REVIEWS

Drug Delivery by Program or Sensor Controlled Infusion Devices

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Abstract: The prolonged controlled administration of drugs could benefit the treatment of several diseases. In some instances variable delivery rates are required, e.g. in the treatment of diabetes. Program controlled externally portable devices and fixed rate implantable pumps are rapidly gaining clinical acceptance. Widespread use of the considerably more complex implantable devices with variable rates for use in diabetes therapy is hampered by the persistant problem of the incompatibility of insulin with the pump at body conditions. The ideal devices, feed-back controlled implants, cannot be realized since long-term implantable sensors, e.g. of glucose, are not yet available. Prospective clinical trials are running for all applications to clarify the cost-benefit-risk relationships.

Program- or sensor-controlled infusion devices portable on or in the body can serve as substitutes for an impaired body function or for the long-term administration of drugs. The latter is only indicated when their customary administration as tablets, injections or short-term infusion is not possible or fails to produce satisfactory therapeutic results. Hence controlled infusion devices may be applied when the half-life of the drug in the body is too short, its dosage is critical (side effects!) or local administration is necessary and outpatient management is desirable. This review emphasizes the use of the new devices as an artifical organ, namely, as replacement for the function of the cells of the pancreas to supply insulin in diabetics. Therefore, these infusion devices are sometimes somewhat euphorically and inaccurately called "artificial pancreas" or "artificial beta cell" (1).

The history of controlled insulin delivery over the past two decades follows a pattern characteristic for many new methods that attract strong public attention. Early studies in 1964 by Kadish (2) that describe a simple infusion system for insulin and glucagon controlled through glucose measurements have attracted little attention in professional circles and have fallen into oblivion. The time had not yet come for their technical realization and broad application. Other groups (3–7) began to take up the subject again at the beginning of the 1970's. Then the technical means became available, and the growing demand from the medical world and society (approx. 4 % of the population in the industrial nations is diabetic) forced a break-through through intense studies by several scientific research groups and the industry and by a growing public awareness of the diabetes problem. A glucose sensor-controlled, computerized infusion device for insulin and glucose or glucagon, the Biostator® from Miles Company, resulted as the first product (4). Since it was designed as a bedside unit, its application is restricted to short-term use in the hospital. Several types of portable and therefore more widely applicable insulin infusion devices, nevertheless without sensor, were developed in parallel, e.g. the so-called Mill-Hill Infusor (Muirhead, GB) based on motor-driven syringes (8) and different types of peristaltic pumps from Siemens, Germany (9, 10). A number of products with motor-driven syringes followed, primarily from the USA. The good metabolic adjustment achievable with the pumps with at times spectacular therapeutic successes in mitigating retinopathy and neuropathy led to a pump euphoria. The devices became quickly and sometimes uncritically wide-spread, primarily in the USA. It is estimated that world-wide approximately 15 000 insulin pumps were sold until the end of 1983, 70 % of these on the American market. The rapid flourishing of the method with relatively little confirmation on the basis of comparative long-term studies and benefit-risk estimates led to technical, pharmacological and medical problems. From 1982 onwards, these were reflected in reports on pump functional faults, complications at the infusion site, frequent cases of hypoglycemia and acetonemia, insulin precipitation and a number of mortalities with pump therapy that were at first sight alarming. This led to a depression with partial overemphasis of the risks and downplaying of the advantages of the method. Depending upon the situation in their country and their own experiences, the different investigator groups are now entering a period of a more realistic assessment of the infusion devices. Several publications (11–13) provide a good summary of the situation from different medical aspects.

This article is primarily intended to provide an analysis of the present technical state of development (Spring 1984) with a brief summary of the medical problem.

Possibilities and Provisional Limitations of Therapy with Externally Portable and Implantable Drug Delivery Systems

1. Metabolic Adjustment – Non-Brittle Diabetes

Published statements on clinical results remain highly contradictory. On the one hand a great number of publications claim: Metabolic adjustment under pump conditions is clearly better than the conventional injection therapy (see (14) as an example). Another school of diabetologists contends: Metabolic adjustment is equally efficient under pump conditions as with intensified injection therapy (3–5 injections plus 3–5 blood sugar measurements per day). It should be mentioned that the latter statement came from comparative studies that employed pump therapy with all needles placed exclusively subcutaneously (as summarized in (11)). Assuming its accuracy and reproducibility, this finding suggests that the equally efficient metabolic adjustment by conventional

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methods can only be explained by the more frequent blood-sugar control, more intensive training and medical care. Therefore the contradiction between the two statements can be readily resolved. With the first group, the comparison was made with traditional and practicable injection therapy, i.e. therapy acceptable to the average patient consisting of maximally two injections and few blood-sugar measurements per day. Moreover, only urine-sugar measurements are performed regularly for many patients with a complete blood-sugar profile for one day per week or every two weeks. The inconvenience to which the second group with conventional injections is exposed appears not to be acceptable in general diabetological practice.

However, all these previous results are rather sporadic and of an episodic character. The actual value and the limits to pump therapy must be established in prospective long-term studies. Some are running. The practical and ethical problems of treating a sufficiently large number of volunteers for several years with this method are, nevertheless, considerable. The acceptance by the patients appears to diminish after one or at the latest two years even when their physical condition has clearly improved. The discomfort in daily life with the present-day technology with external devices is still so high that after a certain time a poorer metabolic control is accepted more readily than being dependent on the infusion devices. The interpretation of the results of these studies is hampered by the technical and practical problems and can thus lead to premature and incorrect conclusions by using inappropriate catheter routes, infusion programs and insulins and devices.

2. *Brittle Diabetes*

Clinical investigators who have experience with intravenous (i.v.), intraperitoneal (i.p.) or intramuscular (i.m.) catheter routes (13, 15–18), unanimously attested the superiority of metabolic management with these routes in general, but especially in the case of the brittle diabetic. In cases were the s.c. route provides no satisfactory results, the i.p. or i.v. route usually yield the desired success. Some groups also report a better metabolic control with the central access routes than with the s.c. method for non-brittle diabetics (13, 15). Moreover, peripheral insulinemia is largely normalized with the i.p. route, in contrast to all other named routes. The more invasive clinical intervention when placing the catheter (necessary only every few months to a year) and the need for the patient to be tied to the device oppose the wide adoption of the i.p. or i.v. route on a similar scale as the s.c. route. Decoupling the device from an inserted i.p. catheter is indeed possible and is practized occasionally, but it probably increases the risk of peritonitis which is otherwise very slight with correct long-term application. However, all these problems with the central routes no longer arise with the use of implantable devices. Wide-ranging long-term studies with optimal metabolic adjustment and the least complications are conceivable only with implantable devices.

3. *Analgesics Against Severe Persistant Pain*

The application of portable or implantable delivery systems is conceivable for patients with severe continuous pain under the following conditions: a. when the discrete administration of analgesics does not produce the desired sustained effect, and therefore analgesics, normally opiates, must be infused over long periods; and b. when mobility of the patient is desired, e.g. when the patient should freely move postoperatively in the hospital or should be discharged home in his customary surroundings. The possibility to send home patients who might otherwise be tied to the hospital bed with conventional therapy improves the quality of life for the patient and results in noteworthy cost savings.

The opiates or other analgesics are infused peridurally (intrathecally) with an uniform flow to reduce the systemic action and side-effects such as addiction or the risk of respiratory paralysis. In the case of short-term application (days to months) externally portable devices are satisfactory (19). With long-term application (months to years) for continous pain patients, implants are indicated (20, 21). It is currently being disputed whether implantation is indicated for the largest group of patients suffering pain, cancer patients in the terminal stage with an average life expectancy of 6 to 9 months. Several hundred devices have been implanted for this indication in the USA, which, however, may be attributed to the fact that so far no approved external device has been on the market there. The implantation method rapidly became wide-spread (perhaps too rapidly?), but studies on the exact definition of the indication for pumps on the basis of investigation of the benefit/risk ratio are still to be made. Clearly, the costs/benefit ratio is very favorable for cancer patients who can be discharged from the hospital with the pump therapy.

The requirements of the devices depend upon the drug used, the catheter route and local medical opinion. Flow rates from a few tenths up to a few milliliters per day are needed, and sometimes the possibility of administering extra-doses during pain attacks is considered advantageous. In the cases of catheter access to the spinal cord, a long-term reservoir with a completely enclosed infusion tract is necessary or at least of great advantage, since they avoid infections that may occur with external devices.

4. *Chemotherapy*

As is the case with insulin and opiate therapy with pumps, mainly anecdotal results are available with chemotherapy as well (22–24). Comparative prospective studies that compare pump therapy with alternative methods are lacking, though several thousand devices have been implanted. Good results are reported with local infusion of Floxuridin (FUDR®) into liver arteries for the treatment of liver metastases. The substance is largely inactivated in the liver with little systemic exposure of the body to the drug, so that the severe side-effects of chemotherapy (vomiting, hair loss, etc.) are reduced, and the cytostatic action can be intensified in and limited to the liver. Since the method has only palliative effect and is not entirely free of complications, only broad studies can provide statements on the benefit/risk/cost relationships. Nevertheless, application has rapidly spread even without such studies, once again primarily in the USA.

5. *LH-RH* (luteinizing hormone of the adenohypophysis, releasing hormone)

Most authors (e.g. 25, 26) agree in principle on the therapeutic success of the application of the hypophysis hormone LH-RH with infusion pumps. After failure of all other means, pregnancy was made possible for 20 to 40 % of the women treated. Experiments are still being performed with regard to the optimum time intervals between the infusions, optimum doses and catheter routes (s.c. or i.v.)

6. Further Drugs

The indications mentioned earlier for the drug-delivery systems apply to a number of further drugs that can only be mentioned here. Experiments are being performed with antibiotics, labor inducers, labor inhibitors, growth hormones, vasopressin, calcitonin, glucagon, somatostatin, antiarrhythmic drugs, psychopharmaceuticals, dobutamins, antihypertensives (possibly with pressure-sensor feedback), spasmolytics and antirheumatic agents (27, 28). In the Mediterranean countries, deferoxamine is already infused s.c. on a routine basis with external pumps in the treatment of thalassemias.

Device Technology

Externally Portable Devices

Approximately 30 different devices are commercially offered for insulin delivery alone. The majority are motor-driven syringes. The syringes are in part commercially available disposable plastic products with a volume of 1 to 3 ml (for one to three days supply), in part plungers or cylinders that are specially designed to achieve high accuracy or for reasons of pump drive design. With one model, the syringes are supplied pre-filled as cartridges. The second pump principle to be encountered is the peristaltic or roller pump.

Pumps with electromagnetically driven pistons and two passive valves and a pre-filled plastic insulin reservoir have been clinically tested for some time but have not yet reached the commercial stage. The technical data of the various types cannot be discussed here individually. Reference is made to what currently must be considered the most comprehensive survey on this topic (29). Fig. 1 and Fig. 2 show representative examples of the syringe and peristaltic pumps. The peristaltic pump is also used in an electronic version for drugs such as morphine and cytostatics.

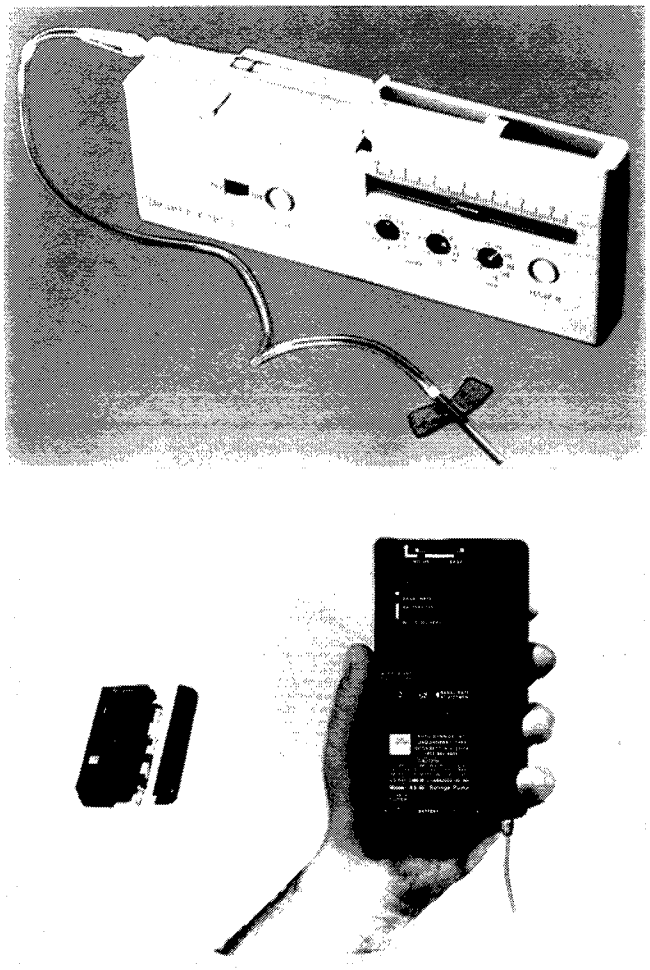

Fig. 1 Two types of syringe pumps: above Microjet MC2 from Miles, USA, manufactured by Cané, Italy; below AS*6C from Autosyringe/Baxter Travenol, USA (from company leaflets).

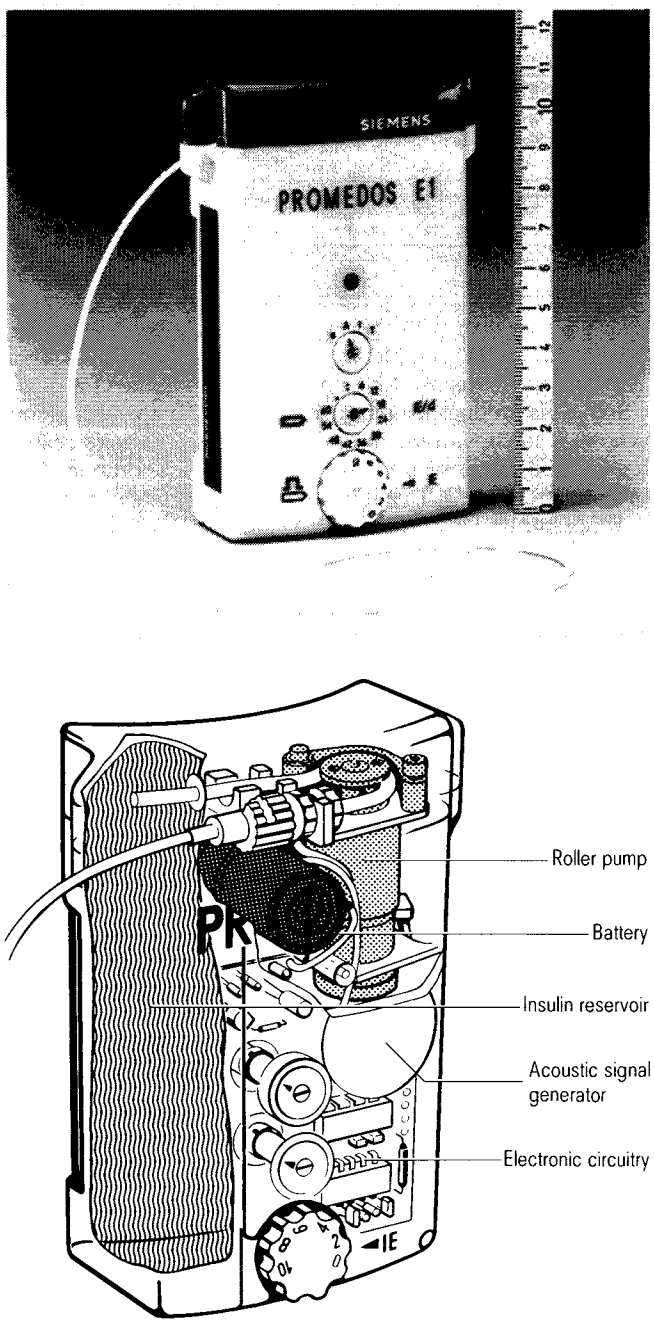

Fig. 2 Externally portable insulin pump that operates according to the roller pump principle, type PROMEDOS E 1 from the Siemens Company, Germany. Above: external view, below: interior.

Two developmental trends can be detected with the external devices: a. Simplification of operation with restriction to a constant basal rate for 24 h with superimposed prandial short-time boli. The prices for commercially available devices are at or below $ 1000. b. Highly sophisticated electronics with ability for programming basal rate and prandial dose profiles, automatic pump stop with non-operation and various other alarms. The prices extend up to $ 2500 per device.

With the general trend towards miniaturization of the devices, the reservoirs (syringes) are reduced more and more in size. Nearly all devices are suitable only for the s.c. route. The device shown in Fig. 2 represents an example with a long-term reservoir (30 ml) for the central catheter route (currently mostly i.p.), which is better from the point of view of metabolic regulation.

With the use for drugs other than insulin, the requirements for programming are more modest, and the ability to set a constant rate is usually sufficient. With central access routes, there is a need for a long-term reservoir that can contain at least a few centiliters because of the limited solubility of some drugs (FUDR, morphine, labor agents).

Implantable Devices

With implantable devices, the number of active companies is clearly lower than with the external devices because of the greater technical complexity. Only one company offers implants commercially for human use at present (Infusaid, USA). This product is a purely mechanical pump. A titanium bellows is filled with the infusion liquid through a pierceable septum and is pressurized by means of an evaporating fluid (freon) (30) (Fig. 3). The fluid is driven out through a capillary flow resistor into a suitably placed catheter. According to the Hagen-Poisseuille law, the supply rate depends upon the differential pressure between the bellows interior and the catheter tip and the viscosity of the fluid, in addition to the fixed dimensions of the capillary. The pressure in the bellows interior varies considerably with temperature and filling condition (because of the recoil force of the bellows). A change of 1°C induces a change of the internal pressure (and thus the rate) of approximately 4 % (31), and temperature fluctuations of 5°C can be easily imagined to occur 1 cm below the skin. The variability of the rate as a function of the filling level, full compared with empty, amounts to approximately 7 % (31)!

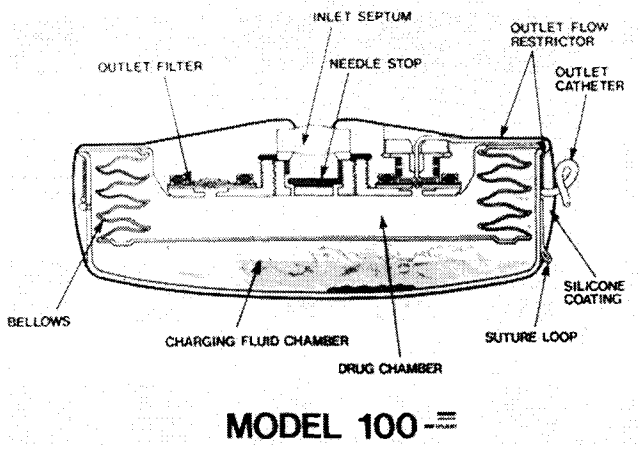

Fig. 3 Bellows pump from the Infusaid Company, USA (from company leaflet).

The pressure at the catheter tip fluctuates with the barometric pressure (height above sea-level), which is superimposed upon the physiological pressure at the site of application (e.g. in the vein or in the peritoneum). The viscosity is a function of the temperature. The viscosity is selected as high as possible with insulin infusions in order to achieve the desired low flow rate with the largest possible capillary lumen (minimization of the risk of clogging because of possibly precipitated insulin). All these factors together can lead to rate fluctuations of ±50 % under conditions that a person can be subjected to in daily life. Apparently users of the devices can cope with these fluctuations by special precautionary measures when flying, mountaineering, in the sauna, with fever, etc.

The rates of these devices can only be changed on a long-term basis by replenishment and therefore are only conditionally suitable for diabetes therapy. This statement concerns the commercially available devices. Naturally, a rate control by valves is conceivable, but because of the risk of large quantities of the drug flowing into the body in the case of a leaking valve (the drug is pressurized!), this has not yet been used in man.

Devices with controllable variable rates are necessarily electromechanical. The information transfer from the external programming or control device takes place electromagnetically or magnetically; storage in the implant occurs electronically. The drug delivery itself is necessarily a mechanical process.

Fig. 4 Implantable insulin pump that operates according to the roller pump principle, type PROMEDOS I 1 from Siemens Company with externally portable programming unit in the background.

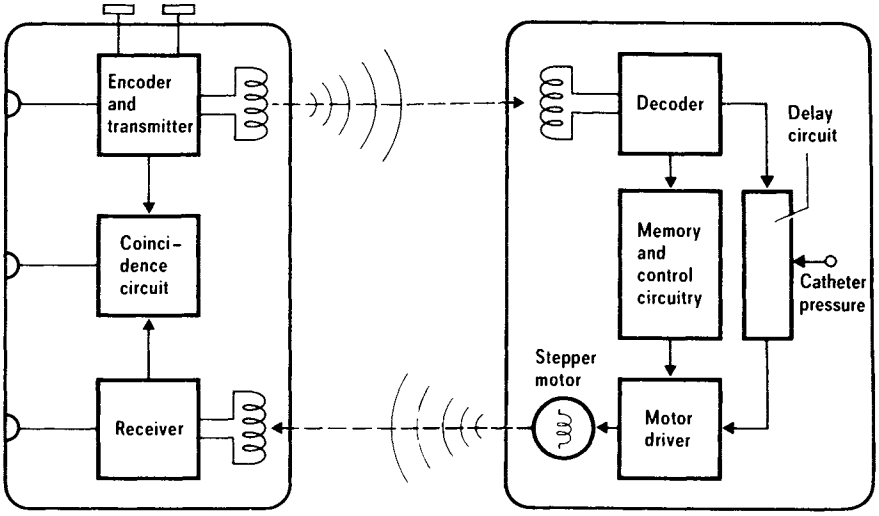

Fig. 5 Block circuit diagram of the devices of Fig. 4, signal transfer for programming the implant and for its monitoring.

Among the pumps with variable rates, only peristaltic pumps have so far been used clinically. The first pumps of Sandia-Laboratories and of Siemens Company (e.g. Figs. 4, 5) were implanted for insulin therapy during early 1981, and since 1983 devices from Medtronic Company were used in humans with morphine and cystostatic agents, and in animals also with insulin (32, 10, 33). A valve-piston pump, in principle comparable to a conventional membrane pump with the necessary sophistication, has been developed in cooperation between the John's Hopkins University, Parker Hannifin and Pacesetter, and it is undergoing animal experimentation (34). In fact, the valve-piston principle ranks among the earliest designs for drug delivery, with Bessman reporting on animal experiments as early as 1975 (40). This approach was discontinued. The same happened to another design described in (41) where the valve and piston were integrated in a plate of piezoelectric material. Already in the early 1970s and more recently, other groups were experimenting with pumps that operate according to the electro-osmotic principle (35–37) – nevertheless still in a very early development phase – and yet others with magnetic pellets (38). The latter consist of implantable plastic matrices in which the drug is distributed as in depot preparations. Iron particles are embedded additionally. The administration rate can be influenced by applying an external magnetic alternating field.

The general characteristics of the different pump principles have been compared recently (39). Only the main advantage or disadvantage that currently promotes or hampers their use for general drug-delivery purposes will be stated here.

Magnetic Pellets (38)

The rate control is not yet satisfactorily solved. This technique is in the early development stage.

Electro-Osmotic Pump

The problem of the consumption of the electrodes (with the design according to (35, 36) or that of the valves (37) as well as the replenishment of the reservoir are not satisfactorily solved.

Vapor-Pressure Pumps

Because of the simplicity of these bellow-capillary pumps they are well-proven for non-critical drugs that can be administered at predetermined rates with some variability as a result of varying external conditions.

For controlled drug delivery at variable rates, pumps of this type are not yet available, since the required totally leak proof valves are still lacking.

Syringe Pumps

While in wide-spread use for external devices and s.c. infusion (Fig. 1), they are technically difficult to realize for implantable devices (plunger return, replenishment valve); this approach has apparently not yet been attempted.

Valve-Piston and Membrane Pumps

The central problem is the susceptibility of the pumps to air bubbles located in or arising from the drug solution: gas in the pump chamber hampers the aspiration of further liquid because of its compressibility. Quantities of a few μl are able to prevent the pump from working. No means are reported so far to overcome this problem. The pulsated (non-physiological) delivery can also be a disadvantage with this principle when applied to the i.v. catheter route.

Peristaltic Pumps (e.g. Roller Pumps)

The quasi-continuous delivery that is also insensitive to bubbles and external influences permits a broad rate and application range. These pumps are already used clinically as external devices; with implants (exemplified by Fig. 4, 5) only higher stability requirements for the insulin preparation prevent their wide-spread use (this problem applies more or less to all other pumps as well, in addition to their other problems).

Drug Stability

Three new parameters, that do not occur with customary drug storage administration to this extent, arise with the administration of drugs using pumps.

a. the higher temperature (body temperature),
b. continuous movement by the pumping process and the motions of the pump user,
c. contact with different and partially new materials.

The drugs were not originally developed for this application, and they can be damaged under such conditions. Insulin is a particularly sensitive substance. All commercially available insulin preparations precipitate when they are subjected long enough to the conditions mentioned, the majority of them after a few days. Precipitation is as a rule connected with the loss of biological activity and clogging of the pump channels or

of the catheter. Apart from the evident precipitation of insulin with strong pH-shifts, either because of CO_2 diffusing in or because of substances leaching from the surrounding material, the mechanisms of precipitation with negligible pH-change are not yet completely clarified. It is assumed that upon contact and adsorption to hydrophobic boundary surfaces, the insulin molecules change their spatial structure; the molecules denaturize in this case and then combine to form oligomers (43, 44). These aggregates are anchored at rough spots on the device material, in dead spaces or joints in the pump tract, and can be compressed into solid blocks. One can attempt to counteract this phenomenon by solubility-increasing additives (e.g. zinc) and by additives which prevent drug deposition on the surfaces. Detergents can serve in this function, such as polyethylene-prolypropylene-glycol (43, 44), or lecithin (45, 47) in a concentration range of 10 to 50 ppm. A series of further additives have been examined (47, 48).

The results currently remain unsatisfactory for long-term insulin applications in implants. It can at present not be predicted if and when the necessary break-through with such additives will take place. In addition to the use of additives, completely new ideas might be necessary in order to emerge from the present dilemma. Other approaches such as sulphatation of the insulin (49) or the use of acidic insulins must be considered along with techniques that stand in opposition to the present trend towards native neutral mono-component insulin for diabetes therapy. Commercial standardized acid insulins from Hoechst have yielded excellent results over several years of use in externally carried devices with long-term reservoirs (according to Fig. 2).

Glucose Sensor

A severe handicap for the general introduction of therapy with externally applied pumps is at present the need for the patient to repeatedly measure the blood-sugar level. Consequently a long-term implantable glucose sensor could provide the solution of this problem, operated in the ideal case with feedback to the insulin pump. Fig. 6 shows diagrammatically such a potential device. Although the development of glucose sensors has been tackled for more than 10 years, a sensor stable even for a few days only has not yet become available for wide clinical use. A sensor in the form of a needle applied s.c. that is exchanged every few days would at least relieve the patient from piercing the skin several times daily for glucose measurements and would increase the safety against hypoglycemia and hyperglycemia, especially at night, by triggering alarms. Sensor development is currently directed towards this more modest objective since the realization of an implantable sensor which is stable for a number of years appears to lie in the uncalculable future. For long-term sensors, the principle of electrocatalytic oxidation of glucose on platinum electrodes is favored (50) (Fig. 7) that operates according to the formulae:

$$\text{Anode:}\quad \underset{\text{(glucose)}}{C_6H_{12}O_6} + H_2O \xrightarrow{Pt} \underset{\text{(gluconic acid)}}{C_6H_{12}O_7} + 2H^+ + 2e^-$$

$$\text{Cathode:}\quad \tfrac{1}{2}O_2 + H_2O + 2e^- \xrightarrow{Pt} 2OH^-$$

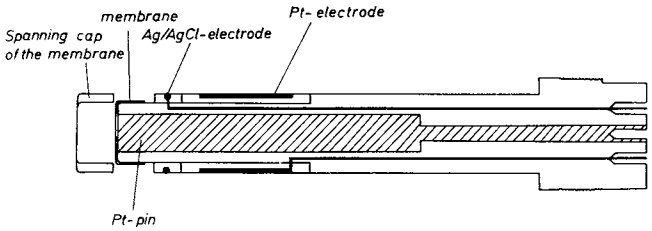

Fig. 7 Diagrammatic construction of a sensor that operates according to the electrocatalytic measuring principle (according to (50)).

The handicap of this sensor is the fact that apart from the glucose in the body, further substances that are oxidizable on the platinum electrodes and/or act as oxidation poisons are present or can arise during the measurement. This necessitates a high complexity of the design of the electrodes and of the electronic post-processing system for obtaining a glucose-specific signal (50, 51). A further general problem is the deposition of connective tissue on the sensor membranes. With the electrocatalytic sensor it is attempted to counter this phenomenon by using membranes with diffusion resistance that is high compared with that of the deposits. In this way the sensor properties are determined ideally only by the membrane properties. The low material transfer in turn requires an

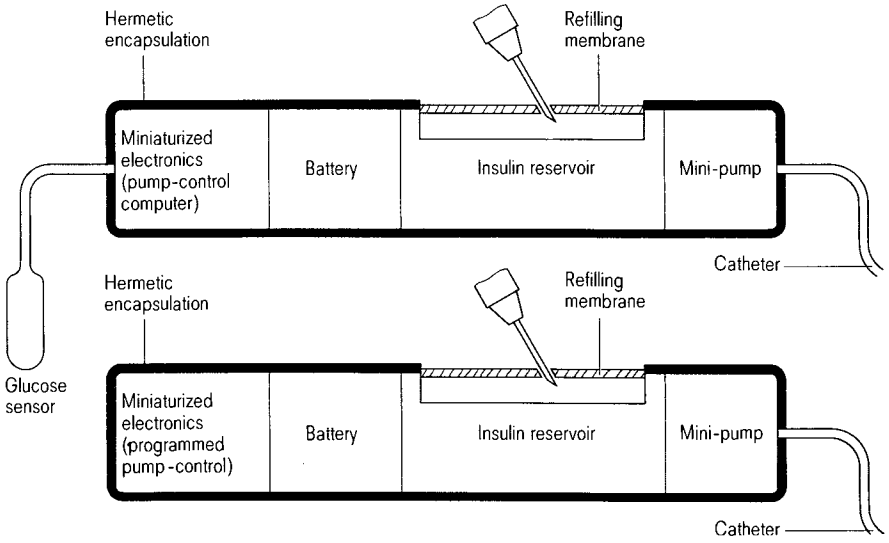

Fig. 6 Diagram of sensor-controlled implantable insulin delivery device that is targeted for development (above) and of a currently feasible program-controlled implantable device (below).

extremely high sensitivity of the measuring sensor which is achieved by artificial enlargement and special technology of the platinum surface amongst other techniques. The sensors constructed according to this principle have been tested ex-vivo (in the outflowing full blood). Routine use as implant is not to be expected in the coming years.

With the second sensor type, the enzymes sensor, glucose is specifically converted by the enzyme glucose oxidase (GOD) or glucose dehydrogenase by releasing H_2O_2. Either the H_2O_2 concentration or the reduction of the O_2 consumed is measured at a polarographic electrode (52) (Fig.8). The following formula describes the glucose oxidase reaction:

$$C_6H_{12}O_6 + H_2O + O_2 \xrightarrow{GOD} C_6H_{12}O_7 + H_2O_2$$

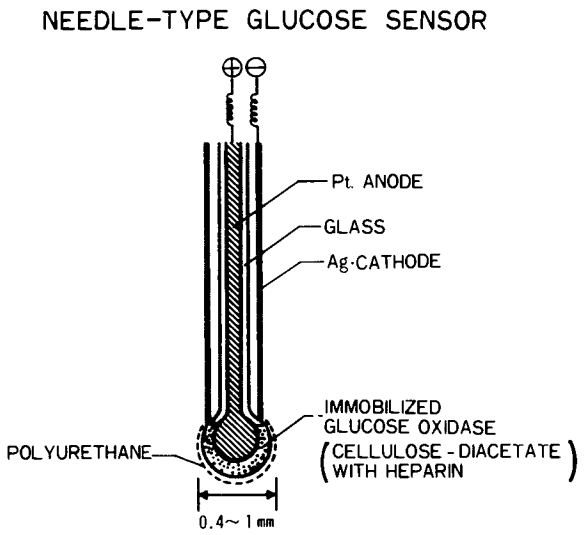

Fig. 8 Diagrammatic construction of a needle-shaped glucose sensor that operates on an enzymatic measuring principle (according to 53)).

In the current view, it is unlikely that this type will be suitable as a long-term sensor, since the enzymes have only a limited life (they are destroyed in particular by H_2O_2) and the sensor signal collapses because of coating by connective tissue (controlling this phenomenon in a similar manner to that with the electrocatalytic sensor has not yet been attempted or it is not possible because of the limited sensitivity of the enzyme electrode). With the sensors designed as needles and applied s.c., service times of up to one week are reported (53). The development is still in the laboratory stage with individually produced prototypes of electrodes. The problems of reproducible and cheap manufacture which, as experience with other sensors teaches, should represent the central problem, still oppose wide application. Furthermore, the problems of storing the electrodes and their possible pretreatment before application must be solved. (They must be in steady state when applied.)

Summary and Prospects

The development of the miniaturized insulin delivery devices has departed from its euphoric phase and is now restricted to exploit their proven advantages. A great deal of research work must still be performed before a broad and sustained break-through takes places. Diabetologists must prove conclusively – unfortunately with often still inadequate means – that the pump therapy 1) is better than alternative procedures for normalizing the metabolism, and 2) this normalization leads to avoidance of the feared late complications. This necessitates protracted and prospective investigations. Engineers and pharmacists must develop delivery systems and insulin preparations to permit long-term implantation at high reliability. The break-through for achieving adequate insulin compatibility with the pumps has not yet been made. Since the use of the method still suffers from the frequent blood-sugar measurements by the patient, real large-scale application, i.e. extending beyond the diabetic problem cases, is only to be expected with the availability of a long-term implant and glucose sensor. Such systems will very probably be widely used even before it is possible to prove any reduction in late complications, since the illness would no longer be apparent for the diabetic patient. Availability of a sensor is indeed not to be expected in the coming years, because of the problems inherent to it.

Because of the still pending clarification of fundamental problems it is at present difficult to predict how long the phase of cost-intensive research will continue. If this lasts too long, wide application may no longer result because in the meantime alternative therapy procedures have become available. For instance, this could be the implantation of B-cells in plastic housings (hybrid pancreas). In this case there are still many fundamental and even more difficult problems to be solved, such as cultivation of the cells, their reproduction or their replacement by new cells in the human body and those of the incapsulated membranes. The transplantation of the pancreas, or parts thereof does not provide an alternative to pump therapy because of the limited number of donors. Further alternatives are conceivable that may arise from studies on the causative mechanisms of diabetes mellitus and its subsequent prevention (Cyclosporin treatment, for example). However, no solutions are expected from this in the short term.

A practical possibility is the development of oral or aerosol insulin preparations although no metabolic control comparable with pumps is likely because of their poor absorption characteristics.

The situation with other drugs such as morphine and cytostatic agents is different. Here one appears to just enter the euphoric phase of development. Since there is no need to wait for late complications, drug stability problem are much less severe and usually no sensor is required, the value and limitations of the method will be recognized much sooner, and in a few years either routine application of pumps will have become established or the method will have disappeared again. A multitude of drugs still await testing for effective use with delivery systems. Thus, the research with external and implantable delivery systems will extend over many years phase-shifted for the different drugs before one or another system emerges for routine application.

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