Continuous subcutaneous insulin infusion in diabetes mellitus

A year's prospective trial

A G DAVIES, D A PRICE, C A HOULTON, J L BURN, B A FIELDING, AND R J POSTLETHWAITE

Royal Manchester Children's Hospital; Department of Child Health, University of Manchester; and Bolton General Hospital

SUMMARY Thirteen children aged between 8 and 16 years were entered into a 12 month prospective trial comparing continuous subcutaneous insulin infusion with intensified conventional treatment. Two of seven children on insulin infusion withdrew after eight and nine weeks, and three of six children on conventional treatment withdrew after four to eight weeks. Withdrawals in both groups were related to dissatisfaction with the techniques.

The group on insulin infusion treatment achieved a mean plasma glucose of 9.8 mmol/l (176.4 mg/100 ml), a median M value of 50 mmol/l (900 mg/100 ml) and a mean glycosylated haemoglobin of 9.1% during the year. This represents a significant improvement compared with the previous values, and also when compared with the conventional treatment group whose trial values of a mean plasma glucose of 15.5 mmol/l (279 mg/100 ml), median M value of 167 mmol/l (3006 mg/100 ml), and glycosylated haemoglobin of 10.4% were not significantly different from those before the trial.

Two children on insulin infusion developed subcutaneous abscesses in the early months. There was an increased incidence of diabetic ketoacidosis in this group, but no difference in the incidence of serious hypoglycaemia between the two groups. The children reported improved well-being when using insulin infusion and continued with the technique after the trial finished. Insulin infusion offers an acceptable means of improving glycaemic control for some diabetic children.

Continuous subcutaneous insulin infusion was first described by Pickup *et al* in 1978¹ and subsequently there have been reports of studies of several years' duration in insulin dependent diabetics.²⁻³ The use of this treatment in children is less well documented⁴⁻⁸ as the reports concern fewer children with a shorter treatment duration. The possible benefits from better glycaemic control are more likely to occur if improvement in control can be sustained over long periods, and we describe a 12 month prospective controlled trial, initiated in 1982, comparing insulin infusion with intensified conventional treatment in 13 poorly controlled, insulin dependent diabetic children.

Improvements in control with any new technique may not, of course, be attributable to the technique, but rather to the increased interest and attention by medical attendants and patients.⁹ Preliminary dis-

cussions had indicated that multiple daily injections (three or four each day) would be unacceptable to patients and parents. The conventional treatment group was, therefore, kept on a twice daily insulin regimen but with increased and comparable attention to control by parents and the medical team.

Methods

Patients. The diabetic clinic at the Royal Manchester Children's Hospital consists of 95 children aged between 6 months and 18 years, and the mean glycosylated haemoglobin of the clinic is 10.4% (normal range 5.5% to 8.5%). Thirteen children with poor glycaemic control and their parents gave fully informed consent to a randomised prospective trial comparing continuous subcutaneous insulin infusion and intensified conventional treatment.

The children fulfilled the following entry criteria:

- (a) Mean glycosylated haemoglobin value above 10% in the past 12 months.
- (b) Mean plasma glucose concentration above 10 mmol/l (180 mg/100 ml) in blood sugar profiles.
- (c) Clinical impression that control was poor.
- (d) Ability to quantify blood sugars at home using an Ames Glucometer.
- (e) Twice daily insulin regimen.
- (f) Transport available to come to hospital monthly.
- (g) Telephone at home.
- (h) Willingness to enter either group in the trial.

The children were using MC Actrapid and Monotard (Novo) and were transferred to Human Actrapid and Human Monotard for a one month 'wash out' period before the trial. Those children randomised to insulin infusion were admitted to the ward for initial assessment and training in the use of this method. Those children randomised to intensified conventional treatment were admitted to the ward for assessment. All children were then followed up with twice weekly telephone calls and a clinic visit every four weeks at which blood for glycosylated haemoglobin determination was taken. A divided 24 hour urine collection for albumin estimation, a full blood sugar profile collected into lithium heparin bottles, and simultaneous Glucometer readings were collected by the parents and children the day before the clinic visit. There was good correlation between Glucometer readings and the plasma glucose concentration.

The plasma glucose concentration was measured using a glucose oxidase method and glycosylated haemoglobin was measured using a Boehringer mini-column method with aldimine inhibition. Urine albumin was measured by an ELISA method and creatinine by a semiautomated alkaline picrate method. Albumin values were compared with an established normal range.¹⁰ The glomerular filtration rate was estimated using a Cr-EDTA method. Bone age was assessed using the TW2 system.

The M value,¹¹ a transformation of blood glucose which gives weighting to hypo- and hyperglycaemia, is calculated from the plasma glucose using the formula:

$$M \text{ value} = \frac{\sum |10 \times \log_{10} \frac{\text{plasma glucose}}{4.44}|^3}{n}$$

Conventional statistics were used to assess significance. The M values were not normally distributed and the albumin results needed logarithmic transformation to ensure normality.

Moderate hypoglycaemic reactions are defined as episodes of hypoglycaemia in which carbohydrate has to be given by a third party, and severe hypoglycaemic reactions require treatment with glucagon or intravenous dextrose. Ketoacidotic episodes are defined as those that required treatment with intravenous fluids and insulin.

Technique of continuous subcutaneous insulin infusion. The pump used was the Autosyringe AS6C-U100 model which delivers a fixed basal rate of short acting insulin; in this trial Human Actrapid was used. The single basal rate was adjusted to achieve a blood sugar concentration before breakfast of between 4 and 7 mmol/l (72.1 and 126.1 mg/100 ml). A manually controlled and variable boost of insulin is given approximately 30 minutes before each meal. All children used Ames Glucometers and Dextrostix to monitor their own blood sugar, and they had been accurately measuring their own blood sugar for at least six months before the trial.

The trial required one blood sugar to be measured each day, but clearly if control was poor or they were unwell, more frequent estimations were made. The blood sugar concentration was measured either before or 60 minutes after a meal, before bed, or very occasionally at 3.00 am. The timing of the estimation was varied each day, so that a composite profile of blood sugar estimations could be established each week.

By the end of the trial all children had dropped the midmorning snack and had either omitted the midafternoon snack or reduced it to a single 10 g portion of carbohydrate.

Technique of intensified conventional treatment. Similar care and attention relating to diet and blood sugar testing was paid to this group. Care was taken not to make too many insulin dose changes because control might then become more unstable. The twice weekly telephone review tried to ensure compliance with good diabetic practice.

The diet conformed to the recommendations of the British Diabetic Association. The study was approved by the local ethical committee.

Results

Baseline comparison and anthropometric data. The initial characteristics of the children in the two treatment groups are shown in Table 1. There are no statistical differences between the two groups. The mean glycosylated haemoglobin value fell insignificantly in both groups between selection for and start of the trial. Examination of height and weight

Table 1 Baseline comparison of the two treatment groups (mean (SD))

	Continuous subcutaneous insulin infusion group (n=7)	Intensified conventional treatment group (n=6)
Boys:girls	5:2	4:2
Age (years)		
Mean	13.4	15.4
Range	8.5 to 15.9	12.9 to 18.5
Duration of diabetes (years)	8.8 (3.0)	6.5 (4.0)
Height (cm)	155.7 (14.4)	160.9 (8.1)
Height standard deviation score	-0.05 (0.92)	-0.58 (0.84)
Height velocity standard deviation score (previous 12 months)	+0.32 (0.71)	+0.41 (2.22)
Weight (kg)	49.33 (12.10)	51.42 (8.50)
Ponderal index (kg/m ³)	20.00 (2.68)	19.99 (1.57)
C peptide (pmol/l)	30 (28)	21 (10)
Mean plasma glucose (mmol/l)	13.9 (5.2) (n=54)	15.4 (6.6) (n=46)
Glycosylated haemoglobin (%)	11.53 (2.09)	11.82 (1.47)

Conversion—SI to traditional units: C peptide 1 pmol/l $\approx$ 3.0 ng/l; plasma glucose 1 mmol/l $\approx$ 18.02 mg/100 ml.

velocity charts for the whole year of the trial failed to show any clinical abnormality and the TW2 bone age remained within normal limits.

Detailed statistical analysis has not been used on the growth data because all but one child were in the midst of puberty. The ponderal index increased to 20.76 kg/m² in the insulin infusion group and decreased to 19.82 kg/m² in the conventional treatment group. Neither of these changes were significant. One child on insulin infusion, who had a tendency towards obesity, continued with this trend, increasing her ponderal index from 24.5 to 26.3 kg/m² but decreasing her insulin dosage from 1.42 to 1.07 u/kg per day.

The C peptide concentrations indicate that none of the children had appreciable endogenous insulin secretion.

Withdrawals from the trial. Two patients withdrew from the insulin infusion group, one after losing confidence because of recurrent hypoglycaemia due to pump failure at 8 weeks, and the other at 9 weeks after surgical drainage of a subcutaneous abscess. Three patients withdrew from the conventional treatment group after 4, 6, and 8 weeks. Failure to improve glycaemic control sufficiently to warrant the increased effort and attention to their diabetes led to disillusionment.

Insulin dosage. The pretrial insulin dosage was mean (SD) 1.12 (0.16) U/kg/day for the insulin infusion group and 1.04 (0.21) U/kg/day for the conventional treatment group. At the end of the trial insulin dosage was mean (SD) 1.06 (0.22) U/kg/day for the former and 1.12 (0.10) U/kg/day for the latter group. There were no significant changes in insulin dosage between the groups or between the beginning and end of the trial.

The basal insulin rate was mean (SD) 41% (5%) for the insulin infusion group with before breakfast,

lunch, tea, and supper boosts of 19% (3%), 15% (3%), 15% (2%) and 10% (2%) respectively.

Glycaemic control.

(i) Mean plasma glucose

The plasma glucose value, calculated from all laboratory measurements of samples collected at home for each child over eight week periods, is shown in Fig. 1 as the mean and standard error of the mean. The concentration fell significantly in the insulin infusion group between trial induction and week 8 ($P < 0.02$, Student's *t* test) and also fell significantly ($P < 0.001$) between weeks 48 and 56. There are no significant changes in the mean plasma glucose concentrations in the conventionally treated group. In the insulin infusion group the mean plasma glucose concentration was significantly below the initial assessment value throughout the trial, with the exception of week 48, and the mean concentrations were always significantly less than those in the conventional treatment group.

The plasma glucose concentration over the treatment year is mean (SEM) 9.8 (0.4) mmol/l for the insulin infusion group and 15.5 (0.8) mmol/l for the conventional treatment group ($P < 0.001$) (see Fig. 2). The fall in the mean plasma glucose concentration for the treatment year, when compared with the initial assessment, is significant for the insulin infusion group ($P < 0.001$) but there are no significant changes in the mean plasma glucose for the conventional treatment group.

(ii) Mean plasma glucose profiles

The cumulative plasma glucose profiles (mean (SEM)) for the 24 hour period were higher in the conventional treatment than in the insulin infusion group. The significance of differences between the two groups is shown in Fig. 2. There was no

Fig. 1 Plasma glucose (mean (SEM)) for each eight week period of the trial for the continuous subcutaneous insulin infusion (CSII) and intensified conventional treatment (ICT) groups.

Conversion-SI to traditional units: plasma glucose 1 mmol/l $\approx$ 18.02 mg/100 ml

significant difference between the two groups before lunch, before supper, at night, and at 3.00 am. The only postprandial rise in the insulin infusion group is seen at breakfast ($P < 0.001$) but a postprandial rise is seen at all meals in the conventional treatment group; this rise is significant at breakfast ($P < 0.01$).

Fig. 2 Cumulative plasma glucose (mean (SEM)) profile for the trial period for the continuous subcutaneous insulin infusion (CSII) and intensified conventional treatment (ICT) groups.

Conversion-SI to traditional units: plasma glucose 1 mmol/l $\approx$ 18.02 mg/100 ml

(iii) Plasma glucose M values

The details of changes in M values are shown in Table 2. No significant changes occurred in the conventional treatment group. The fall in M value in the insulin infusion group is significant at weeks 8, 16, 24, and 56 ($P < 0.05$, Mann Whitney U Test) and is significantly less than conventional treatment values at weeks 16, 24, and 56 ($P < 0.05$). The median M value for the treatment period is significantly lower in the insulin infusion than in the conventional treatment group ($P < 0.01$).

Table 2 Blood glucose M values (mmol/l) in the two treatment groups

	Continuous subcutaneous insulin infusion group			Intensified conventional treatment group		
	Median	Mean	Range	Median	Mean	Range
Before trial	156	146	62 to 229	140	164	126 to 237
Induction	147	142	75 to 203	148	168	72 to 324
Weeks of trial						
8	82	139	23 to 363	193	180	151 to 196
16	59	53	15 to 82	190	189	123 to 253
24	47	58	28 to 115	119	163	88 to 283
32	66	67	23 to 110	95	141	93 to 234
40	30	74	29 to 212	65	27	42 to 716
48	52	124	30 to 304	261	21	87 to 289
56	21	38	2.3 to 117	167	175	143 to 216
Total trial year	50	83	2.3 to 363	167	191	42 to 716

Conversion-SI to traditional units: plasma glucose 1 mmol/l = 18.02 mg/100 ml.

(iv) Glycosylated haemoglobin

The glycosylated haemoglobin value over the whole treatment period is mean (SD) 9.1% (0.9%) for the insulin infusion group and is 10.4% (0.2%) for the conventional treatment group ($P < 0.001$) (see Fig. 3). The fall in glycosylated haemoglobin when compared with the initial assessment, is significant ($P < 0.05$) for the children treated with insulin infusion but fails to reach significance in the conventional treatment group. The value of children withdrawing from the trial is mean (SD) 11.1% (2.3%), 18 months after trial induction.

There has been improvement in one patient's necrobiosis lipoidica during the year on insulin infusion.

Renal function. The glomerular filtration rate was raised in both insulin infusion (mean (SD) 158 (8) ml/minute/1.73m²) and conventional treatment (150 (22) ml/minute/1.73m²) groups and had fallen by 10% in the former and 1% in the latter group at the end of the trial. Neither of the changes reached statistical significance. Albumin excretion rates were within two SDs of normal age matched controls in all children except for one member of the insulin infusion group whose daytime albumin excretion rate was raised at 284 µg/minute/1.73m² and whose night-time albumin excretion rate was raised at 268 µg/minute/1.73m². Unfortunately he withdrew from the insulin infusion group after 9 weeks.

The albumin creatinine ratio at night-time was raised more than two SDs above normal in four other patients. Two children from the insulin infusion group had values of 20.4 and 38.0 mg/mmol (expressed as 10×mg/l of albumin divided by mmol/l of creatinine) and two children from the conventional treatment group had values of 14.6 and 16.3 mg/mmol. The ratio was normal in all children at the end of the trial, being 9.1, 6.5, 7.0 and 11.3 mg/mmol respectively.

Complications of treatment. There was no significant difference in moderate or severe hypoglycaemia between the two groups, seven episodes occurring in the insulin infusion group and four in the conventional treatment group. Six episodes of ketoacidosis occurred in the former but none in the latter group ($P < 0.05$). Most episodes seemed unavoidable and unrelated to treatment, being caused by appendicitis or food poisoning, but in one child there was no identifiable cause for the ketoacidosis. Subcutaneous abscesses, related to the needle site, occurred in two patients using insulin infusion. One abscess required surgical drainage and was associated with withdrawal from the trial. One child had several abscesses which responded to antibiotic treatment; they were prevented by more frequent rotation of the infusion site. Pump failure caused one patient many problems with hypoglycaemia and led to withdrawal from the trial.

Acceptability of treatment.*(i) Continuous subcutaneous insulin infusion*

Five children completed the trial and all said they felt happier and healthier. The parents concurred with this, and four families independently reported a profound improvement in mood. Six children reported no difficulty in learning the techniques but one had some initial problems with insertion of the subcutaneous needle which were resolved within a few days. One child stopped gymnastics and rugby but this did not upset him. Other children pursued these sports and some took up other activities.

Meal time flexibility is a definite advantage for a varied adolescent life style. Smaller less conspicuous pumps were desired by all wearers, but even so none wanted to stop using this method after the trial.

(ii) Intensified conventional treatment

Three children completed the trial, and on questioning said they felt little different, but all commented that they did not wish to continue with the regimen. All children were given the option of insulin infusion after the trial and one has begun to use a pump.

Fig. 3 Plasma glucose (mean (SEM)) and glycosylated haemoglobin (HbA_{1c}) (mean (SD)) for the trial period in the continuous subcutaneous insulin infusion (CSII) and intensified conventional treatment (ICT) groups.

Conversion—SI to traditional units: plasma glucose 1 mmol/l ≈ 18.02 mg/100 ml

Discussion

The average standard of glycaemic control in children and adolescents is poor. A large and reputable clinic¹² has recently reported a mean glycosylated haemoglobin of 11.8% (normal range 4.9% to 7.3%). In this trial we selected children with poor control, determined by the selection criteria of a glycosylated haemoglobin value above 10% and a mean blood glucose concentration above 10 mmol/l (180 mg/100 ml) for the past year. The 12 month trial showed that insulin infusion improved glycaemic control in these diabetics, and the improvement is superior to that obtainable by intensification of a conventional twice daily insulin regimen. Summation of plasma glucose and glycosylated haemoglobin values over the year gives a more realistic assessment of the degree of glycaemic control achieved than that obtainable by the analysis of trends over shorter periods. Those using conventional treatment showed no alteration in the mean plasma glucose concentration but there was a small, statistically insignificant, improvement in the glycosylated haemoglobin value. This discrepancy suggests there were periods of undocumented lower blood glucose concentrations: the incidence of reported hypoglycaemia, however, was similar in both groups.

Adult experience with insulin infusion has documented long term improvement in glycaemic control but the reported experience in children⁴⁻⁸ is limited to eight months. The improvement in glycaemic control is sustainable for the period of the report. Our own study confirms glycaemic improvement for up to 12 months and in fact the improvement is currently seen for up to 2 years, the mean glycosylated haemoglobin value of the pump users being mean (SD) 8.2% (0.9%) over the second year with no ketosis or abscesses seen.

The study was not designed to test the 'control-complications hypothesis' but the results are encouraging. Renal function improved (but not significantly) in both groups, and improvement in the glomerular filtration rate was greater in the insulin infusion group. These changes agree with the Steno Study Group¹³ experience. Improvement in necrobiosis lipoidica during insulin infusion has been reported previously¹⁴ but whether the improvement is coincidental or secondary to this cannot be assessed.

Acceptance of both insulin infusion and conventional treatment is not universal. We did not formally test the psychological effects of treatment but it is clear there is an initial honeymoon period during which insulin infusion is embraced enthusiastically. Minor difficulties and problems then occur,

and these last for several months during which the method is re-evaluated and either accepted or rejected. After several more months flexibility is exploited, meal times are moved and snacks are dropped. A benefit for the individual child is mood improvement noted by both parents and children. Other workers^{6,7} report no deterioration in psychological indices and an improvement in 'locus of control' tests. Demands are made on diabetic children by professionals, parents, and themselves to improve glycaemic control but it is debatable whether conventional management allows them to attain this. It would not be surprising if a technique, such as insulin infusion, by allowing improved control, might improve such indices. A thought should be spared for those children who could not tolerate the technique, because it is possible for them to consider themselves 'failures' and to become demoralised further. Sympathetic support and counselling is important for subjects who find the techniques too difficult.

Insulin infusion need not interfere with sport, and many games can be played while wearing the pump. Sports involving deliberate body contact require removal of pump and cannula, and the pump should be removed for water sports. Pump disconnection is safe for several hours.¹⁵

Complications did occur in patients using insulin infusion. Subcutaneous abscesses occurred early on in the trial but were avoided by increasing the routine changing of the subcutaneous needle to alternate days. No further infections were seen. Severe hypoglycaemia, as seen in this trial, occurs during any aggressive intensification of insulin treatment,¹⁶ and we were cautious about setting very tight pre-breakfast blood sugar concentrations. This may explain the mean blood sugar concentration of 9.8 mmol/l (176.6 mg/100 ml) and low mean basal insulin dosage (41%) compared with the 58% basal rate and mean blood sugar of 5.3 mmol/l (95.5 mg/100 ml) recently reported by Pickup *et al* in adult patients.¹⁷ Pump malfunction caused one child to withdraw from the study. The failure of any mechanical device is always a small risk and unexpected changes in control should prompt expert examination of the pump. All patients revert to conventional treatment if they are concerned about their pump.

There was a high incidence of diabetic ketosis in the insulin infusion patients. Mostly the ketosis seemed unavoidable but two children had only trivial infections and in another child no adequate explanation could be found. An increased incidence has been noted before,¹⁸ and this may be due to a smaller insulin reserve in these patients. The early detection of ketones by urine analysis if the blood sugar is high is advisable, and must be followed by

early contact with the medical team. In unexplained ketosis the pump, catheter, needle site, and infusion materials must be carefully checked and changed. Most problems have simple explanations but may surprise the individual; as one child discovered, when he found a leaking cannula caused by the undetected bite by his hungry pet hamster.

Alarm over deaths in diabetics using insulin infusion led to a review by the Centre for Disease Control.¹⁹ Only two deaths were related to this; one person died from bacterial endocarditis developing from a subcutaneous abscess and one patient died of hypoglycaemia after pump malfunction. Clearly insulin infusion is still an experimental technique, and other problems²⁰ may well be identified as experience grows.

Good diabetic management is dependent, in part, on good blood glucose monitoring. In shorter term studies⁴⁻⁸ more frequent testing has been carried out. Others may consider once daily testing insufficient and this may explain why the glycosylated haemoglobin value has not come into the normal range. Acceptability and understanding, however, form the basis of compliance, which is vital in the management of children.

Those using insulin infusion insisted on continuing with treatment and this is consistent with other reports. This contrasts with the reluctance of those on intensive conventional treatment to continue, perhaps providing the best evidence of acceptability. The insulin infusion patients are now in the routine diabetic clinic. During the second year they have not required greater attention than that required by other diabetic children.

It is not clear what proportion of diabetic children and adolescents will benefit from insulin infusion but this study shows there is such a group, who are not identified by previous good control. It is therefore possible that these patients may be able to maintain better than average glycaemic control through adolescence, a time when control can be most difficult, which may lessen their likelihood of developing microvascular complications.

We thank Professor I B Houston, Dr G M Addison, and J R Lane for technical support and advice; the Biochemistry Department, Hope Hospital, Salford, for estimation of glycosylated haemoglobin; Dr D B Gordon for statistical advice; the Salford Department of Medical Illustration and Mrs K Cordwell for help in manuscript preparation.

Novo Laboratories, UK provided Human Actrapid, Human Monotard and also measured the C peptide values. We are grateful for their support and interest. Funding from the North West Regional Health Authority, the Wallness Children's Kidney Project, and Marks and Spencers PLC is gratefully acknowledged.

References

- Pickup JC, Keen H, Parsons JA, Alberti KGMM. Continuous

subcutaneous insulin infusion: an approach to normoglycaemia. *Br Med J* 1978;*i*:204-7.

- Mecklenburg RS, Benson JW, Becker NM, *et al*. Clinical use of the insulin infusion pump in 100 patients with type 1 diabetes. *N Engl J Med* 1982;**307**:513-8.
- Schade DS, Santiago JV, Skyler JS, Rizza RA. *Intensive insulin therapy*. Amsterdam: Excerpta Medica, 1983.
- Tamborlane WV, Sherwin RS, Genel M, Felig P. Outpatient treatment of juvenile-onset diabetes with a preprogrammed portable subcutaneous insulin infusion system. *Am J Med* 1980;**68**:190-6.
- Riley WJ, Silverstein JH, Rosenbloom AL, Spillar R, McCallum MH. Ambulatory diabetes management with pulsed subcutaneous insulin using a portable pump. *Clin Pediatr* 1980;**19**:609-14.
- Rudolf MC, Ahern JA, Genel M, *et al*. Optimal insulin delivery in adolescents with diabetes: impact of intensive treatment on psychosocial adjustment. *Diabetes Care* 1982;**5**(suppl 1):53-7.
- Shiffrin A, Desrosiers M, Moffatt M, Belmonte MM. Feasibility of strict diabetes control in insulin-dependent diabetic adolescents. *J Pediatr* 1983;**103**:522-7.
- Greene SA, Smith MA, Baum JD. Clinical application of insulin pumps in the management of insulin dependent diabetes. *Arch Dis Child* 1983;**58**:578-81.
- Worth R, Home PD, Johnston DG, *et al*. Intensive attention improves glycaemic control in insulin-dependent diabetes without further advantage from home blood glucose monitoring: results of a controlled trial. *Br Med J* 1982;**285**:1233-40.
- Davies AG, Postlethwaite RJ, Price DA, Burn JL, Houlton CA, Fielding BA. Urinary albumin excretion in school children. *Arch Dis Child* 1984;**59**:625-30.
- Service F, Molnar G, Rosevear J, Ackerman E, Gatewood L, Taylor W. Mean amplitude of glycaemic excursions, a measure of diabetic instability. *Diabetes* 1970;**19**:644-55.
- Ellis D, Becker DJ, Daneman D, Lobes L, Drash AL. Proteinuria in children with insulin-dependent diabetes: relationship to duration of disease, metabolic control, and retinal changes. *J Pediatr* 1983;**102**:673-80.
- Steno Study Group. Effect of strict metabolic control on eye and kidney function in insulin-dependent diabetics with background retinopathy. *Lancet* 1982;*i*:121-4.
- Waldausl W, Freyler H, Bratusch-Marrain P, Vierhapper H, Brunder H. Kontinuierliche subkutane insulin-infusion. *Dtsch Med Wochenschr* 1983;**108**:570-7.
- Krzentowski G, Scheen A, Castillo M, Luyckx AS, Lefebvre PJ. A 6-hour nocturnal interruption of a continuous subcutaneous insulin infusion. 1. Metabolic and hormonal consequences and scheme for a prompt return to adequate control. *Diabetologia* 1983;**24**:314-8.
- Barbosa J, Johnston S. Severe hypoglycaemia during maximized insulin treatment of diabetes in a randomized clinical trial. *Diabetes Care* 1983;**6**:62-3.
- Pickup JC, Bending JJ, Collins ACG, Keen H. Reversal of insulin resistance in type 1 diabetes after treatment with continuous subcutaneous insulin infusion (letter). *Br Med J* 1984;**288**:796-7.
- Peden NR, McKendry JBR, Braaten JT. Acute uncontrolled diabetes during long term continuous subcutaneous insulin infusion. *Diabetes* 1983;**32**(Suppl 1):36A.
- Teutsch SM, Herman WH, Dwyer DM, Lane JM. Mortality among diabetic patients using continuous subcutaneous insulin-infusion pumps. *N Engl J Med* 1984;**310**:361-8.
- Bronwlee M, Cerami A, Li JL, Vlassara H, Martin TR, McAdam KPWJ. Association of insulin pump therapy with raised serum amyloid A in type 1 diabetes mellitus. *Lancet* 1984;*i*:411-3.

Correspondence to Dr Alan Davies, Royal Manchester Children's Hospital, Pendlebury, Manchester M27 1HA.

Received 27 July 1984