Effects of aldose reductase inhibitor treatment in diabetic polyneuropathy—a clinical and neurophysiological study

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SUMMARY The efficacy of treatment with an aldose reductase inhibitor (1,3-dioxo-1H-benz-deisoquinoline-2(3H)-acetic acid, AY-22,284, Alrestatin) on peripheral nerve function in diabetic polyneuropathy was assessed. Thirty patients with long-standing diabetes and slight to moderate neuropathy participated in the double-blind placebo trial. Clinical examination, sensory threshold determinations for vibratory, tactile and thermal stimuli, conduction velocity measurements and studies of automatic function were performed to evaluate the treatment. Significant differences favouring Alrestatin over placebo were found for many of the measured variables, whereas no changes occurred on placebo. The apparent improvement of neuropathy occurred despite persisting hyperglycaemia. The results indicate that aldose reductase inhibitor treatment may be of value in diabetic polyneuropathy, and provide support for the sorbitol pathway hypothesis of diabetic polyneuropathy.

Polyneuropathy is one of the well-known complications of diabetes mellitus.¹ The exact cause of the polyneuropathy is not clear despite considerable knowledge of chemical, physiological and histological alterations in diabetic nerves.² The aetiological hypothesis of the polyol pathway, initially proposed for galactosaemic and diabetic cataract,³ has been suggested also for diabetic nerve damage.⁴ With high serum glucose levels, some glucose will escape glycolytic breakdown and instead be metabolised to sorbitol and fructose. Enzymes involved in this process are aldose reductase and sorbitol dehydrogenase. Sorbitol and fructose will accumulate in tissues freely permeable to glucose, like lens and nerve⁴⁻⁶ and this accumulation would then cause osmotic damage to the nerve.⁷ Indirect evidence for this sequence of events is provided by studies on galactose-fed rats, in which an inverse relationship was found between nerve dulcitol (galactitol) and water content on the one hand and motor conduction velocities on the other hand.⁸ Inhibition of aldose

reductase would prevent sorbitol accumulation and, provided the hypothesis is valid, prevent or improve diabetic neuropathy. Such an inhibitor, Alrestatin (1,3-dioxo-1H-benz[de]-isoquinoline-2(3H)-acetic acid, AY-22,284) proved effective in preventing dulcitol and sorbitol accumulation in lenses and sciatic nerves of galactosaemic and streptozotocin-diabetic rats, respectively.⁹ The inhibitor reduced the deficit in motor nerve conduction velocity in galactose-fed rats.¹⁰ The demonstration of a therapeutic effect of this inhibitor in diabetics with polyneuropathy would provide strong support for the sorbitol pathway hypothesis of polyneuropathy development.

The present report describes beneficial effects of Alrestatin in patients with long-standing diabetes and slight to moderate polyneuropathy.

Methods

Patients

Thirty patients (20 men and 10 women, 15 insulin-dependent (ID) and 15 non-insulin-dependent (NID) with stable diabetes (mean duration of disease 18.3 years, range 3-44) were enrolled in the study. All but three patients had clinical signs of polyneuropathy (that is at

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Table 1 Patients participating in the study

	Drug	Placebo	Total
Insulin-dependent	3 males (3 csp) 3 females (3 csp) (Age 50.5 ± 13.8 years) (Dur 26.3 ± 8.0 years)	7 males (5 csp) 2 females (2 csp) (Age 43.9 ± 13.2 years) (Dur 21.4 ± 6.7 years)	15
Non-insulin-dependent	4 males (4 csp) 4 females (4 csp) (Age 59.9 ± 11.3 years) (Dur 10.9 ± 5.5 years)	6 males (5 csp) 1 female (1 csp) (Age 58.6 ± 7.1 years) (Dur 15.7 ± 14.8 years)	15
Total	14	16	30

Dur = duration of diabetes mellitus. csp = clinical signs of polyneuropathy.

least two of the following three abnormalities: absent ankle jerks, clinically detectable distal sensory impairment, wasting of the short toe extensor muscles). The presence of decreased conduction velocities as evidence of polyneuropathy was an inclusion criterion. Patients are described in more detail in table 1.

Diabetes was considered stable: (a) if variations of fasting blood glucose within 6 months before the beginning of the study did not exceed $\pm 75\%$ of the value obtained within 10 days prior to the study and (b) if the weight of the patients had been at a steady level for the last 6 months. Females with childbearing potential were not included. Patients with anaemia, bleeding tendency of any kind, liver disease or malignant disease, abnormal chest X-ray and patients with any signs or symptoms of other systemic disease giving rise to polyneuropathy were not included. Increased serum levels of creatinine or urea as signs of renal insufficiency disqualified patients from the study, while albuminuria of moderate degree was accepted. Patients with known alcohol or drug abuse were not accepted.

Informed consent was received from all patients. Approval was given by the Ethical Committee of the Medical Faculty of Uppsala University, the Drug Division of the Swedish Board of Health and Welfare and the Food and Drug Administration, USA.

Drug administration

After randomisation patients were given Alrestatin or placebo (supplied by Ayerst Laboratories, New York) in a double-blind manner. Fourteen patients received active drug and 16 placebo (table 1). Duration of the treatment was 12 weeks and the dose of the drug was 2.0 g/day during the first week, 4.0 g/day for weeks 2-6 and 8.0 g/day for weeks 7-12. Each patient took four tablets of identical appearance four times a day throughout the study, irrespective of treatment or dose.

To verify patient's compliance, returned tablets were counted at every dispensation occasion. Blood levels of Alrestatin were also analysed (fluorimetric determination performed by Ayerst Research Laboratories, Montreal, Canada). For this purpose a serum specimen was taken before treatment and one hour after the morning dose at 1, 3, 6, 8 and 12 weeks of treatment.

Concomitant medication. All patients had their standard diabetes medication (insulin or oral antidiabetics). Three patients in addition had treatment for hypertension, one had digitalis, one had levothyroxine, one had acetazola-

mide for glaucoma and a few occasionally took anal gesics.

Evaluation of efficacy of treatment

(1) **Clinical examination.** A thorough clinical and neurological examination was performed at the beginning of the study and after 6, 8 and 12 weeks of treatment. A brief physical examination was made after 1, 3 and 10 weeks of treatment. Subjective effects and complaints were monitored at each visit. Neurological examination included assessment of touch (to cotton wool), pain (pin-prick) and thermal (cold piece of metal) sense. Discriminative sensation was examined by figure writing with a knitting needle (dermolexia according to Bergström *et al*)¹¹ on finger tips and dorsum of feet. Muscle atrophy and weakness were assessed clinically. Stretch reflexes were scored +++ (increased), ++ (normal), + (weak) or absent.

(2) **Sensory threshold determination.** Quantitative measurements of sensory thresholds were performed for vibratory, tactile and thermal stimuli. For vibration sense a handheld vibrometerU (MAB AB, Sweden) producing 100 Hz sine wave vibration was used. The amplitude of the vibrating plastic probe was recorded by an accelerometer and monitored in μm on a digital display. Threshold determination was performed at three sites: the dorsal aspect of the second metacarpal bone, the middle of tibia and the dorsal aspect of the first metatarsal bone.

The sense of touch was tested with a plastic probe, producing 10 Hz rapid indentations to the pulp of the forefinger and the big toe. The size of probe movement was displayed digitally in μm .

Temperature sense was determined as the "warm-cold difference limen" with a "Marstock" thermostimulator.¹² Temperature change was monitored by a pen recorder and read off with an accuracy of 0.5°C. Determination was made on the thenar surface of the hand and the lateral aspect of the dorsum of the foot.

Detailed descriptions of these equipments and methods are presented in method studies.¹²⁻¹⁵ Determinations were made on one side, always the same in a given patient. In the following the modalities of sensation and sites of measurements will be referred to as vibr/carp, vibr/tib, vibr/tars, touch/finger, touch/toe, temp/hand, and temp/foot.

Pretreatment values were determined twice within 10 days prior to treatment. During the study measurements were made after 6 and 12 weeks of treatment. Normal

values have been presented elsewhere.^{13 14}

(3) *Conduction velocity measurements.* Motor conduction velocities (MCV) of the ulnar, median and tibial nerve on one side and sensory conduction velocities (SCV) of both sural nerves were determined. Standard technique with surface electrodes was used;¹⁶ for the sural nerves averaging technique was applied. F-responses¹⁷ were recorded with the MCV measurements. Pretreatment values were obtained twice within 10 days prior to the treatment. During the study, measurements were made after 6, 8 and 12 weeks of treatment. Skin temperature of hand and foot was monitored at each measurement.

(4) *Sympathetic function* was assessed by recording GSR (galvanic skin response), that is the electrodermal response to a stimulus causing a startle reaction. GSR is useful for an estimation of skin sympathetic function.¹⁸ Recordings were made from the palm of one hand and the sole of one foot prior to treatment and after 12 weeks of treatment. Normal responses were established from 35 healthy subjects, aged 25-65 years, mean 40 years.

At each visit blood pressure was measured after 5 minutes rest, immediately at standing up and after 2 minutes standing.

(5) *Ophthalmic examinations* including visual acuity, examination of the anterior chamber and the lens and funduscopy after pupil dilatation, were made by an ophthalmologist prior to treatment and at the end of treatment.

(6) *Safety evaluations.* ECG was recorded prior to treatment and after 6 and 12 weeks of treatment.

Blood chemistry and urinalysis was performed repeatedly during the study. Thus, fasting glucose, 2-hour post-prandial glucose (standard breakfast was given), serum creatinine, urea, ASAT, ALAT, LD, CK, triglycerides and cholesterol, haemoglobin, blood cell counts (including differential count) and urinalysis with quantitative glucosuria and albuminuria were determined prior to the treatment and at 1, 6, 8 and 12 weeks of treatment. Glycosylated haemoglobin¹⁹ was assessed before treatment and at 6 and 12 weeks of treatment. Endogenous creatinine clearance was performed before and at the end of treatment. Body weight was recorded at each visit.

Methods of result analysis

Clinical examination. Impairment of sensation (summary of touch, pin-prick and temperature) was scored in the following manner:

slight impairment	1
moderate impairment	2
marked impairment	3
absent sensation	4

This scoring was applied to regions of the lower limb (toe, distal and proximal half of foot, distal, middle and proximal third of lower leg) and similarly in hands. Sum of score for treated and non-treated patients were compared before and after treatment. *Dermolexia* was also

scored 1-4 with increasing impairment before statistical analysis.

Sensory threshold determination. The lowest ("best") threshold value of the two pretreatment values was taken as the initial threshold, except when the change from first to second determination was more than -50% or +100%; in such cases the mean of the two determinations was used. The reasons for this procedure were (a) using the best value will minimise error advantage to the drug; (b) -50% and +100% correspond roughly to confidence intervals of variation of the methods.¹³ A change exceeding this interval between the two determinations indicate that one of the values is erroneous and the mean is probably a better estimation of the "true" threshold. Then

the ratio $\frac{m_1}{m_x}$, where m_1 is the pretreatment threshold and m_x determinations during and after treatment, was calculated. Thus, a ratio above 1 indicates an improvement (reduction) of threshold. Mean ratio for patients on drug and patients on placebo were then compared.

Conduction velocities. The mean of the first two values was taken as pretreatment value and changes from this value at subsequent determinations were analysed statistically.

Statistical methods employed included Student's *t* test for dependent and non-dependent variables, linear regression analysis and *t* test for regression coefficients. P-values are one-tailed, unless otherwise stated.

Results

Before treatment the groups of patients were comparable as to age and duration of the diabetes (table 1). Sex distribution was uneven (table 1), but did not influence the results. As illustrated by fig 1 the degree of diabetic control was uniformly moderate throughout the study with no differences for glycosylated haemoglobin (Hb A₁), glucosuria and fasting or 2-hour post-prandial glucose between patients on drug and placebo. Body weight was stable or showed only minor fluctuations in all patients except one (on drug), who complained of nausea and lost 5.5 kg during treatment.

Diabetes therapy was unchanged throughout the study in all patients except one ID placebo patient. His metabolic control deteriorated more than could be accepted and the insulin dose was slightly increased in the 9th week of the study.

One ID patient on placebo withdrew after about 4 weeks because of an non-specific urticaria (which she had experienced previously). Another ID patient (also on placebo) was excluded after finishing the study, as critical review of his data revealed that he had no convincing objective signs of polyneuropathy (despite some subjective complaints). Thus, 14 patients on Alrestatin and 14 patients on placebo

Fig 1 Hb A₁ (glycosylated haemoglobin), fasting glucose, 2-h post-prandial glucose and glycosuria of patients during the study.

remained for analysis. One ID patient discontinued Alrestatin after 8 weeks because of liver reaction (see below), but he is included in the analyses.

The severity of polyneuropathy was slight to moderate. Two patients (one ID and one NID) on drug and one patient (NID) on placebo were asymptomatic. Two patients (one ID and one NID), both on drug, had pronounced neuropathic pain of the lower limbs.

Before treatment no difference in degree of neuropathy was found between patients on drug and patients on placebo, when clinical findings, conduction velocities and sensory thresholds were assessed (cf tables 3 and 4). Apart from sensory thresholds (see below) no difference in effect of treatment was found between ID and NID patients.

SUBJECTIVE IMPROVEMENT

As shown by table 2 improvement of sensation and reduction of symptoms was reported more frequently

Table 2 Subjective improvement at end of study: number of patients

	Drug	Placebo
Marked improvement	2	0
Good improvement	1	2
Slight improvement	4	2
No change	5	7
Deterioration	0	2
(Asymptomatic)	(2)	(1)
Total	14	14

and was more pronounced among patients on the drug than on placebo. One of the patients with painful neuropathy reported slight relief towards the end of treatment, while the other reported no change.

CLINICAL EXAMINATION

Table 3A shows that the mean score of sensory impairment was reduced ($p < 0.01$) for patients on active treatment. No change occurred for placebo patients. The difference between the two groups of patients was statistically significant at the end of the study ($p < 0.05$). Discriminative sensation (dermoxia) improved in patients on Alrestatin, as shown in table 3B. Some, but not significant, improvement was found in placebo patients. At the end of treatment statistically significant differences favouring Alrestatin were present between the two patient groups.

Stretch reflexes

All patients but two (both on placebo) had one or more diminished or absent stretch reflex bilaterally at the beginning of the study. After the treatment period improvement of reflexes had occurred in seven patients on active treatment and in four patients on placebo. A deterioration was observed in one patient in each group. Plantar responses were flexor in all patients.

Muscle wasting

Muscle wasting was restricted to the short toe extensor muscle, which was moderately to markedly

Table 3 Evaluation of sensation

(a) Clinical scoring of sensory impairment. Mean score $\pm$ SEM				
Before treatment				At end of treatment
Drug		6.08 $\pm$ 1.05	$\longleftrightarrow$	4.08 $\pm$ 0.99
		NS		$\uparrow$ p < 0.05
Placebo		6.83 $\pm$ 1.06	$\longleftrightarrow$	6.83 $\pm$ 1.13
				NS
(b) Dermolexia (discriminative sensation). Mean score $\pm$ SEM				
Before treatment				At end of treatment
Finger pulp	Drug	1.35 $\pm$ 0.13	$\longleftrightarrow$	1.00 $\pm$ 0.00
		NS		$\uparrow$ p < 0.05
	Placebo	1.64 $\pm$ 0.22	$\longleftrightarrow$	1.35 $\pm$ 0.16
				NS
Dorsum of foot	Drug	2.85 $\pm$ 0.20	$\longleftrightarrow$	1.92 $\pm$ 0.22
		NS		$\uparrow$ p < 0.05
	Placebo	2.71 $\pm$ 0.26	$\longleftrightarrow$	2.57 $\pm$ 0.25
				NS

atrophied in most patients. Weakness was not found or was restricted to slightly impaired dorsiflexion of the toes. No change of muscle wasting or weakness occurred in any patient during the study.

SENSORY THRESHOLD DETERMINATION

No difference in sensory threshold elevation was found between the two groups of patients before treatment. There was good agreement between sensory thresholds and clinically evaluated sensory impairment (fig 2A). A correlation was found also between improvement of sensory thresholds and reduction of sensory impairment at clinical examination (fig 2B).

Threshold ratios (see Methods) after 6 and 12 weeks of treatment were compared for patients on

Alrestatin and patients on placebo. The differences between mean ratio for each type of threshold for drug and placebo are illustrated in fig 3. Vibration thresholds for ID patients were improved at all sites of measurement, the degree of significance increasing with duration of treatment. Improvement of other sensory modalities was less pronounced, but still statistically significant for temp/foot. NID patients showed a similar pattern, but differences against placebo were less pronounced. The lack of statistical significance for touch/finger and touch/toe, which showed a definite improvement of mean ratio, is explicable by a particularly large variation for this parameter. Figure 3C illustrates the analysis of all the patients. Vibration sense again showed the most improvement with increasing differences versus

Fig 2 Correlation between methods of sensation assessment. (A) Before treatment. Plotting of score of sensory impairment at clinical examination versus age-related (upper normal limit at a given age = 1) sensory threshold (mean of all modalities and sites of measurement). (B) At end of treatment. Plotting of reduction of clinical score versus percentual reduction of sensory threshold (mean of all modalities and sites of measurement).

Fig 3 Differences between mean ratio of sensory thresholds (cf text) for drug and placebo at 6 and 12 weeks of treatment (that is the more positive value, the better result for treated patients compared to placebo patients). Degree of statistical significance at both occasions given to the right in graphs (NS = not significant; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$).

placebo with increasing time on treatment.

CONDUCTION VELOCITY MEASUREMENTS

Before the study, there was no difference in motor conduction velocity between the groups of patients. Mean MCV of the ulnar and median nerves were slightly reduced while a marked lowering of tibial nerve MCV was present (table 4). Table 4 shows the results of MCV measurements. Mean MCV of the ulnar nerve was improved after 6 weeks of treatment ($p < 0.05$) and at end of treatment ($p < 0.01$) in patients on active treatment. Median and tibial nerve MCV showed differences between the two groups of patients after 6 weeks of treatment ($p < 0.05$), for the median nerve in favour of Alrestatin and for the

tibial nerve in favour of placebo, but later no change of MCV in these nerves was found.

Skin temperature variation may have contributed to the difference of MCV change for the tibial nerve after 6 weeks of treatment (table 4) but had no influence on the other differences found.

Analysis of distal latencies from the MCV measurements revealed no difference between the groups of patients on any occasion.

For F-responses a difference between the groups of patients, in favour of Alrestatin, was found for the ulnar nerve at the end of treatment ($p < 0.01$).

SCV of the sural nerves was often not measurable, despite the use of averaging. There were too few patients in whom SCV could be measured to allow

Table 4 Motor conduction velocities before treatment and change of conduction velocity from pre-treatment value after 6, 8 and 12 weeks of treatment. Mean $\pm$ SD, m/s

	Drug	Placebo	
Median nerve MCV	47.0 $\pm$ 5.6	47.2 $\pm$ 4.3	
Change 6 weeks	+1.00 $\pm$ 3.46	-1.07 $\pm$ 1.89	$p < 0.05$
8 weeks	+0.57 $\pm$ 3.47	-1.07 $\pm$ 2.43	
12 weeks	+0.41 $\pm$ 3.55	-0.28 $\pm$ 2.23	
Ulnar nerve MCV	45.8 $\pm$ 4.8	47.2 $\pm$ 6.7	
Change 6 weeks	+1.53 $\pm$ 3.28	+0.64 $\pm$ 4.76	$p < 0.05$
8 weeks	+3.17 $\pm$ 3.98	+0.35 $\pm$ 2.16	$p < 0.01$
12 weeks	+3.10 $\pm$ 3.06	-0.21 $\pm$ 3.35	
Tibial nerve MCV	34.1 $\pm$ 3.9	32.6 $\pm$ 5.8	
Change 6 weeks	-0.21 $\pm$ 2.39	+1.61 $\pm$ 2.14	$p < 0.05$
8 weeks	-0.14 $\pm$ 1.91	+0.92 $\pm$ 2.87	
12 weeks	+0.42 $\pm$ 2.44	+0.72 $\pm$ 3.16	

Lower normal limits for the laboratory: median and ulnar nerves 48 m/s, tibial nerve 42 m/s.

statistical analysis or any conclusion.

AUTONOMIC FUNCTION

Symptoms from mild to moderate dysautonomia were common. Impotence of varying degrees was present in 13 of the 20 men included. Dryness of hands and feet had been noticed by 13 patients. No patient suffered from postural hypotension. Three patients on active treatment stated that the ability to sweat in hands and feet was slightly improved towards the end of treatment while no patient on placebo reported any change. Impotence was not changed at all.

In the actively treated patients mean voltage of GSR in the foot was improved, though not to a statistically significant degree, but GSR of the hand showed no improvement. No change was found in the placebo patients. Some reduction of mean postural fall in systolic blood pressure, both immediately after assuming the erect posture and 2 minutes later, was found in the actively treated patients, though this was not statistically significant.

When a summary of all variables used for evaluation of polyneuropathy was assessed, signs of improvement were found in 13 out of 14 patients treated with Alrestatin. The remaining case was unchanged. Three placebo patients showed improvement, six remained unchanged and five showed some deterioration.

Serum Alrestatin was detectable in all patients receiving active treatment and increased with increase in dosage, but the interindividual variation was marked.

OPHTHALMIC EXAMINATION

Diabetic retinopathy was common and evenly distributed among patients on drug and placebo. Cataract of varying degree was present in 10 patients, six of whom had active treatment. No improvement of retinopathy was found. No change of cataract was seen in actively treated patients, but no attempt was made to quantify density of cataract.

SIDE EFFECTS

Subjective symptoms of adverse reactions were few (table 5). One ID patient complained of epigastric distress, nausea, heartburn and general feeling of illness shortly after having received the dose 8 g/day. He discontinued medication for two days and felt better. Reinstating treatment caused symptoms to reappear rapidly. At examination there was tenderness over the liver site and elevation of liver transaminase levels were marked (ASAT 4.34 μ kat/l, ALAT 9.75 μ kat/l; normal range < 0.6 μ kat/l for both). A slightly elevated alkaline phosphatase value was also present (5.9 μ kat/l; normal range 0.8-4.8

μ kat/l). Bilirubin was normal. Treatment was stopped and symptoms gradually disappeared during the first week thereafter. Slightly increased transaminases were still present after 2 and 4 weeks, but normal values were regained at control visit 2 months after discontinuing the drug.

Table 5 Side effects: number of patients

	Drug	Placebo
Liver reaction (causing discontinuance of treatment)	1	
Asymptomatic elevation of liver transaminases	2	1
Nausea, bad appetite, weight loss	1	
Mild constipation	1	2
Increased night sweating		1
Fatigue		1

Another two ID patients on drug showed slight elevations of liver transaminases (maximal values 0.88 and 2.55 μ kat/l for ASAT and ALAT respectively), without concomitant subjective complaints. Normal values were again found after the end of treatment. Mean values for ASAT and ALAT showed an increase during treatment in patients on Alrestatin, as illustrated in fig 4. For this analysis the patient with the pronounced liver reaction and a placebo patient who at three times showed alcohol-dependent elevation, were excluded.

Increased urinary albumin was present in 18 patients at the beginning of study (4 ID and 6 NID on the drug, 5 ID and 3 NID on placebo). During treatment dose-related significant elevations of albuminuria values were found in all patients on active treatment, suggesting increases of renal albumin leakage. Values corresponding to pretreatment findings were regained rapidly (one week) after the end of treatment. However, when this unexpected finding was scrutinised, it was found that Alrestatin-containing urine samples did cause dose-related blank peak in the immuno-nephelometric analysis of urinary albumin,²⁰ and it could be shown that the increased values were explained entirely by this laboratory artefact. Thus, no conclusion about influence of Alrestatin on renal albumin excretion can be drawn from the findings. Other laboratory measures mirroring renal function (creatinine, urea, endogenous creatinine clearance) showed no changes.

All other safety evaluations remained unchanged during the study.

Discussion

The results of the present clinical trial indicate a beneficial effect on diabetic polyneuropathy when the aldose reductase inhibitor Alrestatin was given. The

Fig 4 Mean and SD of ASAT and ALAT during treatment (one patient on drug with pronounced liver reaction and one placebo patient with slight alcohol-dependent elevations are excluded). * = $2p < 0.05$.

differences against placebo depended mainly on improvement in treated patients, but partly also on some deterioration among placebo patients (fig 2B). This fact does not impair the conclusion, as both real improvement and prevention from further damage to the nerves should be regarded as a beneficial effect of treatment.

The sensory threshold determinations used here are accompanied by pronounced intra-individual variation.¹³ This variation is randomly distributed and therefore should not bias a comparison between groups of patients. On the contrary, this variation may be an obstacle to detection of differences between groups. All values in fig 3 are at zero or clearly positive, that is changes observed favour active treatment. Most variables also show a tendency to increase with longer duration of treatment, which may be an indication of a dose-response-relationship.

Conduction velocities (and F-responses) were improved only in the ulnar nerve. Several earlier studies have detected increases of MCV with institution of conventional treatment in experimental^{10 21} and early human diabetes (without overt neuropathy).²²⁻²⁴ In experimental diabetes alterations of physiological properties of the nerves usually precede morphologic changes,²⁵ but the latter will ultimately occur.²⁶ Patients in the present study had been diabetic for several years; they had with few exceptions clinical signs of polyneuropathy (table 1) and had more pronounced MCV reduction (table 4) than patients in the above-mentioned studies,²²⁻²⁴ suggesting morphologic changes underlying their neuropathy. These factors may explain why increases of MCV of median and tibial nerves were not forth-

coming in the present study. Absence of MCV improvement is not incompatible with restored clinical function in polyneuropathy, as exemplified in the Guillain-Barré syndrome.²⁷ Decrease of MCV is mainly a result of demyelination, but reduction of axonal diameter also plays a role. With remyelination, reduced thickness of the myelin sheath and diminished axonal diameter develop, *per se*²⁸ and by changing the optimum ratio of axonal diameter to total myelinated nerve fibre diameter^{29 30} giving rise to persistent lowering of conduction velocity. In many chronic polyneuropathies demyelination and remyelination occur simultaneously³¹ and this may apply also in diabetes.^{26 32} Thus, it may even be suggested that conduction velocity is not sufficient as single parameter to evaluate improvement of chronic diabetic polyneuropathy.

The stimulus for GSR is an emotional or startle reaction,¹⁸ which may be expected to be evoked more easily the more unfamiliar the situation is to the subject. Consequently, in the present study stimulus for GSR may have been stronger at the first than at the last visit. Taking this into account, it cannot be excluded that the small improvement of autonomic function is more significant than indicated by the statistical analysis. Thus, a beneficial effect of Alrestatin on sympathetic function would not be unreasonable. Diabetic autonomic neuropathy is assumed to have a poor prognosis,³³ but impaired autonomic function and even pandysautonomia in the Guillain-Barré syndrome^{34 35} illustrate that postganglionic fibre damage in peripheral neuropathy may be reversible. In the Guillain-Barré syndrome the nerve damaging process is self-limited, but an

analogous situation may be obtained in diabetes, provided the nerve damaging process is inhibited. Postganglionic sympathetic nerves are C-fibres. The reduction of temperature threshold in the foot (fig 3A and C) further indicates improvement of small fibre function.

ROLE OF THE SORBITOL PATHWAY

The fact that improvement of the polyneuropathy was found in Alrestatin-treated patients without simultaneous improvement of diabetic control is an important feature of the present study.⁶ Hyperglycaemia is a pre-requisite for the hypothesis of the sorbitol pathway. Clear correlation between poor diabetes control and development of signs of polyneuropathy³⁶⁻⁴¹ and improvement of nerve function with metabolic restoration have been shown.^{22-24 42} Such relationships and apparent spontaneous variation of neuropathic symptoms may be explained by the fact that the sorbitol pathway is rapidly activated as blood glucose increases^{7 43} and that sorbitol accumulation is reduced when blood sugar is controlled.⁶ The rapid activation may also explain why signs of polyneuropathy are often present when diabetes is first diagnosed,^{23 24 40} as hyperglycaemia probably has been present for some time before diagnosis.⁴⁰

In rats diabetic polyneuropathy manifests itself in two steps, first a functional derangement without visible morphologic changes^{25 44} and later on structural damage.^{26 45} The first step probably precedes structural changes throughout the progress of the neuropathy. It can be assumed that changes of this physiological impairment are responsible for the rather rapid variations of MCV observed when diabetes is properly treated. Alrestatin treatment probably acts in the same way. Whether impairment due to structural changes could also be improved by long-term treatment, cannot be evaluated from the present data.

A causal relationship between dulcitol accumulation, increased osmotic pressure and impaired nerve function is plausible in galactosaemia.^{8 46} The assumption of analogous events in diabetes is attractive. However, sorbitol accumulation in diabetes is less pronounced than dulcitol accumulation in galactosaemia⁵ and morphologic evidence of corresponding osmotic nerve damage in diabetes is lacking. Aldose reductase is located mainly in the Schwann cell,⁴⁷ while in recent years increasing evidence suggests that the well-known segmental demyelination in diabetic polyneuropathy^{32 48} is secondary to preceding axonal damage.^{45 49-51} Other chemical alterations occur in diabetic nerves, such as decreased lipid synthesis⁵² and decreased myoinositol content^{7 21 53 54} and it is likely that the aetiology of

diabetic polyneuropathy is multifactorial. The present results, however, support the idea that the sorbitol pathway plays a role in the development of widespread peripheral nerve damage in diabetes.

Two clinical studies on the effect of Alrestatin have been published previously. Culebras *et al*⁵⁵ observed slight improvement of sensory nerve conduction velocities when Alrestatin was given intravenously during 5 days to ten patients. Gabbay *et al*,⁵⁶ giving a dose of 4 g/day oral treatment during 4 weeks to four patients, found no beneficial effect. Therapeutic attempts have also been made with myo-inositol with contradictory results in both humans and animals.^{21 53 57-59}

In the present study the only side effects of importance were signs of liver cell damage: a clear reaction in one patient and asymptomatic elevation of ASAT and ALAT (table 5). One patient in the study of Gabbay *et al*²⁷ developed rapidly transient elevation of SGPT (= ALAT). Whether this will be an obstacle to the eventual routine use of this drug needs further evaluation.

To summarise, the present results support the aetiologic role for the sorbitol pathway, which in turn gives further support for a causal relationship between the hyperglycaemic state and the development of polyneuropathy. This implies, first extra effort to attain optimal metabolic control in diabetics, and second, provided the present findings are confirmed by similar and long-term studies, aldose reductase inhibitor treatment may be of certain value. If so, treatment should probably be instituted early in the course of diabetes—perhaps when the first clinical or even neurophysiological sign of polyneuropathy appears.

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