

## PAPERS AND SHORT REPORTS

## Effect of near normoglycaemia for two years on progression of early diabetic retinopathy, nephropathy, and neuropathy: the Oslo study

KNUT DAHL-JØRGENSEN, OLAF BRINCHMANN-HANSEN, KRISTIAN F HANSEN, TROND GANES, PETER KIERULF, ERLEND SMELAND, LEIV SANDVIK, ØYSTEIN AAGENAES

### Abstract

Forty five insulin dependent diabetics were randomised to treatment with continuous subcutaneous insulin infusion (CSII), multiple insulin injections (five or six daily), or conventional twice daily insulin injections. Near normoglycaemia was obtained with CSII and multiple injections but not with conventional treatment ( $p < 0.01$ ). Hypoglycaemic coma was observed less frequently with CSII than with multiple injections and conventional treatment ( $p < 0.001$ ), but blood glucose concentrations below 2.5 mmol/l (45 mg/100 ml) were more common. After two years fewer retinal microaneurysms and haemorrhages had developed in the patients given CSII and multiple injections compared with those given conventional treatment, in whom the number had increased significantly ( $p < 0.01$ ). Motor nerve conduction velocity deteriorated in the patients given conventional treatment; in those given CSII it was unchanged during the first year but had improved after two years ( $p < 0.01$ ). Glomerular hyperfiltration was reduced with CSII, but no change occurred in urine albumin excretion rates.

Long term near normoglycaemia may prevent the progression of early stages of late diabetic complications.

### Introduction

Evidence from animal experiments suggests that correction of hyperglycaemia prevents or retards the development of late diabetic complications.<sup>1,2</sup> Similar observations are not yet available in man. Circumstantial evidence from clinical observations indicates an association between hyperglycaemia and the development of late diabetic complications.<sup>3,5</sup> Whether fewer complications in the "well controlled" patients is due to the effectiveness of treatment or the mildness of the disease itself is still unresolved.<sup>6</sup> This problem can be solved only by randomised clinical trials, but results so far have been disappointing.<sup>7-12</sup> Some patients in these studies may have passed the stage in which the progression of late complications could be influenced by the return of metabolite values to normal.<sup>7</sup>

A controlled, prospective trial in patients with diabetes of shorter duration and less pronounced complications than those in most other studies was therefore designed. Multiple insulin injections (now being used to treat an increasing proportion of the diabetic population) and insulin pump treatment were compared with conventional twice daily injections. We present the results after two years.

### Patients and methods

The study protocol was approved by the ethical committee of the Norwegian Council for Science and the Humanities. Forty five insulin dependent diabetics were studied.<sup>9,10</sup> They had serum C peptide concentrations (after glucagon stimulation) below 0.1 nmol/l. During the two months before the study home blood glucose monitoring was introduced and baseline results obtained. All patients used twice daily insulin injections. They were then randomly assigned to three modes of treatment: continuous subcutaneous insulin infusion (CSII), multiple insulin injections, or continued conventional treatment with twice daily injections of insulin (controls). Block randomisation was performed to ensure comparable groups (table I).

In the control group a mixture of regular and isophane insulin was injected before breakfast and dinner. In the group receiving multiple injections isophane insulin was given at bedtime. During CSII a constant basal rate of regular insulin was infused. In the groups treated by CSII and multiple injections additional regular insulin was infused or injected, respectively, before each meal (four to six times daily). Two different pumps were used for CSII: Nordisk infuser (Nordisk Gentofte, Denmark) or Autosyringe AS6C

Aker University Hospital, N-0514 Oslo 5, Norway

KNUT DAHL-JØRGENSEN, MD, registrar, paediatric department  
KRISTIAN F HANSEN, MD, chief physician, medical department B  
ERLEND SMELAND, MD, research fellow, hormone laboratory  
ØYSTEIN AAGENAES, MD, chief physician, paediatric department

Ullevål University Hospital, Oslo

OLAF BRINCHMANN-HANSEN, MD, chief physician, department of ophthalmology  
PETER KIERULF, MD, chief physician, clinical chemistry department

Laboratory of Clinical Neurophysiology, National Hospital, Oslo

TROND GANES, MD, chief physician

MedStat Ltd, Oslo

LEIV SANDVIK, BSc, medical statistician

Correspondence to: Dr Dahl-Jørgensen.

(Travenol, USA). Only highly purified porcine insulin preparations were used (Nordisk, Novo).

During the first year a 24 hour blood glucose profile on filter paper was obtained weekly with sampling before and 90 minutes after each meal and at bedtime, and occasionally at 4 am.<sup>13</sup> During the second year profiles were obtained fortnightly. Mean values of all profiles were used. The frequency of subjective hypoglycaemia was recorded by the patients and reported at each visit. Each episode of ketoacidosis, subcutaneous infection, and hypoglycaemic coma (defined as unconsciousness) was recorded. Haemoglobin A<sub>1</sub> concentration was determined monthly by agar gel electrophoresis (Glytrac, Corning) after elimination of labile haemoglobin A<sub>1</sub> (normal range (2 SD) 5.4-7.6%). The interassay coefficient of variation was 5%.<sup>14</sup>

Twenty four hour urine samples were collected six to 18 times (mean 14) from each patient during the study. Urinary albumin excretion was determined by an immunonephelometric method (normal range (2 SD) 2-27 mg/24 h). The interassay coefficient of variation was less than 7%. The glomerular filtration rate was calculated from plasma clearance of edetic acid labelled with chromium-51 (Amersham, England) essentially as described by Brøchner-Mortensen<sup>15</sup> and related to body surface (normal range (2 SD) 79-131 ml/min.1.73 m<sup>2</sup>).

Motor nerve conduction velocities were measured in the ulnar, peroneal, and tibial nerves. To distinguish between acute "metabolic" and chronic "structural" neuropathy measurements were performed every three to six months.<sup>16</sup> The nerve was stimulated percutaneously with a bipolar surface electrode. Motor responses were recorded with surface electrodes, Medelec MS 92 equipment being used. Skin temperature was kept within narrow limits throughout the study.

Eye examinations were performed on both eyes as described<sup>9,10</sup> and included a test of visual acuity, direct and binocular indirect ophthalmoscopy, and split lamp biomicroscopy (in cycloplegia). A 35 mm standard colour photograph of the fundus (both eyes) covering a 30° field of the retina was produced, with the photograph centred at half the distance between the fovea and the temporal edge of the optic disc. Microaneurysms and haemorrhages were counted as "red spots" from the photographs, and mean values for both eyes were used. A magnifying grid with 45 areas was applied directly on to the negatives, which were coded by a technician, and the number of red spots was counted blind by the ophthalmologist.

The presence of cotton wool spots was determined by indirect ophthalmoscopy, by binocular microscopy, and from the colour photographs of the fundus. One eye was randomly chosen for fluorescein angiography of the standard area, and the frame representing the late capillary/early venous phase was selected. The ophthalmologist who evaluated the angiograms was

blind to the identity of the patient, treatment group, and time of examination. Owing to allergy to fluorescein in one patient receiving CSII and pregnancy in another, angiography was not performed in these patients. The angiograms obtained at randomisation and after two years of study were evaluated in each subject, and the retinopathy was graded as unchanged, improved, or deteriorated.

**Statistical analysis**—A two sided Wilcoxon rank sum test was used for differences between groups. For differences within groups a two sided Wilcoxon sign rank test was used. For the variable microaneurysms and haemorrhages one sided Wilcoxon tests were used. The skewed distribution of this variable necessitated a logarithmic transformation before evaluation of p values. The Fisher-Irwin test was used to compare frequencies. Correlations were calculated by Pearson's correlation coefficient. The level of significance was chosen as 5%.

## Results

### CONTROL OF BLOOD GLUCOSE CONCENTRATIONS, AND ACUTE COMPLICATIONS

Near normoglycaemia was obtained during the first months of CSII and multiple injections and maintained over the two years of the study. Control of blood glucose concentrations was slightly better with CSII than multiple injections (NS), both these forms of treatment being significantly better than conventional treatment throughout the two years ( $p < 0.01$ ) (fig 1). Hypoglycaemic coma was less common in the patients receiving CSII than in those receiving multiple injections and conventional treatment ( $p < 0.001$ ), but blood glucose values below 2.5 mmol/l (45 mg/100 ml) were more common (table II). Two episodes of ketoacidosis and eight subcutaneous abscesses were observed during treatment with CSII; no such episodes were observed in the other treatment groups (table II).

### RETINOPATHY

Retinopathy was equally distributed in the three groups at the start of the study (table I). No significant difference in the number of microaneurysms and haemorrhages was observed between the groups initially (table III). A transient increase in microaneurysms and haemorrhages was observed in the group receiving CSII at three months. At two years the numbers of microaneurysms and haemorrhages in the groups given CSII and multiple

TABLE I—Characteristics of patients at start of study (after block randomisation to treatment groups). Values are means (ranges)

Treatment group	Age (years)	Duration (months)	Sex (M:F)	Haemoglobin A <sub>1</sub> (%)	Serum creatinine (μmol/l)	Blood pressure (mm Hg)	Grade of retinopathy* (No of patients)			
							1	2	3	4
Conventional (n=15)	26 (18-36)	152 (81-240)	7:8	9.5 (7.6-14.6)	79 (58-97)	124/78 (110-140/65-100)	3	5	5	2
Multiple injections (n=15)	26 (19-42)	154 (81-250)	7:8	9.4 (7.0-11.7)	78 (53-101)	129/79 (105-170/70-90)	3	4	5	3
CSII (n=15)	26 (18-32)	153 (77-280)	7:8	10.1 (8.0-12.9)	77 (47-114)	122/78 (110-145/60-95)	5	3	5	2

\*As assessed from fluorescein angiograms<sup>9,10</sup>: grade 1=no microaneurysms; grade 2= $\leq 3$  microaneurysms; grade 3= $> 3$  microaneurysms; grade 4=presence of hard exudates.

Conversion: SI to traditional units—Creatinine: 1 μmol/l $\approx$ 11.3 μg/100 ml.

TABLE II—Mean (SEM) details of diabetic control and hypoglycaemia. Acute complications of treatment expressed as number of complications during study (and number of patients affected)

	CSII		Multiple injections		Conventional treatment	
	At randomisation	After two years	At randomisation	After two years	At randomisation	After two years
<b>Glycaemic control:</b>						
Haemoglobin A <sub>1</sub> (%)	10.1 (0.4)	8.7 (0.3)**	9.4 (0.4)	9.1 (0.4)	9.5 (0.4)	10.2 (0.5)
Mean blood glucose (mmol/l)	8.9 (0.7)	5.3 (0.3)**	9.0 (0.8)	6.4 (0.3)**	7.9 (0.7)	7.9 (0.5)
Fasting blood glucose (mmol/l)	9.1 (0.9)	4.6 (0.3)**	8.1 (1.0)	5.8 (0.6)	8.2 (1.0)	8.2 (0.8)
Within day SD of blood glucose (mmol/l)	3.5 (0.2)	2.2 (0.7)*	3.4 (0.2)	2.5 (0.2)	3.7 (0.3)	3.2 (0.3)
Within day range of blood glucose (mmol/l)	10.0 (0.6)	6.1 (0.6)*	9.7 (0.5)	7.1 (0.6)	10.7 (0.8)	8.7 (0.8)
<b>Hypoglycaemia:</b>						
Symptomatic hypoglycaemic episodes/week/patient	2.3 (0.6)	1.7 (0.3)	1.5 (0.3)	1.2 (0.2)	1.8 (0.4)	1.3 (0.3)
% Of home blood glucose values <2.5 mmol/l	6 (2)	11 (2)*	8 (3)	7 (1)	12 (3)	6 (1)
<b>Acute complications:</b>						
Hypoglycaemic coma		2 (2)††		14 (6)		13 (7)
Subcutaneous abscess		8 (6)†		0		0
Diabetic ketoacidosis		2 (2)		0		0
Insulin requirement (U/kg body weight)	0.80 (0.06)	0.68 (0.05)**	0.72 (0.02)	0.72 (0.03)	0.78 (0.04)	0.76 (0.03)
Body weight (kg)	68.6 (2.4)	70.5 (2.3)	71.7 (2.6)	75.1 (2.9)*	71.7 (2.7)	71.1 (2.7)

Change in values during study v change in group receiving conventional treatment: \* $p < 0.05$ , \*\* $p < 0.01$ . Group given CSII v groups given multiple injections and conventional treatment: † $p < 0.01$ , †† $p < 0.001$ .

Conversion: SI to traditional units—Glucose: 1 mmol/l $\approx$ 18 mg/100 ml.

injections were similar to those observed at the time of randomisation, whereas the number in the group given conventional treatment had increased significantly ( $p < 0.01$ ). Significantly fewer microaneurysms and haemorrhages developed during the two years in the groups given CSII and multiple injections combined than in the group given conventional treatment ( $p < 0.05$ ).

During the first three to six months half of the patients receiving CSII and multiple injections (seven and eight, respectively) developed transient cotton wool spots in the retina. None of the patients receiving conventional

## NERVE FUNCTION

Mean motor nerve conduction velocities were normal at the start of the study (table V). No significant changes were observed during the first year in the three groups. Motor nerve conduction velocity had increased significantly after two years in all nerves tested in the group given CSII and was faster in this group than in the group given conventional treatment, the difference being up to 6 m/s (nervus ulnaris). Mean motor nerve conduction velocity was reduced in two nerves and unchanged in one in the group given

TABLE III—Number of retinal "red spots" (microaneurysms and haemorrhages) in the three treatment groups. Values are geometric means (95% confidence intervals)

Treatment group	No of microaneurysms and haemorrhages			
	At randomisation	At three months	At one year	At two years
CSII (n=15)	2.4 (0.8 to 5.6)	6.4 (1.7 to 19.1)*	3.5 (1.0 to 9.0)	3.2 (0.5 to 10.8)
Multiple injections (n=15)	8.1 (0.9 to 19.0)	8.0 (3.0 to 19.1)	8.0 (4.0 to 19.1)	10.9 (3.4 to 31.4)
Multiple injections + CSII (n=30)	4.6 (2.5 to 8.0)	7.1 (3.5 to 13.9)	5.7 (2.7 to 11.2)	6.1 (2.7 to 12.7)
Conventional (n=15)	4.3 (1.7 to 9.3)	5.7 (2.0 to 13.8)	4.5 (2.0 to 11.2)	13.7 (5.4 to 33.5)**†

Change from number at randomisation: \* $p < 0.05$ , \*\* $p < 0.01$ .

Change in groups given CSII and multiple injections v change in group given conventional treatment: † $p < 0.05$ .

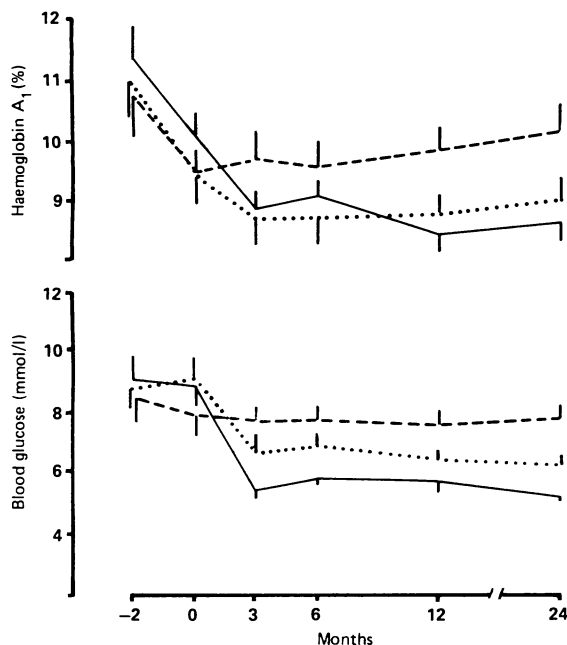


FIG 1—Mean (SEM) haemoglobin A<sub>1</sub> and blood glucose concentrations (24 hour profiles) during two years of treatment in patients receiving conventional treatment (—), multiple injections (---), or CSII (···). In the two months before randomisation all patients used twice daily insulin injections.

Conversion: SI to traditional units—Glucose: 1 mmol/l ≈ 18 mg/100 ml.

treatment did so. We previously described the relation between the development of such changes and the large and rapid fall in blood glucose concentration in these patients.<sup>9,10</sup> After one year the cotton wool spots had regressed in all but two patients. After the first year new cotton wool spots developed in only two patients, both of whom were receiving multiple injections.

The results from the blind ranking of the fluorescein angiograms obtained during the first year have been described.<sup>9,10</sup> Table IV lists the number of patients in whom retinopathy, assessed by fluorescein angiography, improved, deteriorated, or remained unchanged during the study. Deterioration was noted in eight of the 15 patients receiving conventional treatment and seven of the 15 receiving multiple injections but in only four of the 13 receiving CSII, but this difference was not significant. Visual acuity did not change significantly throughout the study.

One patient developed transient severe preproliferative retinopathy in both eyes during the first three months of CSII, but CSII was continued and the changes regressed spontaneously without laser treatment.<sup>8</sup> After nearly three years of CSII she still had only minimal changes, which she had had at randomisation.

conventional treatment and was unchanged in two nerves and reduced in one in the patients receiving multiple injections (table V). A significant negative correlation ( $r = -0.40$ ,  $p < 0.01$ ) was found in all the patients combined between the change in motor nerve conduction velocity (sum of all three nerves) and the change in haemoglobin A<sub>1</sub> concentration.

## KIDNEY FUNCTION

Mean urinary albumin excretion was in the upper normal range in the two months before randomisation and did not change significantly during the two years (fig 2). Eleven patients had above normal excretion ( $> 27$  mg/24 h), which did not change regardless of treatment group. The month to month

TABLE IV—Number of patients in whom retinopathy improved, deteriorated, or remained unchanged during study

	Treatment group		
	Conventional (n=15)	Multiple injections (n=15)	CSII* (n=13)
Improved	1	1	1
Unchanged	6	6	8
Deteriorated	8	7	4

\*Angiography not performed at two years in two patients because of pregnancy and allergy to fluorescein.

variation in urinary albumin excretion, estimated as the coefficient of variation in individual patients, was large: in the group given CSII, mean 45% (range 31-92%); group given multiple injections, 62% (11-123%); group given conventional treatment, 45% (14-88%) (NS).

The glomerular filtration rate decreased significantly during CSII for six months, from 119 (SEM 4) to 111 (4) ml/min.1.73 m<sup>2</sup> ( $p < 0.05$ ), but no significant change occurred with multiple injections (116 (4) to 112 (5) ml/min.1.73 m<sup>2</sup>). The initial glomerular filtration rates correlated with the initial haemoglobin A<sub>1</sub> concentrations ( $r = 0.47$ ,  $p < 0.01$ ). In the group given conventional treatment glomerular filtration rate was 114 (3) ml/min.1.73 m<sup>2</sup> after eight to 10 months (not measured initially).

Blood pressures and serum creatinine concentrations were within the normal range initially (table I) and did not change throughout the study. No correlation was found between the initial systolic and diastolic blood pressures, degree of retinopathy, smoking habit, glomerular filtration rate, and urinary albumin excretion or between the changes in glomerular filtration rate, urinary albumin excretion, and haemoglobin A<sub>1</sub> concentration. The patients who developed cotton wool spots in the retina did not have a higher initial glomerular filtration rate, urinary albumin excretion, or blood pressure than those who did not, nor was there any difference in the change in urinary albumin excretion or in glomerular filtration rate between these two groups.

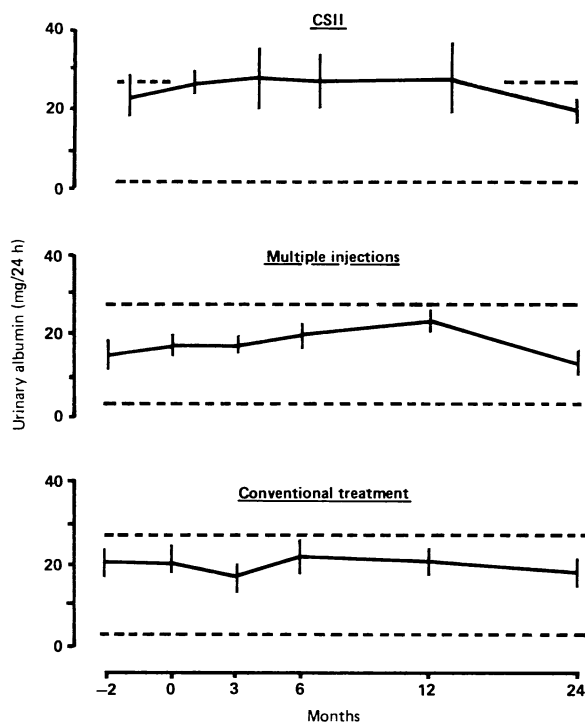


FIG 2—Mean (SEM) urinary albumin excretion in the three groups of patients. Broken lines indicate normal range.

TABLE V—Mean (SEM) motor nerve conduction velocity initially, and change in values during study (m/s)

	CSII		Multiple injections		Conventional treatment	
	Initial value	Change	Initial value	Change	Initial value	Change
Nervus ulnaris	57.3 (2.5)	1.7 (2.5)**	58.0 (1.1)	1.9 (1.4)	60.0 (2.0)	-3.9 (1.4)
Nervus peroneus	43.2 (1.1)	2.9 (1.4)*	42.5 (1.1)	0.4 (0.9)	44.4 (1.5)	0.3 (1.4)
Nervus tibialis	45.8 (1.0)	1.9 (0.8)**	46.2 (1.6)	0.7 (1.5)	48.5 (2.1)	-2.6 (1.9)

Compared with change in group given conventional treatment: \* $p < 0.05$ , \*\* $p < 0.01$ .

## Discussion

This prospective, randomised study shows that long term near normoglycaemia obtained with CSII and multiple injections prevents the progression of early stages of some late diabetic complications. A "point of no return" in the development of complications has been postulated, beyond which strict control of blood glucose concentrations might no longer influence the rate of progression.<sup>7</sup> Early intervention might increase the chance of influencing the process leading to irreversible complications, and the patients in this study had a shorter duration of disease and less severe complications than those in most other controlled, prospective studies.<sup>7, 11, 12</sup>

We previously described the relation between transient deterioration of retinopathy and the large and rapid fall in blood glucose concentrations when multiple injections and CSII were started.<sup>9, 10</sup> In the long term, however, significantly fewer microaneurysms and haemorrhages developed in patients treated with CSII and multiple injections than in those given conventional treatment. This is the first prospective randomised study showing directly that the development of microaneurysms and haemorrhages can be reduced by near normoglycaemia. Eschwege *et al* reported fewer new microaneurysms in patients receiving two or three insulin injections daily compared with single injections.<sup>17</sup> Their study, however, was criticised because of the great number of crossovers between treatment groups and the small, if any, group difference in blood glucose control. The number of microaneurysms and haemorrhages was not reported in the Steno study.<sup>18</sup> In the Kroc study no significant change in microaneurysms and haemorrhages was ob-

served during one year.<sup>19</sup> Different methods of assessing retinopathy exist. In the present study microaneurysms and haemorrhages were counted, because the standard method of comparing colour photographs—for example, the modified Airly House retinal grading system<sup>20</sup>—discriminates less well in early stages of retinopathy. Counting microaneurysms and haemorrhages in more advanced retinopathy is difficult, and standard comparison of photographs may then be a more reproducible method.<sup>19</sup> Owing to the lack of angiograms at two years in two patients receiving CSII we used the colour photographs and counted microaneurysms and haemorrhages in both eyes in all patients. When we evaluated the fluorescein angiograms at two years less progression was noted in the group given CSII than in the groups given conventional treatment and multiple injections. These differences, however, were not significant. The Steno group reported a slight improvement in retinopathy by this method in patients receiving CSII compared with conventional treatment, but only marginal differences were found after two years.<sup>18</sup> Similar results were reported after two years from the Kroc study.<sup>21</sup>

In the group given conventional treatment peripheral nerve function deteriorated during the two years of the study. Motor nerve function was unchanged during the first year and improved during the second year of CSII. This implies that even if the motor nerve conduction velocity was initially within normal ranges it was not optimal in these patients at the start of the study. In fact, the improvement observed during CSII was greater than that observed with aldose reductase inhibitor treatment.<sup>22</sup> The results were evidently not compatible with reversible acute "metabolic neuropathy"<sup>16</sup> as no significant changes in motor nerve conduction velocity

were observed during the first three months after randomisation when blood glucose concentrations were lowered. In several clinical studies improvement of motor nerve conduction velocity during CSII has been reported in patients with clinical or symptomatic neuropathy.<sup>23-27</sup> Few patients were included in these studies; only two studies included a control group.<sup>23, 27</sup> Frequent measurements of nerve conduction velocity initially to correct for acute reversible effects were not reported. Service *et al* reported no effect after four months but improved nerve function after eight months.<sup>27</sup> Our study reported symptomatic relief of painful neuropathy.<sup>24</sup> In the Steno study autonomic nerve function was improved at two years in patients receiving CSII.<sup>18</sup> Delayed progression of chronic asymptomatic peripheral neuropathy by near normoglycaemia or improvement, as in the present study, has not previously been shown.

Early glomerular hyperfiltration is well documented in insulin dependent diabetes mellitus.<sup>28</sup> Animal studies suggest that hyperfiltration has a role in the pathogenesis of late diabetic glomerular lesions.<sup>29, 30</sup> In man the progression from microalbuminuria to clinical overt nephropathy is associated with early glomerular hyperfiltration.<sup>31</sup> Whether glomerular hyperfiltration without microalbuminuria may be deleterious in diabetics is not known. In the present study a highly significant correlation between blood glucose control, as estimated by haemoglobin A<sub>1</sub> concentration, and glomerular filtration rate was found. Furthermore, glomerular hyperfiltration improved during CSII. This agrees with results of previous studies in patients with microalbuminuria.<sup>32, 33</sup> Interestingly, glomerular filtration rate improved with CSII, whereas no significant change was noted with multiple injections. This may im-

part be explained by the better control of blood glucose concentrations obtained with CSII compared with multiple injections.

Two years of near normoglycaemia in our patients did not lead to a reduction in urinary albumin excretion, which at the start of the study was normal or only slightly increased. This adds new information to the results of studies of patients with more advanced diabetes, which were conflicting.<sup>11 12 33</sup> In the Kroc study urinary albumin excretion fell significantly during eight months of CSII in those patients who had raised excretion at the start of the study.<sup>11</sup> One objection to that study was the small number of urine specimens collected.<sup>34</sup> The intraindividual variability of urinary albumin excretion is a problem in the study of incipient diabetic nephropathy. We used repeated 24 hour urine collections, which are necessary to minimise the variations. In a recent prospective, randomised study in patients with microalbuminuria no change in urinary albumin excretion was found during one year of CSII.<sup>12</sup> The Steno study group reported a smaller increase in microalbuminuria in patients receiving CSII than in those receiving conventional treatment over two years.<sup>32</sup> These patients had had diabetes for longer, were older, and had higher urinary albumin excretion than our patients initially. Thus a longer observation period may be needed in our Oslo study to see whether progression will occur in patients given conventional treatment, or improvement in those given CSII or multiple injections.

Few studies have addressed the practical clinical problem of which intensified insulin regimen, CSII or multiple injections, is most effective on a long term basis.<sup>35</sup> Short term studies gave conflicting results with regard to glycaemic control.<sup>36 37</sup> Schiffrin and Belmonte compared CSII and multiple injections in a crossover study with six month treatment periods and reported better fasting blood glucose concentrations with CSII but similar mean blood glucose and haemoglobin A<sub>1</sub> concentrations.<sup>38</sup> In the present study all variables of blood glucose control (haemoglobin A<sub>1</sub> concentration, mean and fasting blood glucose concentrations, and the within day range and SD of blood glucose concentrations) were slightly better during treatment with CSII compared with multiple injections. The consistency of the data was striking, but the differences were small and not significant.

No difference in the frequency of mild symptomatic hypoglycaemia was observed between the groups, but asymptomatic hypoglycaemia was more common with CSII. The decreased awareness of hypoglycaemia may be explained by a reduction in adrenergic symptoms, which was noted in many patients. The frequency of hypoglycaemic coma, however, was strikingly reduced with CSII, despite lower mean blood glucose concentrations. This may be due to smaller within day variations in blood glucose concentrations. Conflicting results regarding severe hypoglycaemia during intensified treatment have been reported.<sup>39 40</sup> The patients receiving CSII and multiple injections enjoyed a more flexible lifestyle but gained weight. This became a problem in only three patients. The insulin requirement decreased with CSII in accordance with the increased insulin sensitivity reported with this treatment.<sup>41</sup> The main problem with CSII was subcutaneous infections, the frequency and causes being similar to those reported by others.<sup>39 40 42 43</sup> Diabetic ketoacidosis was less common in our study.<sup>35 42 43</sup>

In conclusion, the present study showed that near normoglycaemia may prevent the progression of early retinopathy and peripheral neuropathy and reduce glomerular hyperfiltration. As shown by most variables, concerning both glycaemic control and late complications, CSII was slightly superior to multiple injections, both being superior to optimised conventional treatment with twice daily injections.

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