PAPERS AND SHORT REPORTS

Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study

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Abstract

In a study of retinopathy during one year of tight blood glucose control 45 type I (insulin dependent) diabetics without proliferative retinopathy were randomised to receive either continuous subcutaneous insulin infusion, multiple insulin injections, or conventional insulin treatment (controls). Near normoglycaemia was achieved with continuous infusion and multiple injections but not with conventional treatment. Blind evaluation of fluorescein angiograms performed three monthly showed progression of retinopathy in the control group, transient deterioration in the continuous infusion group, and no change in the multiple injection group. Half the patients receiving continuous infusion and multiple injections developed retinal cotton wool spots after three to six months. These changes regressed in all but four patients after 12 months. Control patients did not develop cotton wool spots.

Patients who developed cotton wool spots are characterised by a larger decrement in glycosylated haemoglobin and blood glucose values, more frequent episodes of hypoglycaemia, a longer duration of diabetes, and more severe retinopathy at onset. A large and rapid fall in blood glucose concentration may promote transient deterioration of diabetic retinopathy.

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Introduction

Retinopathy is one of the most common disabling complications of insulin dependent diabetes. Some 15-30% of young insulin dependent diabetics receiving conventional treatment lose vision later in life.[1] A longitudinal study showed that patients who developed retinopathy had poorer diabetic control as estimated by glycosylated haemoglobin (HbA_{1c}) values than patients who did not develop retinopathy.[2] Hyperglycaemia is believed to be of major importance in the development of diabetic complications.[3,4] Near normoglycaemia can now be obtained in large patient populations with either multiple insulin injection treatment[5] or continuous subcutaneous insulin infusion with insulin pumps.[6,7]

Initial case reports described improvement of retinopathy during near normoglycaemia,[8] but two controlled trials, the Steno[9] and the Kroc study,[10] reported a slight deterioration of retinopathy. These studies were done in patients with established background retinopathy and long durations of diabetes. Possibly a "point of no return" had been passed at which progression of retinopathy could no longer be influenced by return of metabolite values to normal.[9] Some uncontrolled studies reported similar results.[11-13] We reported one patient with transient proliferative retinopathy during continuous subcutaneous insulin infusion.[14]

We have designed a controlled, prospective trial in patients with shorter durations of diabetes and less background retinopathy than in other controlled studies and reported transient worsening of retinopathy after six months of continuous subcutaneous insulin infusion and multiple injections of insulin.[15] This paper reports the results after one year, showing the association between rapid improvement of blood glucose control and worsening of retinopathy. It is also the first study to record transient worsening of retinopathy during multiple insulin injection treatment.

Patients and methods

The study protocol was approved by the ethical committee of the Norwegian Council for Science and the Humanities. Forty five C peptide negative insulin dependent diabetics aged 18-42 years with a history of the disease for more than seven years were included in the study after giving written, informed consent. During two months before the study ("preperiod") home blood glucose monitoring was introduced and baseline results obtained. All patients used two daily insulin injections. They were then randomly assigned to three different modes of treatment: either continuous subcutaneous insulin infusion, multiple insulin injections, or continued conventional treatment with two daily injections of mixed insulin (controls). Block randomisation was performed to ensure comparable groups (table I).

In the control group a mixture of rapid and isophane insulin was injected before breakfast and dinner. In the multiple injection group rapid acting insulin was injected before each meal (four to six times daily) and isophane insulin given at bedtime. Patients were free to inject the dose at mealtimes either through a subcutaneous butterfly needle taped to the abdomen or by conventional injections. Two different pumps were used for continuous subcutaneous infusion. Three patients used a Nordisk Infuser (Nordisk Gentofte, Denmark) and 12 the AutoSyringe AS6C (Travenol, USA). Only highly purified porcine insulin preparations were used (Nordisk, Novo). Continuous subcutaneous infusion and multiple injection treatment were started and optimised during five days in the diabetes unit. The patients were followed up by two of us in the outpatient clinic after one and three weeks and monthly thereafter.

HbA_1 was determined monthly by agar gel electrophoresis (Glytrac, Corning) after elimination of the labile fraction (normal range (2SD) 5·4-7·6%; coefficient of variation < 5%).[16] HbA_{1c} was determined by ion exchange chromatography (normal range (2SD) 4·2-6·0%; coefficient of variation < 3%).[16] Daily home blood glucose monitoring was performed by all patients with Haemoglucotest 1-44 (Boehringer Mannheim) before meals. A 24 hour blood glucose profile on filter paper was performed weekly, with sampling before and 90 minutes after each meal and at bedtime, and once a month at 4 am. Only the results of the filter paper method[17] were used for statistical analysis. The frequency of subjective hypoglycaemia was recorded by the patients and reported at each visit.

Eye examinations were performed at the start and end of the preperiod and after three, six, and 12 months. The retina of each eye was screened by indirect ophthalmoscopy and binocular split lamp biomicroscopy. Colour photographs of the retinas were obtained. Fluorescein angiography was performed in one eye. To ensure comparable groups patients were block randomised according to degree of retinopathy at the first examination. Grading was performed as follows based on the fluorescein angiogram, fundal photographs, and results of ophthalmoscopy: grade 1, no microaneurysms; grade 2, one to three microaneurysms; grade 3, more than three microaneurysms or haemorrhages, or both; grade 4, hard exudates. Colour photographs and angiograms were evaluated blindly by a senior ophthalmologist, the identity of the patient and number of the examination being masked. The fluorescein angiograms were ranked on a five point scale, ranging from 1 for the "best" picture to 5 for the "worst" in each patient. After demasking the pictures a mean rank for each examination was calculated for each group.

Means in different groups were compared by a two sided Wilcoxon rank sum test, frequencies by a two sided exact Fisher-Irwin test, and means before and after treatment by a two sided Wilcoxon signed rank test. The level of significance was taken as 5%.

Results

The mean blood glucose concentration improved substantially with the introduction of continuous subcutaneous infusion and multiple injections of insulin and remained near normal for one year (fig 1). No such improvement was seen in the controls. Mean blood glucose value was slightly lower in the continuous infusion group than in the multiple injection group (not significant; NS). Blood glucose concentrations became more stable throughout the day as the mean difference between preprandial and postprandial values was reduced during continuous infusion and multiple injections compared with conventional treatment (continuous infusion group: from 1·9 (SEM 0·4) mmol/l (34 (SEM 7) mg/100 ml) to 1·2 (0·4) mmol/l (22 (7) mg/100 ml); multiple injection group: from 1·9 (0·3) mmol/l (34 (5) mg/100 ml) to 0·5 (0·4) mmol/l (9 (7) mg/100 ml); controls: from 1·9 (0·3) mmol/l (34 (5) mg/100 ml) to 2·0 (0·4) mmol/l (36 (7) mg/100 ml)—multiple injection group *v* controls $p < 0.05$). The variation from day to day was reduced similarly.

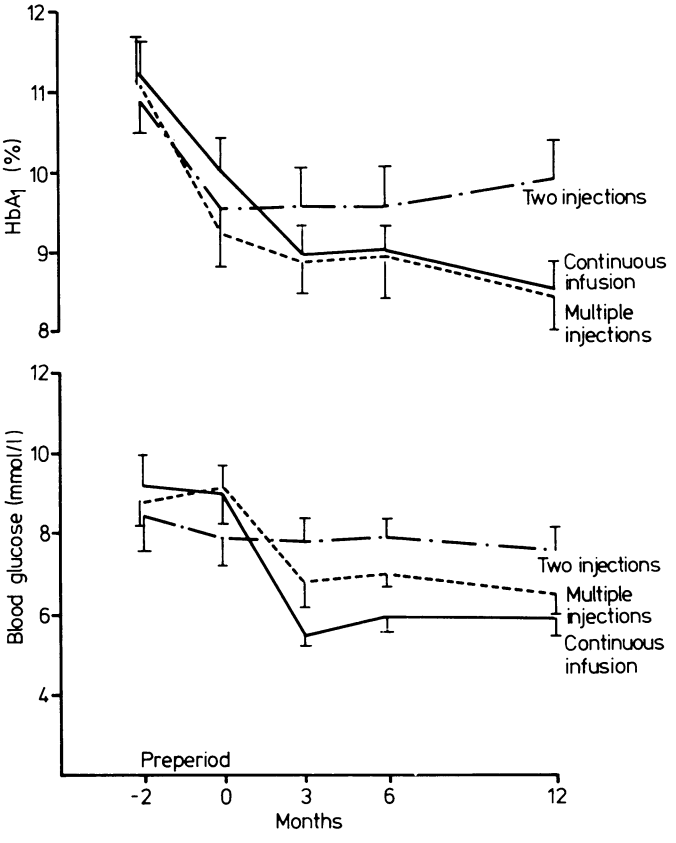

FIG 1—Mean HbA_1 values and blood glucose concentrations (24 hour profiles) during one year of treatment. In preperiod all patients used two daily insulin injections. At time zero patients were randomised to receive either continued conventional treatment (two injections), multiple injections, or continuous subcutaneous insulin infusion with portable pumps. Bars are SEM.

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

The proportion of HbA_1 was substantially reduced in the preperiod in all groups (fig 1), reflecting higher blood glucose concentrations before the study. After allocation a further reduction in HbA_1 was observed in the continuous infusion and multiple injection groups ($p < 0.001$). HbA_1 in the control group was unchanged after allocation and remained higher than in the other two groups for one year ($p < 0.01$).

By "blind" evaluation of the fluorescein angiograms a slight continuous progression of retinopathy was observed in the control group ($p < 0.01$). In the group given continuous subcutaneous infusion a significant deterioration was observed during the first three months of treatment ($p < 0.01$). This deterioration was transient, however,

TABLE I—*Characteristics of patients at start of study (after block randomisation to treatment groups). Mean values expressed with ranges in parentheses*

Treatment groups		Age (years)	Duration of diabetes (months)	Sex (M/F)	%HbA_{1c}	Grade of retinopathy* (No of patients)			
						1	2	3	4
Two injections	(n = 15)	26 (18-36)	152 (81-240)	7/8	8·3 (6·5-12·8)	3	5	5	2
Multiple injections	(n = 15)	26 (19-42)	154 (81-250)	7/8	8·3 (6·3-10·5)	3	4	5	3
Continuous subcutaneous infusion	(n = 15)	26 (18-38)	153 (77-280)	7/8	8·7 (6·8-11·8)	5	3	5	2

*See Methods for definition.

the retinopathy improving from the sixth month ($p < 0.05$). In the multiple injection group no significant changes were detected by this method (table II).

One patient developed transient proliferative retinopathy in both eyes after three months of continuous infusion. Treatment was continued, however,[14] and within three months all retinal changes had regressed without laser treatment.

By indirect ophthalmoscopy and binocular split lamp biomicroscopy 15 patients were identified who developed cotton wool spots after three to six months of treatment: seven were among the 15 patients treated by continuous infusion and eight among the 15 treated by multiple injections. No patient in the control group developed cotton wool spots (table III). This observation was confirmed by blind evaluation of colour photographs of the fundi, which identified new cotton wool spots in eight patients treated by continuous infusion or multiple injections but in none of the controls. Cotton wool spots were typically concentrated in the optic disc area, 1-20 spots (mean 4·6) being found in each patient developing these changes. Cotton wool spots regressed in all but four patients after one year.

Patients who developed cotton wool spots differed in their diabetic control from those treated by continuous infusion and multiple injections who did not develop these changes. HbA_1 decreased from initial values of 11·6 (SEM 0·6)% in those with spots and 10·6 (0·5)% in those without spots (NS) to 8·3 (0·2)% and 9·3 (0·6)% respectively after three months of treatment. Hence HbA_1 decreased significantly more in patients who developed cotton wool spots than in those who did not (3·3 (SEM) 0·5)% *v* 1·3 (0·3)%; $p < 0.01$). Patients who developed cotton wool spots also had a larger decrement in mean blood glucose concentration than the other patients ($p = 0.01$). The reduction in blood glucose was rapid and occurred during the first weeks of continuous subcutaneous infusion and multiple injections (fig 2).

Patients who developed cotton wool spots had more blood glucose values below 2·5 mmol/l (45 mg/100 ml) two to four months after initiation of continuous infusion or multiple injections than had patients who did not develop these spots (14 (SEM 2)% *v* 8 (2)%; $p < 0.05$) (table IV). Episodes of mild symptomatic hypoglycaemia occurred with a frequency of one or two a week in the preperiod, and this did not change significantly after allocation. No significant difference in the frequency of symptomatic hypoglycaemia was observed among treatment groups. Patients who developed cotton wool spots increased the frequency by one a week but the others did not (NS).

The incidence of cotton wool spots was higher among women than men ($p < 0.05$) (table V). The incidence was also higher in patients who already had microaneurysms when treatment began ($p < 0.05$) and in those whose diabetes was of more than 10 years' duration ($p < 0.01$). When reduction of HbA_1 in patients who developed cotton wool spots was corrected for sex, duration of diabetes, and severity of initial retinopathy the difference remained.

TABLE II—*Change in retinopathy during one year of treatment. Results expressed as blind ranking of fluorescein angiograms obtained at various times from randomisation (ranking scale 1 (best) to 5 (worst)). Values are means (SEM in parentheses)*

	Time before and after randomisation (months)				
	−2	0	3	6	12
Continuous subcutaneous infusion (n = 15)	2·1 (0·2)	2·4 (0·2)	3·6 (0·2)**	3·8 (0·2)**	3·0 (0·2)
Multiple injections (n = 15)	2·7 (0·3)	3·0 (0·2)	2·9 (0·2)	2·9 (0·2)	3·4 (0·3)
Two injections (n = 15)	2·3 (0·3)	2·5 (0·2)	3·0 (0·3)*	3·4 (0·2)*	3·9 (0·2)**

Compared with time of randomisation: *p < 0·05; **p < 0·01.

TABLE III—*Prevalence of cotton wool spots before (preperiod) and three to six and 12 months after randomisation*

Treatment group	Total No of patients	No of patients with cotton wool spots		
		Preperiod	3-6 months	12 months
Two injections	15	3	2	1
Multiple injections	15	1	9	2
Continuous subcutaneous infusion	15	1	8	2

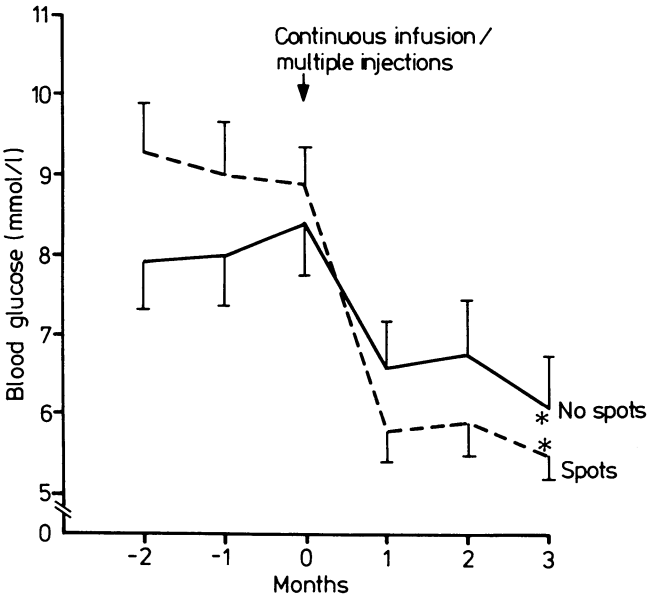

FIG 2—Mean blood glucose concentrations (24 hour profiles) during preperiod and first three months of continuous subcutaneous insulin infusion by portable pumps and multiple injections in patients who developed and did not develop cotton wool spots.

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

TABLE IV—*Change in diabetic control during first months of treatment. Results expressed as difference between start of preperiod and three months after randomisation. Values are means (SEM in parentheses)*

	Patients developing cotton wool spots: continuous subcutaneous infusion/multiple injection groups (n = 15)		Patients not developing cotton wool spots		
			Continuous subcutaneous infusion/multiple injection groups (n = 13)*		Two injections group (n = 15)
Blood glucose (mmol/l)	−3·6 (0·5)	p = 0·01	−1·6 (0·6)	NS	−0·8 (0·5)
% HbA_1	−3·3 (0·5)	p < 0·01	−1·3 (0·3)	NS	−1·1 (0·4)
No of reported hypoglycaemic episodes/week/patient	1·0 (0·6)	NS	−0·2 (0·7)	NS	0·4 (0·3)
% Blood glucose values < 2·5 mmol/l (< 45 mg/100 ml)	9 (2)	p < 0·05	−2 (4)	NS	3 (3)

NS = Not significant.

*Two patients with cotton wool spots in preperiod (one receiving multiple injections, one continuous subcutaneous infusion) excluded.

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

TABLE V—*Characteristics of patients receiving continuous subcutaneous insulin infusion/multiple insulin injections and incidence of cotton wool spots three to six months after randomisation (two patients with cotton wool spots at first examination excluded)*

	Duration of diabetes (years)		Grade of retinopathy†		Sex	
	7-10	>10	1	2-4	M	F
No (%) of patients with cotton wool spots	1/8 (13)	14/20 (70)**	1/7 (14)	14/21 (67)*	5/15 (33)	10/13 (77)*

*$p<0.05$. **$p<0.01$.
†See Methods for definition.

Discussion

This study shows that returning the blood glucose concentration to near normal by continuous subcutaneous insulin infusion or multiple injections of insulin in insulin dependent diabetics with previous average or poor blood glucose control may promote deterioration of retinopathy. The most striking change is the development of cotton wool spots in these patients.

Cotton wool spots in the retina seem to represent microinfarctions in the nerve fibre layer, associated with focal ischaemia.[18 19] Impaired retinal perfusion together with reduced nutrient substrate concentrations during improved blood glucose control may be one plausible hypothesis for this event.[20]

The development of cotton wool spots in our series was clearly related to mode of treatment; no patient receiving two daily injections of rapid or intermediate acting insulin developed cotton wool spots compared with half of the patients treated with continuous subcutaneous infusion and multiple injections. When intensive treatment began the groups were closely comparable in factors known to be relevant in the development of retinopathy—namely, age, duration of diabetes, and degree of diabetic control. The groups were also comparable in the severity of retinopathy at that time.

Cotton wool spots developed predominantly during the first months of treatment and regressed in most patients over three to nine months. The reported half time of cotton wool spots in diabetes is 8-17 months,[21] so the spots observed in our series may have been less damaging to the retina.

The main difference between conventional and intensive modes of treatment is in the resulting blood glucose concentrations. In this study the mean blood glucose concentration was lower in the continuous infusion and multiple injection groups. It may also be important, however, that the difference between preprandial and postprandial values was significantly reduced during intensive treatment.

All groups improved their blood glucose control as compared with before the study. The decrement in blood glucose was similar in patients who did not develop cotton wool spots and controls. Patients who did develop cotton wool spots, however, had a much larger fall in mean blood glucose and HbA_1 values. This suggests that a large fall in the blood glucose concentration may be deleterious for the retina. This large fall in the blood glucose concentration began almost immediately after the start of intensive treatment. Whether the speed or magnitude of blood glucose lowering is the most important factor remains unknown.

Light sensitive ganglion cell function is sensitive to hypoglycaemia. Colour perception reportedly diminishes during prolonged hypoglycaemia.[22] We found no differences in the absolute frequency of subjective hypoglycaemia among treatment groups. This may have been because awareness of hypoglycaemia diminished in many patients in the continuous infusion and multiple injection groups. The frequency of objective hypoglycaemia, defined as a blood glucose concentration below 2·5 mmol/l (45 mg/100 ml), was higher in patients with cotton wool spots in the critical period two to four months after initiating continuous subcutaneous infusion and multiple injections. This suggests that increased hypoglycaemia may be responsible for the development of these spots.

Cotton wool spots usually occur as a late event in retinopathy, preceded by microaneurysms. As expected, development of these spots was more common in patients who already had microaneurysms. Only one patient without microaneurysms developed cotton wool spots. Similarly, those patients whose duration of diabetes was of more than 10 years had a much higher incidence of spots than those whose disease was of 7-10 years' duration. Those patients with a duration of disease of more than 10 years and evidence of microaneurysms (grades 2-4) had a slightly larger fall in HbA_1 value than those with a shorter duration of disease and no background retinopathy. Nevertheless, when the fall in HbA_1 was corrected for the duration and presence of retinopathy patients with cotton wool spots still showed a larger fall in HbA_{1c} than patients without these spots. Patients who developed cotton wool spots were not older than those who escaped this complication.

The incidence of cotton wool spots was greater among women than among men. Conflicting data exist on sex distribution and diabetic retinopathy,[23] and in a previous study in Norway no difference was found.[24] In our series women also showed a larger fall in HbA_1 than men. Possibly women cope more easily with continuous subcutaneous infusions and multiple injections than men. When, however, the decrement in HbA_1 was corrected for sex, men who developed cotton wool spots still had a larger decrement in HbA_1 value than those men who did not, and a similar difference was seen in women.

Transient worsening of retinopathy was also observed in the continuous infusion group with blind evaluation of fluorescein angiograms. Fluorescein angiography visualises in detail microaneurysms, new vessels, and closed capillaries. By using different methods in the evaluation of retinopathy, we elucidated different morphological aspects. This may explain why no deterioration was documented in the multiple injection group and deterioration was found in the control group by fluorescein angiography.

Our results accord with the one year results of the Steno study, which found morphological deterioration of retinopathy during continuous subcutaneous insulin infusion, particularly in the group with the best diabetic control.[9] After two years the degree of retinopathy in the continuous infusion group was equal to or better than that with unchanged conventional treatment,[25] suggesting that the retinal changes were transient in some patients. In the Kroc study retinopathy progressed during eight to 10 months of continuous subcutaneous insulin infusion, particularly in those patients with mild background retinopathy.[10] In some uncontrolled studies the progression of retinopathy could not be retarded during continuous subcutaneous infusion,[11-13] and increased progression was reported in one study.[12] Improved diabetic control in patients with Mauriac's syndrome worsened retinopathy.[26]

The development of cotton wool spots was not reported to be especially frequent in earlier studies. This may be explained by the timing of examinations. We examined after three months, whereas the first examination was performed after six months in the Steno study and eight months in the Kroc study. In some of our patients cotton wool spots disappeared from the third to sixth months.

We speculate whether a point of no return exists, beyond which the progression of retinopathy might no longer be influenced by return of metabolite values to normal. If such a point exists, our data suggest that it may be reached early, perhaps even before microaneurysms develop. It might therefore be favourable to start intensive treatment in patients with a shorter history of diabetes and no background retinopathy.

These findings in our patients suggest why deterioration of retinopathy might have occurred—namely, because of a large and rapid decrement in blood glucose concentration when initiating intensive treatment in patients who already had background retinopathy. The one year results, however, tend to show that in the long run intensive treatment may be less harmful to the retina than conventional treatment.

We have observed a transient deterioration of retinopathy associated with a rapid and large fall in the blood glucose

concentration when initiating treatment with continuous subcutaneous insulin infusion or multiple injections. We do not know whether this will occur if the blood glucose concentration is reduced at a slower rate. So far we have examined the effect of lowering the blood glucose concentration over several months, and after the initial deterioration retinopathy seems to improve. The study is continuing to see if this improvement remains.

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Which drug for the adult epileptic patient: phenytoin or valproate?

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Abstract

A series of 140 previously untreated patients with tonic-clonic or partial seizures were randomised to receive either phenytoin or sodium valproate. There was no difference between the treatment groups in pretreatment variables that might influence outcome.

Sodium valproate and phenytoin in the treatment of tonic-clonic or partial seizures showed no difference in efficacy as regards time to two year remission or time to first seizure. When the possible prognostic factors were studied, including history and results of clinical examination and investigations before treatment; the only factor which influenced the proportion of patients achieving two year remission was type of seizure. Patients with a clinical history of partial seizures did significantly less well than those with a history of tonic-clonic seizures only.

This study showed no major difference in efficacy between sodium valproate and phenytoin in adults with recent onset of epilepsy, irrespective of the type of seizures that the patient suffered.

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Introduction

The overall prognosis for the remission of epilepsy appears good, up to 70% of patients in a community based study achieving long term remission of their epilepsy,[1] compared with the more pessimistic outlook for patients drawn from hospital based populations with chronic epilepsy, in whom roughly 30% achieve remission.[2] The more optimistic outlook is supported by several studies of previously untreated patients, which suggest a high rate of success irrespective of which single anticonvulsant drug is used.[3-7]

The success of monotherapy in these studies demands a serious appraisal of which single anticonvulsant drug should be prescribed first to the patient presenting with epilepsy,[7a] and the need for carefully controlled, long term comparisons of anticonvulsant drugs is plain.[8] We report the results of a randomised, controlled clinical trial comparing the efficacy of sodium valproate and phenytoin in newly diagnosed adult epileptic patients followed up for between two and four years.