# A NEW MINIATURE, OPEN-LOOP, EXTRACORPOREAL INSULIN INFUSION PUMP

D. Rothwell*, I.A. Sutherland*, J.C. Pickup†, J.J. Bending†, H. Keen and the late J.A. Parsons

## ABSTRACT

*This extracorporeal insulin infuser has been designed to be compact, simple to operate, and suitable either for clinical investigations of insulin-dependent diabetes mellitus or for long term treatment of the condition. A syringe driver of unconventional design is used, and the syringe will be available prefilled with insulin, specially formulated at standard strength for long term infusion. The device is electronically controlled to give variable rates of basal infusion, preset by switch and supplemented by bolus infusions demanded by pushbotton prior to meals. Sufficient insulin is carried in the syringe to meet the needs of most diabetics for at least a week without refilling, and the battery life is commensurately long. Signalling of the mealtime dose regime, and of alarm and failure conditions is by audible means. Insulin will most commonly be delivered subcutaneously, though other routes are possible.*

**Keywords:** Insulin, diabetes, infuser, subcutaneous, normoglycaemia

## THE INTRODUCTION

The need for improved metabolic control in diabetics stems largely from the belief that the long-term complications of diabetes (e.g. retinopathy, nephropathy) are due to prolonged exposure of the tissues to abnormal concentrations of metabolites, principally glucose[1].

It is very difficult to mimic non-diabetic insulin secretion patterns and thus achieve near-normal blood glucose levels with intermittent injections of insulin, and this has encouraged research into new ways of delivering insulin to the diabetic[2,3].

One such option is continuous infusion from a portable electro-mechanical, rate-adjustable pump. In recent years extracorporeal open-loop devices, where there is no automatic glucose-sensing and feedback control of insulin delivery rate, have been successfully and increasingly widely used to [illegible]ulin-dependent



diabetics. Here, a slow and continuous delivery of insulin throughout the 24 h is supplemented by boosts at or just before meal-times. Whilst several routes of administration are possible and are undergoing trial (intravenous[4,5]; subcutaneous[6,7]; intramuscular[8]; intraperitoneal[9,10]) our own group conceived and developed continuous *subcutaneous* insulin infusion (CSII)[6,11-13] a system which is now regarded by many as the most practicable long-term open-loop approach for both research and possibly routine treatment in some diabetics[3]. A particular advantage is the avoidance of thrombosis and infection which are special hazards of the previously favoured intravenous route. Furthermore there is no difficulty in the patient replacing a subcutaneous cannula unaided if it has been temporarily removed, either for personal reasons or accidentally.

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The major problems with the first generation of insulin infusion pumps were poor patient acceptability because of the bulk and weight[14] (the Mill Hill Infuser[15], used in most of our initial clinical studies weighs 300 g and measures 144 × 70 × 23 mm), capacity in most pumps for only 1-2 days of insulin, lack of alarm features, unsatisfactory electrical and mechanical reliability and, in some models, a fixed basal infusion rate. The last means that the pump insulin must be diluted to give a dose rate appropriate for each individual patient's needs.

We have, therefore, developed a new custom-designed insulin infusion pump which overcomes the disadvantages of the original infusers. Although it is built with the premise that subcutaneous infusion is the present preferred strategy, the pump design is compatible with research testing of other routes of delivery.

## DESCRIPTION

### Operation

The infuser (*Figure 1*) is a battery-powered syringe driver, taking a special syringe (A) prefilled with standard-strength insulin (100 Units/ml). Loading the infuser is analogous to placing a film cassette in a camera. After taking the syringe from storage in the refrigerator it is equilibrated approximately to the ambient temperature. The plunger is inserted into the piston, and the assembly clipped into the infuser. The slider (C) is then pushed forward to retain the syringe and engage the drive, and the cannula (not shown) is primed by operating the prandial button (B) a number of times.

Most patients wear the infuser in a waist-belt, and connection is made by inserting the cannula needle, usually into the subcutaneous tissue of the abdominal region. This can be effected if necessary by the patient himself.

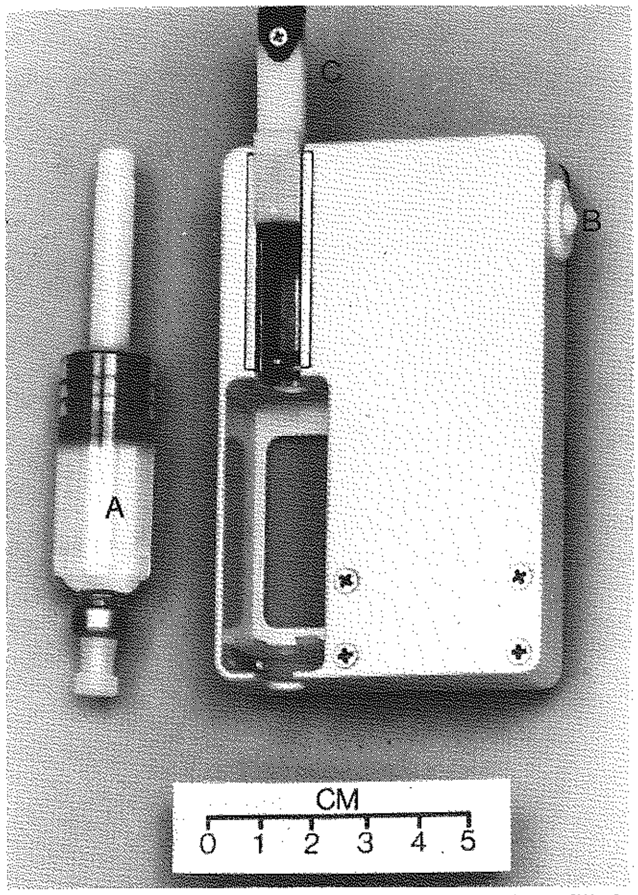


**Figure 1** Production model of the infuser, with prefilled syringe.

There are two basal rate delivery switches, concealed and protected by the lid of the battery compartment (on the underside of the infuser as illustrated in *Figure 1*), and the pushbutton (B) is used to demand additional insulin at mealtimes. The infuser will normally be worn under clothing, and signalling of prandial delivery and of alarm conditions is by audible means.

Ten basal dosage rates ranging from 15 to 50 units of insulin per day (100 U/ml insulin) may be selected by the basal rate switch, and the basal factor switch allows the preset rates to be multiplied or divided by two.

The patient calls for the number of mealtime units required by pressing the prandial button the corresponding number of times. Each press is signalled audibly. 16 seconds is allowed for entry of the demand, which is limited to seven units in any one demand, for safety reasons. An eighth press within the period cancels the demand, a feature which can be used by the patient to correct errors or uncertainty about what dosage has been demanded.

Assuming the call has not been cancelled, after 16 seconds the infuser signals the number of units requested and begins to deliver, one unit at a time, at intervals of 14 seconds. The maximum prandial dosage of 7 units takes less than 100 seconds, and completion is signalled by a one second tone. A further press on the prandial button during delivery causes immediate cancellation, with the same audible signal, and the infuser reverts to basal mode.

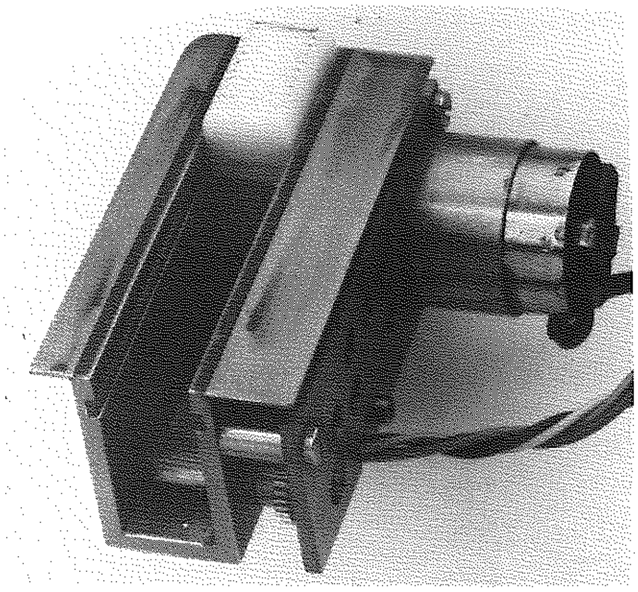

**Figure 2** Prototype motor/drive gearbox.

Insulin is delivered from the infuser incrementally, in shots of 0.75 $\mu$l volume. In basal mode the time between shots determines the mean flow rate, and a prandial unit is measured by counting shots.

**Syringe drive unit**

The infuser has no leadscrew, the drive (*Figure 2*) being transmitted directly to the plain cylindrical plunger of the syringe by means of a splined roller, which forms teeth in the plastic as it turns. The unit comprises a 12 v DC miniature motor (1516E012 Portescap, Reading, Berks) driving the splined roller through a multistage in-line gearbox. After loading the syringe into the infuser the drive is engaged by pushing forward a slider button, thereby forcing the splines of the roller into engagement with the plunger.

The syringe has an effective volume of 5.6 ml, and the design is based on a glass vial. Both body and piston are siliconised to minimize static friction (which otherwise increases over long storage periods). The syringe will be supplied prefilled with 100 U/ml insulin (Nordisk Insulinlaboratorium, Gentofte, Denmark), specially formulated to prevent precipitation and aggregation.

**Electronic control.** (*Figure 3*)

The flow of insulin to the patient is determined in basal mode by timing the intervals between fixed volumetric shots, and in prandial mode by counting shots during continuous (non-incremental) delivery. The angle through which the splined drive roller must rotate to deliver the required shot volume from the syringe is determined by a flag assembly, comprising a light-emitting diode and photodetector mounted at an appropriate stage in the gearbox.

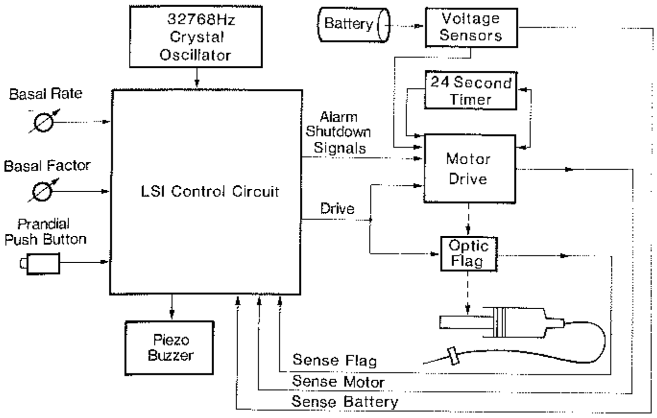


**Figure 3** Block diagram of control system.

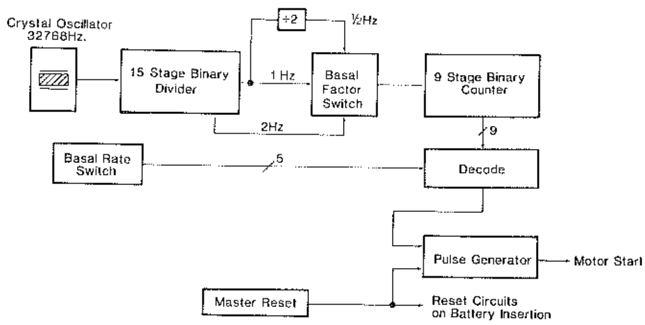


**Figure 4** Clock generator and basal shot timer.

The drive motor is primarily controlled by the chip, but there are over-riding shutdown or alarm controls from an independent time-out circuit, and from battery voltage sensors.

All logic timing operations, and excitation signals for the piezo-electric buzzer are derived from the 32768 Hz crystal oscillator.

The control logic is realised on a single chip, in custom designed large scale integrated (LSI) ISOCMOS circuitry, using the CELLMOS process (Marconi Electronic Devices Ltd). The chip, and other groupings of peripheral active components, are housed in leadless chip-carriers, assembled into a single thick film circuit, and connected to the basal control switches via a double-sided printed circuit.

**Basal Mode.** (*Figure 4*)
The infuser is made operational by fitting the battery. Prior to initiation of basal operation (the normal mode) all circuits are reset, and the infuser delivers a single test shot of 0.75 $\mu$l. This is audibly signalled to the patient as an indication that the infuser is operating correctly.

The time intervals appropriate to the required basal rate are generated from the control oscillator by conventional counting and summing techniques, using decoding logic controlled by the basal rate switch, which is Johnson coded. A basal shot pulse fires the motor control circuitry, and simultaneously restarts the basal timing sequence. The optic flag generates the switch-off pulse, and the flag circuitry is itself switched on and off with the motor, to conserve power.

The maximum time interval between shots, at the minimum flow rate of 75 $\mu$l/day, is 14.22 min. A more typical flow would be 250 $\mu$l/day, with an incrementing time of 4.27 min.

**Prandial mode.** (*Figure 5*)
Prandial mode (PM) is initiated 16 seconds after the first press of the prandial push button, and basal control functions are inhibited. The number of insulin units demanded is stored and signalled

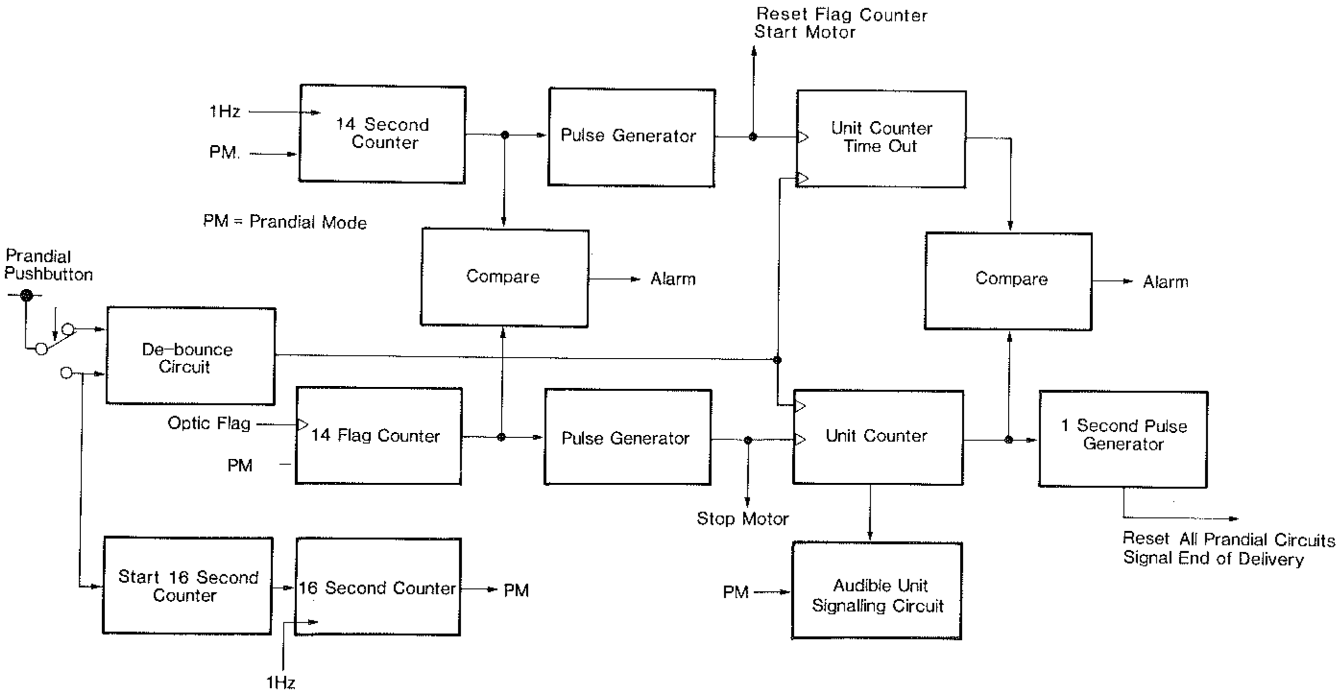


**Figure 5** Prandial delivery control.

audibly to the patient at the end of the 16 second period. Delivery occurs unit by unit, measured by a count of 14 flags, upon which a motor stop signal is generated.

A timer circuit runs in parallel with the flag counter, and fulfills two functions. It initiates unit deliveries at 14 second intervals, and causes an alarm to sound and the infuser to switch off if the appropriate flag count is not completed within the period, either because of a mechanical fault or failure of the flag.

A lack of correspondence between the stored unit count held in separate parallel registers, down-counted respectively by motor stop signals and the parallel time-out circuits, will similarly shut down the infuser.

The end of prandial delivery is signalled by a one second tone, all prandial circuits are reset, and the infuser reverts to basal mode.

A prandial demand of eight units within the 16 second period, or a further press of the push-button during delivery resets the counters to zero. Delivery is terminated, the one second tone is generated, and the infuser reverts, to basal mode.

### Alarm and shutdown

The integrated circuit incorporates self-checking features, and the state of off-chip circuits such as motor drive lines and the flag assembly is regularly checked by the logic. When fault conditions are detected, the infuser is shut down and a repetitive alarm signal sounded.

The motor drive circuit (*Figure 6*) consists essentially of three discrete switching transistors in series with the motor. All three must be switched on by infuser control signals to start the motor. Normal motor switch-off signals act on two of the transistors, one of which is independently switched off if an alarm condition is detected. The third

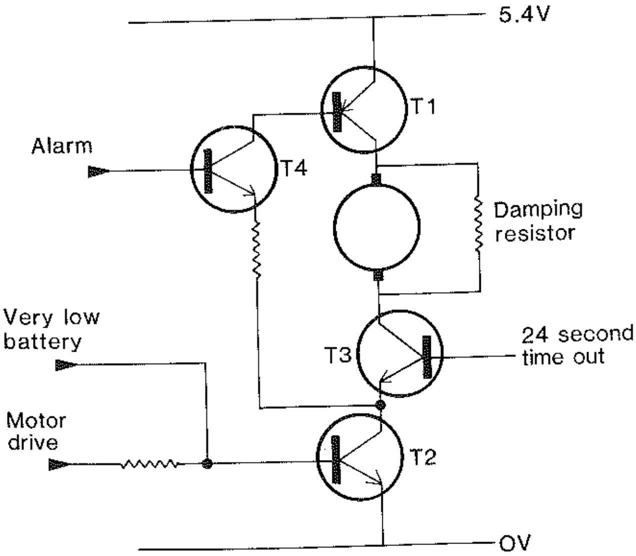


**Figure 6** Elementary motor drive circuit.

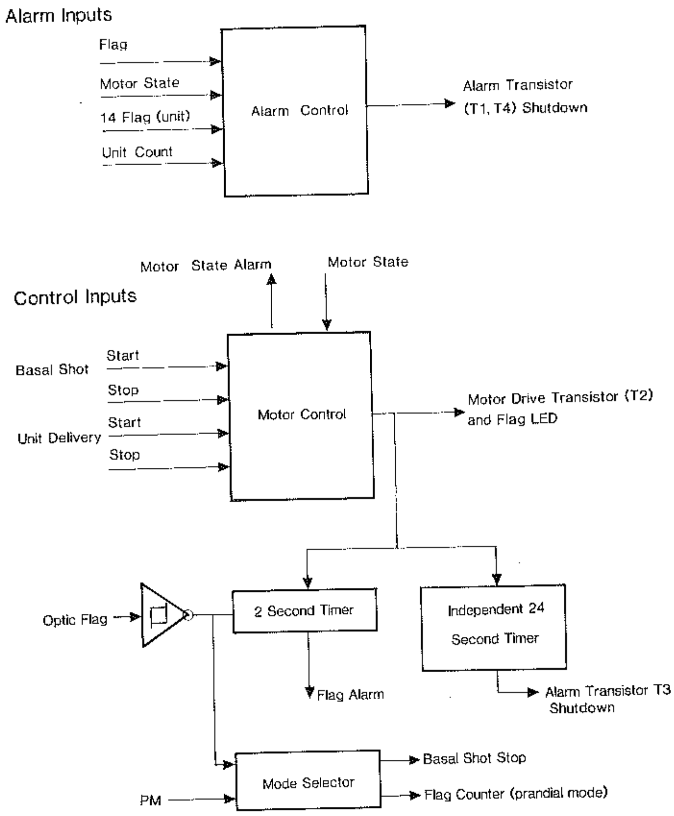


**Figure 7** Main motor control and alarm schematic.

transistor is switched off by a timer circuit independent of any other circuitry, to protect against a catastrophic chip failure which might otherwise leave the motor in the running state. The motor is damped to rest by a parallel resistor.

On-chip monitoring and control circuitry is illustrated in *Figure 7*. The state of the motor drive circuit is interrogated 60 ms after a start demand, and continuously when the motor is off. The alarm circuit is activated if fault conditions are detected in either case.

In basal mode, a failure of the motor to start, due to contamination on the commutator or a stalled gearbox, would be detected by the absence of flag response within 2 seconds of the start signal. Alternatively the symptom might be caused by a failure of the flag circuits, in which case the motor will run for 2 seconds before alarm and shutdown.

Protection against failure in prandial mode has already been described.

Towards the end of its working life the battery voltage dips sharply when loaded, and the battery conductance takes several minutes to recover. At the start of the clock period following each motor demand, the battery is resistively loaded for 31 msec, and the voltage is interrogated by two independent off-chip circuits. The first, operating at 4.1 v, warns of the impending need to replace the battery, causing an alarm to sound during all subsequent motor operations. The second, initiated at 3.1 v, detects that the integrity of operation of the infuser is at risk, and shuts down the infuser to the accompaniment of a continuously sounding alarm signal, which continues until the battery finally fails.

An independent timer operates whenever the motor is running. If a catastrophic chip failure or other fault should leave the motor continuously energized the timer will cut the motor supply after approximately 24 seconds.

**Power source**

The infuser is designed to take a range of batteries with standard dimensions (16.7 mm diameter, 27 mm length approximately), and voltages between 5.0 and 7.0. The 5.4 volt, 350 mA.h mercury battery (Mallory TR114N, or equivalent), or the rechargeable 6.0 volt, 80 mA.h silver-zinc (Medicharge R6B80, or equivalent) are suitable.

**Size, weight and capacity**

Overall dimensions of the commercial infuser are 100 x 60 x 22 mm, and the all-up weight is 200 gm. The insulin capacity is 560 units.

## CLINICAL TRIALS

Prototypes are at present undergoing trials at Guy's Hospital, London, and to date twelve diabetic patients are using the device. Some are new to CSII therapy and others had previously been treated with the first generation Mill Hill 1001HM infuser (Muirhead Medical Products Ltd). Patients are admitted to the Metabolic Ward for five days and nights, during which they receive intensive education on the characteristics and use of the infuser in treating their condition. Frequent self-monitoring of glucose levels is essential in maintaining adequate long-term control, and tuition in the use of the home glucose monitor is given.

During the five days' admission, the individual patient's insulin requirements are assessed, both for continuous basal infusion and for the appropriate meal time bolus (expressed as units of insulin per estimated carbohydrate content in the meal). The patients are then discharged home to continue normal everyday life wearing the infuser. Close outpatient communication on a 24 h basis is continued.

## DISCUSSION

This infusion pump was specifically designed to circumvent the difficulties which we and others have experienced with first generation insulin delivery devices. For example, a questionnaire sent to diabetics who had been treated by a subcutaneous infusion pump (Mill Hill Model 1001 HM) for 3 weeks or more revealed that the main patient complaint was the size and weight of the pump[14]. The present infuser is less than half the size of several initial pumps and thus promises to be much more acceptable to the diabetic patient, an important desideratum in the operation of long-term trials of diabetic control and complications.

An infusion pump for general use should be simple to operate, precise, reliable and reasonably inexpensive.

The operational controls on this pump consist only of a prandial boost press-button and rotary switches for basal rate and x 0.5 or x 2 rate selection. Mounting of the prefilled syringe is straightforward for the patient, and the drive is taken up without lost motion as soon as the drive button is pushed into position. The long-term stability of flow under normal operating conditions is within 5%, and the short-term cyclical variations are considerably less than we have measured in leadscrew syringe drivers. Detailed performance data will be published elsewhere.

Preliminary clinical trials of prototypes for periods of up to 4 months confirm the simplicity and ease of control, the reliability, and the general acceptability to the diabetic patient. We understand, furthermore, that a commercial production model will be comparable in cost to first generation pumps, notwithstanding the improved features.

Alarms for motor malfunction and low battery state give audible warning of these problems and motor over-run due to complete chip failure is signalled, after 24 sec, by motor shut-down. We have tested[16] the effects of pump breakdown (or accidental cannula withdrawal) by deliberately stopping CSII in resting, supine diabetic volunteers. Although plasma glucose concentration rises to a plateau after 4–5 h, the ketone body, 3-hydroxybutyrate, continues to rise and many patients are quite unwell after 9 h of insulin deprivation. This would not be a serious problem in the resting, supine patient (e.g. overnight) and additional insulin quickly restores metabolic normality. However, in the active, fed diabetic, insulin withdrawal is likely to be more serious and we have clinical experience of more rapid metabolic decompensation and malaise after daytime breakdown of first generation infusers[13]. For this reason, motor stop and low battery alarms seem particularly useful. Protection against motor over-run is also necessary because of the potential dangers of hypoglycaemia from insulin overdose. If the infuser were to fail in such a way as to leave the motor running, the insulin accumulated before the 24 second timer cuts the motor (about 3 units) would provide a useful depot in case the shut-down is not immediately noticed.

The controls cover a range of basal rates consistent with our previous experience of CSII, where the mean rate in adults has been about 25 units/day. Facility for division or multiplication of the basal rate by 2 allows for lower doses in children and some extremely insulin sensitive adult diabetics and for dose increases during, for example, intercurrent illness. The disposable pre-filled syringe and the adjustable volumetric rate will eliminate the need to dilute the syringe insulin for dose variation.

A typical prandial insulin boost dose of 5 units will be delivered in approximately one minute. Minimal duration of pre-meal insulin boost delivery is important for optimal control of meal-related glucose excursions. This is partly because the normal delay in insulin absorption from the subcutaneous site produces a protracted entry into the circulation of even an instantaneous bolus injection[13,17], but intravenous delivery is also most effective when administered as a rapid initial boost[18]. These factors explain the superior meal-time glucose control of rapid subcutaneous insulin boost dose delivery compared with square-wave subcutaneous infusions over 30 min of the same amount of insulin[19].

Existing syringe pumps have a 2-5 ml capacity and need refill or change of syringe every 1-2 days. This probably explains the absence of insulin aggregation and precipitation in the reservoir and cannula, a problem which seems to appear after several days or weeks of storage in a pump reservoir[20]. A typical diabetic patient requires 40-50 units of insulin per day, and the capacity of the pump should exceed 7 days of continuous operation for most. The extent of insulin precipitation over periods in excess of 7 days will be tested in clinical trials with insulin formulations designed to avoid this event.

The lack of a suitable implantable glucose sensor has so far frustrated the development of a portable, completely automatic closed-loop insulin delivery device[2,3]. Research in this area is very active. If such a sensor is eventually constructed the present pump could be fairly easily adapted to provide the infusion arm of an externally worn miniature artificial endocrine pancreas.

## SUMMARY

The infuser is designed specifically to meet the requirements of the insulin dependent diabetic patient, and when used in conjunction with regular checks on the level of blood glucose will improve the degree of control in selected patients.

Operational safety is maximized by simplification of the controls, by the incorporation of electronic circuits which check for over and under dosage of insulin, and by audible signalling of alarm conditions and the operational status of the infuser.

The prefilled syringe is simple to load, and the controls straightforward both for clinician and patient. The infuser is small and light enough to be worn under clothing. Because it is unnecessary to see the controls or observe a reading the prandial dosage can be demanded unobtrusively by the patient.

## ACKNOWLEDGEMENTS

We pay tribute to the memory of Dr J.A. Parsons, whose knowledge and enthusiasm guided and inspired our work until his tragic death in a car accident on 11th July 1981.

This has been a cooperative project between the Engineering Department (Mr. D. Rothwell) and the Laboratory of Endocrine Physiology

(Dr I.C.A.F. Robinson), National Institute for Medical Research, Mill Hill, London; and the Unit for Metabolic Medicine (Prof H. Keen), Guy's Hospital London, England.

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Licences world-wide for the insulin infuser are held by Nordisk Insulinlaboratorium, Gentofte, Denmark.

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