study did not differ significantly between the two treatment groups (UCT and CSII) evaluated by ranking of color fundus photographs or fluorescein angiograms, nor according to Retinal Morphology Index (Table 1).

The overall score for the change in retinal morphology from 0 to 2 yr is shown in Figure 3. There was no significant ($P = 0.1$) difference between the distribution of scores in the two treatment groups. In Table 4, the overall scores have been transformed to improvement, no change, or deterio-

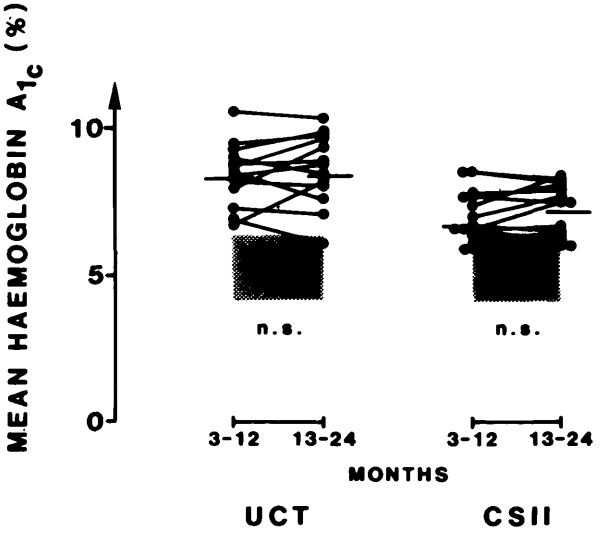

FIGURE 2. Mean hemoglobin A_{1c} during 3–12 mo and 13–24 mo in patients treated with unchanged conventional treatment (UCT) and continuous subcutaneous insulin infusion (CSII). There is no significant difference between 3 and 12 mo and 13 and 24 mo, whereas the difference between treatment groups is significant ($P < 0.01$).

TABLE 4
Change in retinal morphology from baseline to 2 yr

	UCT	CSII	Total
Improvement	2	7	9
No change	2	2	4
Deterioration	10	6	16
Total	14*	15	29*

For abbreviations, see Table 1.
*One patient was excluded from the 2-yr evaluation because he changed from UCT to CSII after 1 yr of follow-up (see PATIENTS AND METHODS).

TABLE 5
Relationships between development of proliferative retinopathy and other important metameters (mean ± SEM or median [range])

	Retinal status after 2 yr		
	Proliferative retinopathy	Background retinopathy	P-values
Number of patients	9	21	
Baseline values			
Retinal morphology index (arbitrary units)	3.6 (3–4)	2.9 (1–4)	<0.05
Macular recovery time (arbitrary units)*	320 ± 61	595 ± 75	<0.05
Oscillatory potential (μV)†	146 ± 28	220 ± 13	<0.05
Posterior vitreous fluorophotometry ($\times 10^{-8}$ g/ml)	21.1 ± 2.6	16.6 ± 1.7	NS
Albuminuria (μg/min)	12 (2–179)	18 (1–893)	NS
Duration of IDDM (yr)	19.5 (12–25)	18.5 (9–23)	NS
Mean arterial blood pressure (mm Hg)	99.1 ± 3.6	100.1 ± 1.7	NS
2-Yr mean blood glucose (mmol/L)‡	8.2 (6.2–12)	8.1 (5.5–15)	NS
Frequency of blood glucose ≤2.5 mmol/L (%)	2 (0–4)	2 (0–16)	NS
ΔHbA_{1c} from 0 to 2 mo (%/mo)	0.8 ± 0.3	0.7 ± 0.2	NS

NS, no significant difference.
*Normal range 336–1089 arbitrary units.
†Normal range 223–317 μV.
‡Multiply by 18 to change to mg/dl.

ration of retinal morphology. Improvement of retinopathy was more frequent among CSII patients than among UCT patients, although the difference was, at most, marginally significant (Patefield's exact test for trends[10] yields a one-sided P-value of 0.046, whereas the test according to McCullagh[11] gives $X^2 = 3.66$, $P = 0.06$, two-sided, based on the asymptotic X^2-approximation). The patient who dropped out because he changed to CSII therapy after 1 yr showed improved retinal morphology after 2 yr.

Four patients in the CSII group had proliferative retinopathy after 2 yr of treatment (two during the first year) compared with five patients in the UCT group (one during the first year). Only one of these nine patients (a UCT patient) had prepapillary proliferations, whereas the remaining eight developed peripheral proliferations.

From Table 5 it can be seen that those patients who developed proliferative retinopathy had significantly worse retinal morphology ranking, macular recovery time, and oscillatory potential at baseline when compared with those who did not develop proliferative retinopathy. No significant differences were seen between the two groups concerning the initial values of posterior vitreous fluorophotometry, albuminuria,[12] duration of diabetes, or mean arterial blood pressure. Likewise, no significant differences were seen between the two groups concerning mean blood glucose levels and frequency of blood glucose values <2.5 mmol/L (45 mg/dl) during the 2 yr of treatment, or between the fall rate of HbA_{1c} during the first 2 mo of treatment (Table 5).

Functional retinal parameters. Changes after 1 yr of near-normoglycemia have been previously reported.[2] A significant deterioration of posterior vitreous fluorophotometry was seen from 0 to 1 yr ($P < 0.05$) and from 1 to 2 yr ($P < 0.05$) in the UCT group (Figure 4). A significant improvement from 0 to 1 yr was, however, found in the CSII group ($P < 0.05$) with no further significant change from 1 to 2 yr. Identical results were found for macular recovery time and oscillatory potential (the latter not measured at 2 yr).

A significant relationship was found between the initial values of macular recovery time and oscillatory potential and the development of proliferative retinopathy (Table 5). Of the patients with initial normal values of macular recovery time (N = 22), oscillatory potential (N = 7), and posterior vitreous fluorophotometry (N = 5), 4 (18%), 1 (14%), and 0 (0%), respectively, developed proliferative retinopathy within the next 2 yr. Of the patients with initial abnormal values (N = 8, 23, and 25, respectively), 5 (63%), 8 (35%), and 9 (36%) developed proliferative retinopathy within the same period. The above differences between the prognostic value of normal values as compared with abnormal values were not significant for any of the three parameters.

Beat-to-beat variation and vibration sense. Results of the change in beat-to-beat variation from 0 to 2 yr are seen for both treatment groups in Figure 5. There was no significant difference between the initial values in the two groups. The deterioration from 0 to 2 yr in the UCT group was significant

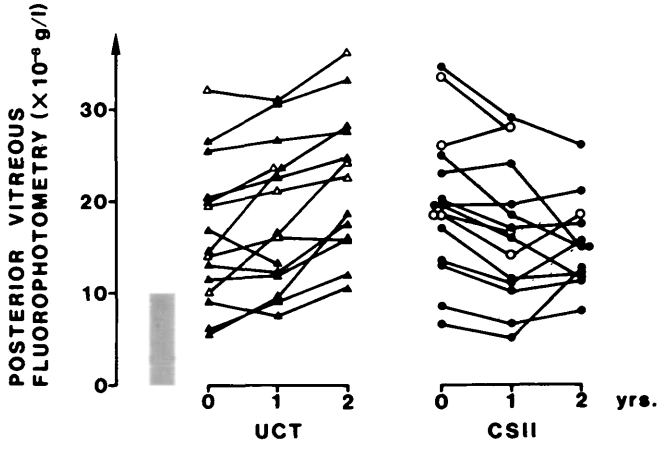

FIGURE 4. Posterior vitreous fluorophotometry measured at 0, 1, and 2 yr in the unchanged conventional treatment (UCT) group and the continuous subcutaneous insulin infusion (CSII) group. Open symbols indicate patients who developed proliferative retinopathy. Shaded areas indicate the normal range. In the UCT group, a significant deterioration was seen from 0 to 1 and 1 to 2 yr, respectively. In the CSII group, as has been previously reported,[2] a significant improvement was seen from 0 to 1 yr, with no further significant change from 1 to 2 yr ($P < 0.05$).

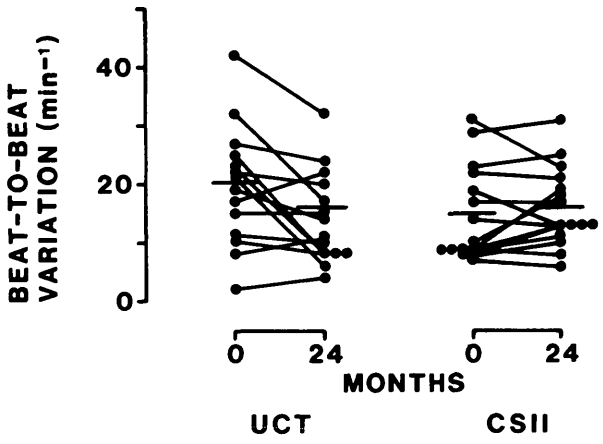

FIGURE 5. Beat-to-beat variation measured at 0 and 24 mo in the unchanged conventional treatment (UCT) group and the continuous subcutaneous insulin infusion (CSII) group. A significant deterioration was seen in the UCT group ($P < 0.05$), but the small improvement seen in the CSII group was insignificant.

($P < 0.05$), whereas the small increase in the CSII group was nonsignificant.

There was no significant change in vibration sense in either of the treatment groups for any of the measured points (first phalanges of hands and feet plus the medial malleoli of the legs).

DISCUSSION

The Steno Study was originally designed as a 1-yr study. The results of the first year showed significantly improved glycemic control, increased well-being,[13] and a tendency toward more frequent deterioration of established retinopathy in the CSII group compared with the UCT group.[2] In spite of the methodologic problems, we decided to make a 2-yr follow-up, the results of which are presented here.

During the second year, the patients visited the outpatient clinic less frequently than during the first year (12 times versus 4 times per year) and took about half as many home samples of blood glucose. This resulted in a small, but insignificant increase in mean blood glucose from the first to the second year, in both treatment groups. In the CSII group, this was accompanied by a significant fall in the frequency of hypoglycemia. This frequency was equal to that found in the UCT group. Insulin pumps therefore seem to be an easy and practical tool to achieve near-normal blood glucose values. The risk of hypoglycemia can probably be reduced by aiming at near-normal blood glucose levels rather than normal blood glucose levels.

The overall score for retinal morphology showed a tendency toward more frequent improvement of retinopathy after 2 yr of treatment with CSII than with UCT, this difference being at most marginally significant. This, together with the first year's results,[2] the trend shown in the Kroc Study (see article by Canny et al., pages 50–55, and article by Kohner et al., pages 56–60, this supplement),[14] and the observations of others,[15] point to the possibility of an initial worsening of retinopathy followed by improvement during long-term CSII therapy. In fact, when comparing the change in retinal morphology during the first 2 yr of CSII (2 improved, 2 were unchanged, and 6 deteriorated, Table 4) with the change during the first year (2 improved, 2 were unchanged, and 11 deteriorated),[2] a significant shift is seen toward more frequent improvement during the second year ($P < 0.05$, two-sided test by the method of McCullagh[11]).

Altogether, nine patients (four CSII and five UCT) developed proliferative retinopathy. In contrast to observations made by others,[15] no spontaneous regression was seen. The development of proliferative retinopathy was related to worse degrees of morphologic and functional retinopathy (Table 5), but neither to the actual mean blood glucose levels during the two treatment years nor to the duration of diabetes. This suggests that a point of irreversibility may exist in advanced cases of background retinopathy.

Still under discussion is whether the rate at which near-normalization of blood glucose levels is achieved by pump therapy might influence the progression of retinopathy.[15] This hypothesis could not be supported from this study, as the rate of decreasing HbA_{1c} during the first 2 mo of therapy was almost identical in the groups of patients who did and did not develop proliferative retinopathy (Table 5).

Prospective studies with more than 100 patients have shown that the macular recovery time[5] and oscillatory potential[6] are of significant prognostic value in selecting those patients at risk of developing proliferative retinopathy. Although not significant, the results of our study showed the same tendency inasmuch as patients who in the follow-up period developed proliferative retinopathy demonstrated as a group significantly more severe functional and morphologic alterations at baseline (Table 5).

Autonomic neuropathy evaluated by beat-to-beat variation showed almost the same changes as did retinopathy. After 2 yr of treatment, a significant deterioration was observed in the UCT group, with an insignificant trend toward improvement in the CSII group. Other studies have shown improvement of nerve conduction velocity by CSII therapy.[16,17]

Although our results support the hypothesis that near-normalization may benefit the further development of diabetic retinopathy and neuropathy, we do not find our results conclusive. This is mainly because of the small number of patients. We are therefore looking forward to the results of other long-term prospective studies.

By courtesy of the Fundus Photograph Reading Center, University of Wisconsin, an evaluation of baseline retinal morphology identical to the evaluation used in the Kroc Study was performed on our fundus photographs at the onset of the study. It should be mentioned, however, that in our study nonstereoscopic fundus photographic technique was applied. The results are given in Table 6. The number in parentheses following the description of retinopathy indicates the equivalent level of retinopathy in the worse eye, according

TABLE 6
Level of patient retinopathy at baseline using "worse eye only" method of classification at the Fundus Photograph Reading Center

Retinopathy level	UCT	CSII	Total
30	4 (26.6%)	0 (0.0%)	4 (13.3%)
40	7 (46.6%)	11 (73.3%)	18 (60.0%)
50	3 (20.0%)	1 (6.6%)	4 (13.3%)
65	1 (6.6%)	3 (20.0%)	4 (13.3%)

For abbreviations, see Table 1.

to a classification described by Davis et al., pages 42–49, this supplement.

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