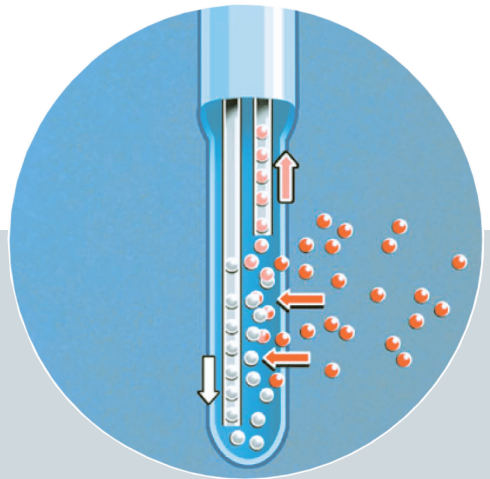


Towards an artificial pancreas

Patients with diabetes whose blood glucose levels are kept close to normal by means of suitable therapeutic measures avoid the risk of dangerous hypoglycemic episodes and develop complications of diabetes considerably less frequently and later than their less successfully treated counterparts. A precondition for this success is close monitoring of blood glucose levels. Therefore, a great deal of research activity has been directed towards the development of sensors that permit near-painless, continuous measurement of blood glucose level. The objective is to develop a system that pairs continuous blood glucose monitoring with an insulin pump and thus acts as an 'artificial pancreas'.



The days when ‘the only choice open to diabetes sufferers was that between death by coma and death by starvation’ [1] passed unmourned into history in 1922, when insulin was first used therapeutically. Even today, however, diabetes has lost none of its fearsomeness, because even today diabetics live in constant fear of overdosage or underdosage of their medicines, especially insulin, and of consequent hypoglycemic episodes and late complications¹ that can result from inadequate treatment and prolonged elevation of blood glucose level. The extent to which the blood glucose level of a diabetic can fluctuate is shown by the results of a study in which the blood glucose level of diabetics was measured continuously using the Accu-Chek® monitor developed by Roche Diagnostics (blue line in Fig. 1). And the extent to which these fluctuations are missed by blood glucose monitoring systems that take measurements only at longish intervals is shown by the black line in Fig. 1. For reference, the blood glucose level of a healthy individual generally ranges between 70 and 120 mg/dl.

Why continuous blood glucose monitoring is desirable

It is difficult to achieve good metabolic control in diabetics. Especially in patients on intensive insulin therapy, good metabolic control calls for frequent blood glucose determinations by patients themselves. The timing and dose of insulin injections have to be adapted to a variety of factors that influence blood glucose level, such as

- carbohydrate intake,
- physical exertion,
- sporting activities,
- stress (including operations, injuries and infections) and also
- rest periods such as periods spent asleep.

In addition to being painful and unpleasant, individual determinations of blood glucose by patients themselves using the conventional invasive techniques provide no more than a snapshot of the patient’s blood glucose level at the moment the blood sample was taken. Continuous glucose monitoring (CGM), by contrast, would detect fluctuations in blood glucose level over a prolonged period and indicate when major deviations from the

¹ See also p. 13.

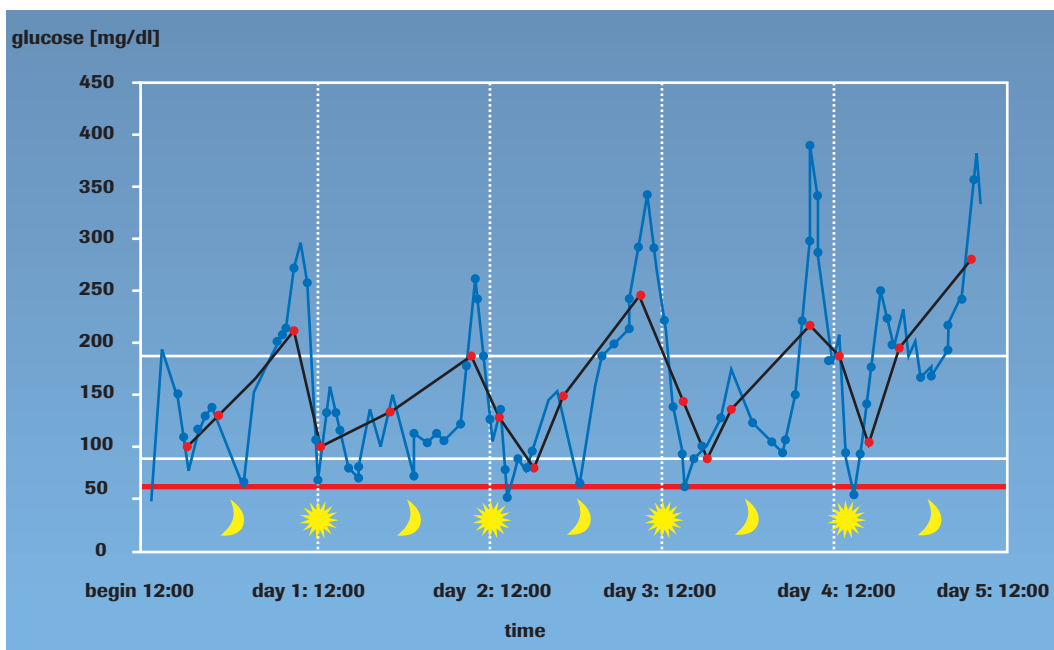


FIGURE 1: Comparison of the results of a series of individual blood glucose determinations (black line) with those of continuous glucose monitoring in interstitial fluid by means of microdialysis (blue line) in a 47-year-old male type 1 diabetic with a body mass in-

dex of 23.8 and an elevated HbA_{1c} level of 8.7%. It is clearly seen that individual blood glucose determinations fail to detect dangerous hypo- and hyperglycemic phases. (Source of figure: R. Kotulla, F. Hoffmann-La Roche Ltd)

normal range occur. Every diabetic could benefit from continuous monitoring of their blood glucose level. Continuous glucose monitoring would be of particular value, however, in

- in intensive insulin therapy, in which it is difficult or impossible to maintain blood glucose at near-normal levels, and thereby avoid hypoglycemic episodes, on the basis of individual blood glucose determinations,
- in diabetics in whom the HbA_{1c} values indicated on p. 49 are not achieved despite intensive insulin therapy,
- in patients who have suffered repeated hypoglycemic episodes,
- in pregnant diabetic patients, in whom HbA_{1c} values fail to detect large fluctuations in blood glucose level,
- in patients with impaired glucose tolerance and
- in newly diagnosed type 2 diabetics.

Continuous blood glucose monitoring provides far more information than HbA_{1c} values, commonly regarded as the body's

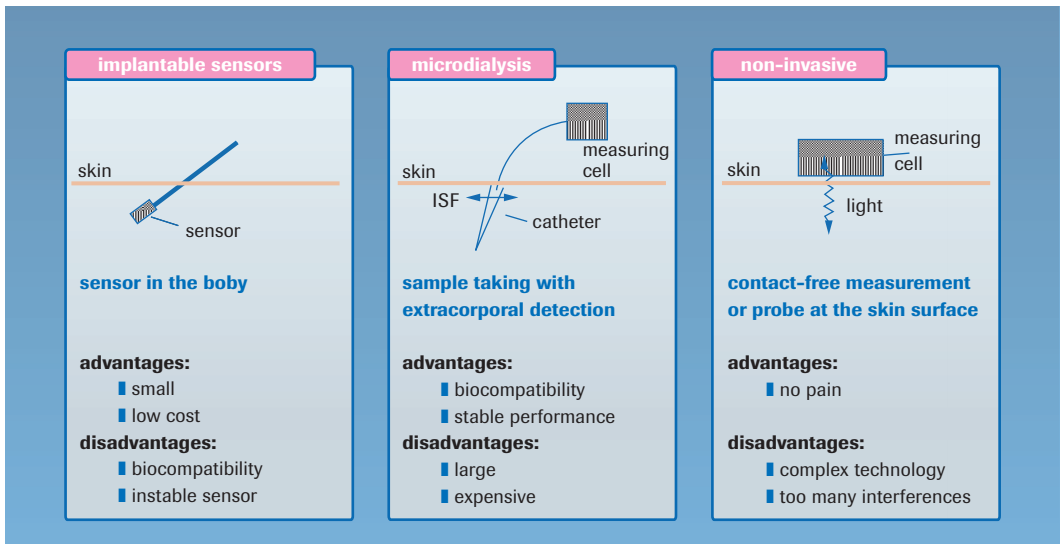


FIGURE 2: Various techniques for continuous glucose monitoring. ISF = interstitial fluid. (Source of figure: R. Kotulla, F. Hoffmann-La Roche Ltd)

‘memory’ of blood glucose levels. Patients whose level of compliance with their prescribed diet and other therapeutic measures is deficient would see how high their blood glucose level rises and might thereby be motivated to take their treatment more seriously. And of course, continuous glucose monitoring could be of inestimable value as a means of testing the efficacy of new oral antidiabetic agents. The development of a glucose sensor suitable for everyday use that provides a continuous series of values that accurately indicate current blood glucose level is also the first step towards the development of an artificial pancreas. According to Professor T. Koschinsky, everyone involved in the treatment of diabetes will find CGM to be just as important a step forward as was the introduction of self-testing of blood glucose by patients [2].

The basic types of system that can be used for this purpose, and the major advantages and disadvantages of these various systems are summarised in Fig. 2. Clinical studies have shown that CGM can be based equally well on measurement of glucose concentration in interstitial fluid² (ISF) as on measurement of glu-

² Interstitial fluid is found between cells and tissues under the skin.

cose concentration in capillary or venous blood [3] (for an explanation of this, please refer to the section on microdialysis). To this end, either the skin must be pierced by minimally invasive glucose sensors (glucose electrodes) or else ISF must be transported out of the body through the skin (e.g. by iontophoresis or microdialysis). In all the systems developed to date, the values measured in ISF are converted into blood glucose values on the basis of periodic parallel blood glucose determinations.

Glucose electrodes

In mid-1999 the US Food and Drug Administration granted initial, limited approval for the use of subcutaneous (below the skin) glucose sensors produced by Medtronic-MiniMed that perform continuous glucose monitoring in ISF over a period of 72 h. These sensors consist of an electrode whose tip contains the glucose-specific enzyme glucose oxidase. The reaction catalysed by this enzyme gives rise to an electrical signal the strength of which is proportional to the glucose concentration in the ISF. The electrodes are inserted into the patient's subcutaneous fatty tissue. Unfortunately, the electrodes show only limited biocompatibility. The human body reacts to the foreign material and in so doing brings about changes in the sensor surface that result in a reduction in detected signals, i.e. 'sensor drift' occurs [4]. In order to compensate for this drift, at least one blood measurement has to be performed each day for the purpose of calibration.

Can it also be done non-invasively?

Use of electromagnetic radiation, e.g. light, is one possible way of determining glucose concentration non-invasively, i.e. without puncturing the skin. Potentially, information about glucose concentration can be obtained by measuring either direct interactions between glucose molecules and electromagnetic irradiation (e.g. measurement of light absorption by spectroscopic methods) or indirect effects of glucose on skin properties (measurement of light scatter). However, only near-infrared light in the wavelength range of 600–1300 nm is able to penetrate intact skin to a depth of several centimeters to reach the deeper layers that are perfused by blood [4]. Light of wavelengths below or above this range is absorbed by water, tissue constituents, skin pigment and blood.

Absorption of light

So far, attempts to determine glucose concentration by means of infrared spectroscopy have yielded sufficiently accurate results only in the laboratory, with the aid of a spectrometer. Attempts to measure glucose accurately through the skin of human subjects have failed because the absorption spectrum of glucose in the near-infrared range does not differ sufficiently from that of other tissue constituents. Moreover, the concentrations of glucose found in tissue are very low compared to those of other light-absorbing substances, in particular water, and the relatively small changes in glucose concentration that need to be detected can be calculated only with the aid of complex mathematical algorithms.

Scattering of light

Calculation of changes in glucose concentration by measurement of diffusely reflected light is actually based on measurement of changes in the refractive index of intracutaneous (within the skin), intravascular (within vessels), interstitial and intracellular fluids. An increase in glucose concentration in these fluids leads to an increase in the refractive index of the fluids concerned. By contrast, the refractive index of the light-scattering interfaces of the skin is unchanged [4]. From these changes in refractive indices, changes in glucose concentration can be calculated. Here again, however, the mathematical analysis is complex, since scattered light is always overlaid by an absorbed component.

The fact that both these techniques are highly temperature-dependent has greatly complicated the development of systems for everyday clinical use based on them.

Reverse iontophoresis

Another possible way of measuring glucose concentration non-invasively is via the sampling of glucose-containing ISF by reverse iontophoresis followed by glucose determination outside the body. In reverse iontophoresis, a weak electrical current is applied to the skin surface in order to transport certain substances (ions, tissue fluid and substances contained therein, e.g. glucose) through the skin and out of the body, instead of into it, as in normal iontophoresis. A system based on this principle and worn as a wristwatch has been available commercially since 2001. A later product based on the same measurement principle

has been available since September 2002, however according to its manufacturer, Cygnus, the GlucoWatch® G2 Biographer may be used only in combination with a blood glucose measuring device. Calibration with blood glucose values is required each time the sensor is changed, i.e. at intervals of about 13 hours. Profuse sweating or a fall in skin temperature can stop measurement, and the electrical current can cause skin irritation.

Simulating the action of capillaries

Of the various techniques that can potentially be used for minimally invasive glucose monitoring, microdialysis, which, like reverse iontophoresis, measures glucose concentration in ISF, seems the most promising [5].

Microdialysis technology aims to simulate the action of capillaries [3]. A catheter incorporating a thin dialysis fibre is introduced into the patient's subcutaneous fatty tissue. The fibre is irrigated with isotonic glucose-free fluid. Via pores in the dialysis fibre and catheter, this irrigating fluid (perfusion solution) is in a state of constant interchange with the ISF surrounding the catheter (Fig. 3a). As a result of the prevailing concentration gradient, glucose migrates from the ISF into the glucose-free perfusion fluid.

The catheter flow rate is selected so as to establish an equilibrium at the external surface of the catheter, i.e. so that the glucose concentrations inside the catheter and in the ISF are the same. The perfusion solution, enriched in this way with glucose from the ISF, is pumped to a glucose sensor situated outside the body, where its glucose concentration is measured continuously (Fig. 3b). Parallel measurement of the concentration of glucose in the blood and ISF makes it possible to derive blood glucose values from all subsequent ISF glucose values.

As glucose is supplied to tissues via the capillaries, abrupt changes in blood glucose levels can cause the glucose levels in the capillaries and ISF to differ (see Fig. 4).

In addition to a physiological time lag, a physical time lag must be taken into account in microdialysis. This delay between a change in the value of a parameter and the detection of such a change is a function of the measurement system and is constant for a given measurement system. It depends upon

- the distance the measurement solution has to traverse from the microdialysis catheter to the measurement site,

- the perfusion rate, which in this case is between 0.1 and 10 $\mu\text{l}/\text{min}$ [5] and of course
- the speed of the detection reaction.

The physical time lag of the Accu-Chek[®] monitor developed by Roche Diagnostics is 30 minutes. The Accu-Chek[®] monitor, which is expected to become available for hospital and ambulant use under medical supervision in July 2003, provides the longest period of continuous measurement of any glucose monitoring system developed to date. It permits measurement of glucose levels at 5-minute intervals for four days. This is equivalent to 288 values per day as compared with the 5–8 values that can be obtained using currently available blood glucose self-testing systems. Calibration with a blood glucose value measured in capillary blood is required once every 24 h. The system is well suited to retrospective determination of blood glucose fluctuations and will be an important tool for determining the optimal insulin dosage regimen for individual patients.

Outlook

Now that a reliable CGM system has been developed, the next step on the road towards an automated or semi-automated pancreas is to pair CGM data with insulin pumps. Such pumps are already available. They permit

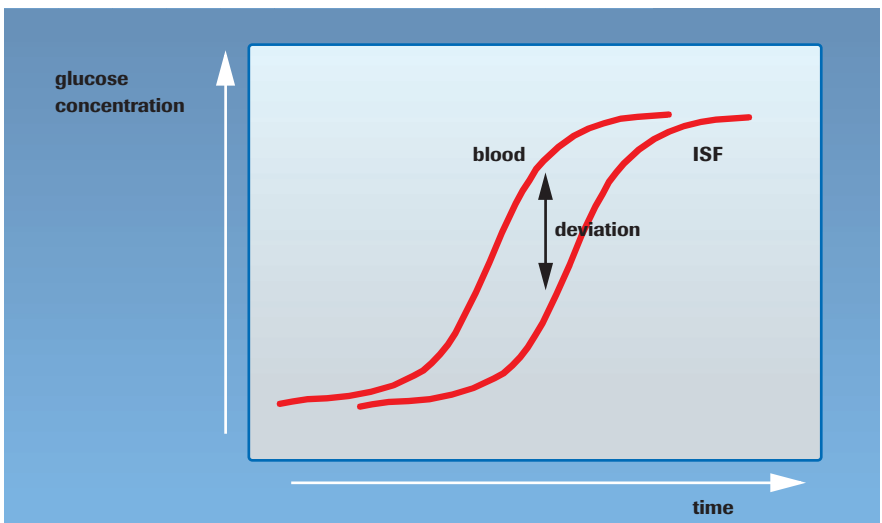


FIGURE 4: Relationship between glucose concentration in blood and that in interstitial fluid (ISF). (Source of figure: R. Kotulla, F. Hoffmann-La Roche Ltd)

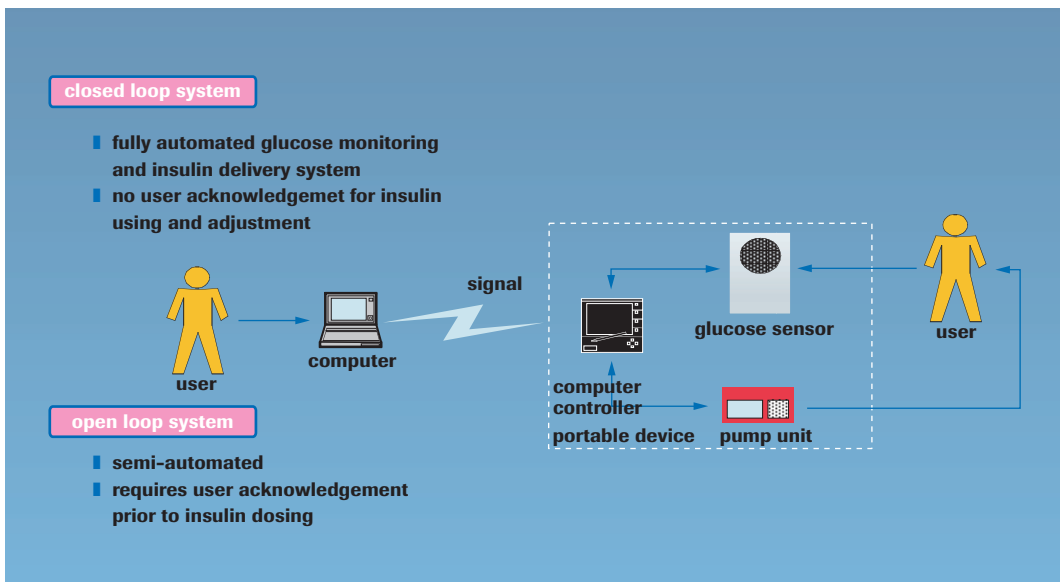


FIGURE 5: In a fully automated ('closed loop') artificial pancreas, a computer controls the amount of insulin delivered by a portable insulin infusion pump on the basis of readings obtained by an in-vivo glucose sensor so as to keep the patient's blood glucose at near-normal levels at all times. The computer calculates the required insulin doses using a feedback algorithm. The

first step on the road to such an artificial pancreas is clinical testing of a semi-automated, or 'open loop', system. In this system, insulin is infused only after acknowledgement or adjustment of the dose by medical staff or the patient. (Source of figure: R. Kotulla, F. Hoffmann-La Roche Ltd)

subcutaneous or intraperitoneal (within the peritoneal cavity) administration of insulins. Notwithstanding the risk of infections that exists with it, the latter variant, in which the catheter lies free in the peritoneal cavity and the pump is implanted in a pocket of muscle in the abdominal wall, seems preferable, since under physiological conditions the pancreas releases insulin into the circulation via the portal vein. The first organ perfused by blood in the portal vein is the liver. About 50 % of the insulin normally released by the pancreas is absorbed during its first passage through the liver, which is an important organ for the hormonal action of insulin. Half of the insulin released by the pancreas thus fails to reach the peripheral circulation and all the other sites of action of insulin. When administered into the peritoneal cavity, insulin is rapidly absorbed through the peritoneum (the epithelial tissue that lines the abdominal cavity and coats the abdominal and pelvic organs). From there it enters the portal circulation directly. This avoids the peripheral hyperin-

sulinemia that can occur with subcutaneous insulin administration [6]. Independently of how, where and in what form insulin is delivered via a pump, however, calculation of the individual insulin doses required is a major problem. Any program designed to calculate the individual insulin doses required must take into account not only the glucose levels measured at the time concerned, but also all the factors referred to above that can influence blood glucose level. For this reason, the first artificial pancreas – or to be more precise, artificial pancreatic β -cell – systems to be developed are probably ‘open loop’ systems. In these, every insulin dose to be delivered by the insulin pump has first to be acknowledged by the patient (Fig. 5). If the value of such semi-automated systems can be satisfactorily demonstrated in clinical studies, closed loop systems can be developed. In these, CGM and insulin administration would be performed fully automatically with no external intervention. Such systems could greatly simplify the life of insulin-dependent diabetics. Fear of dangerous hypoglycemic episodes would then become definitively a thing of the past. Moreover, the higher cost of such systems as compared with present forms of insulin therapy would – without even considering the savings in terms of human suffering – be more than offset by huge savings in terms of the cost of dealing with late complications of diabetes such as renal damage, blindness and need for amputations.

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