
Perspectives in Diabetes

Development of the Implantable Glucose Sensor

What Are the Prospects and Why Is It Taking So Long?

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The development of an implantable glucose sensor for use in diabetes was first suggested in the 1960s (1–3). The sensor would provide an alternative to the present discrete methods of glucose determination that are based on intermittent blood sampling. Continuous glucose sensing would be particularly important in the detection and management of hypoglycemia. It would also allow early detection of hyperglycemia and provide a basis for insulin administration at more appropriate dosages and timing or for automatic insulin delivery from a pump. An implantable glucose sensor could also be used in parallel with other existing or potential forms of insulin replacement, such as transplantation or hybrid islet devices.

Since the 1960s, a modest research effort has been devoted to implantable glucose sensor development. There has been significant progress, a considerable number of publications have appeared, and several candidate implantable glucose sensors have been partially developed. There is no shortage of investigators who feel they have promising approaches. By many standards, implantable glucose sensor research is a relatively mature and well-worked research field. Results of the Diabetes Control and Complications Trial (4) also suggest a clear need for the sensor. Most people with diabetes remain enthusiastic about the possibility of eventually having such a device, although they are unsure about its present status. With all of this, one must ask, *Why has an implantable glucose sensor not yet appeared in the clinic?*

The reasons are subtle. In our view, there exist questions and controversies about several key issues related to sensor design and validation in certain applications. Resolution of these issues requires implantation studies in animals and humans as part of a limited program of focused basic research before extensive industrial development of the sensor and clinical trials can be effectively carried out. It is our experience that this research has not been adequately funded by public sources because of the perception that the technology is sufficiently advanced that industry should assume the responsibility. Industry, however, does not view

support of the remaining research as its mission and either has not embraced sensor development or, in certain cases, has attempted to pursue development without resolution of key scientific issues. This has resulted in ineffective and unsuccessful efforts. There is a need to bridge this important information gap so that effective development can proceed.

We give our perspectives here with the hope that a consensus can develop that leads to a more direct route for clinical introduction of the sensor.

SENSOR CONFIGURATIONS AND POTENTIAL APPLICATIONS

When ultimately implemented, the implantable glucose sensor may take several configurations.

A *short-term intravenous sensor* similar to a catheter would be used in hospitalized patients for up to 72 h. This application may be useful in diagnosis and glycemic stabilization, management of ketoacidosis, and monitoring of surgery and recovery, labor in mothers with glucose instabilities, intensive care of certain neonates, and other similar situations.

A *short-term subcutaneous sensor* would be inserted into subcutaneous tissues of nonhospitalized patients for periods of several days. The sensor would be connected percutaneously to an external data storage and display device in the form of a wristwatch or belt-mounted beeper. This type of sensor will be attractive if it is inexpensive, does not require frequent recalibration, and can be considered disposable. Industry has devoted attention to this application at the expense of other implant applications because of its perceived commercial potential.

A *long-term sensor* would be implanted either intravenously or in tissues for periods of up to 1 year. This sensor could be coupled to an implanted telemetry system that transmits information to an external receiver, making percutaneous components unnecessary. This configuration will have to be easily inserted and retrieved with minimal surgery. Recalibration may be acceptable if simple and infrequent (say, monthly). In each of these configurations, the sensor could be used either as a monitor or as part of an automatic feedback-controlled insulin delivery system.

SENSOR DESIGNS

The most advanced glucose sensors are based on immobilized glucose oxidase coupled to electrochemical systems. One version is the *hydrogen peroxide-based enzyme electrode sensor* (5–12). This design has a membrane containing

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immobilized glucose oxidase coupled to a peroxide-sensitive catalytic anode. Glucose and oxygen diffuse into the membrane, where an enzymatic reaction occurs in which peroxide is produced. The peroxide diffuses through an underlying porous membrane to the anode, where it is electrochemically oxidized to produce the signal current. The external component of the current passes from the anode through the membranes and tissue or blood to a nearby cathode.

The signal of enzyme electrode sensors can be related to glucose concentration when the following conditions are met. First, there must be a means of countering the relatively low ratio of oxygen to glucose in the body, a problem known as the oxygen deficit (13). Ample oxygen must be made available by membrane design or other means to avoid oxygen limitation of the enzyme reaction. Second, electrochemical interference caused by small endogenous molecules that pass through the membrane must be insignificant (14). Third, any change in sensitivity with time due to enzyme inactivation must be accounted for (15). Fourth, the diffusion field in front of the sensor must remain undisturbed.

These conditions can be met in vitro in simple solutions with the peroxide-based sensor, but there are differences of opinion as to whether all are achievable in vivo with this design. Membranes having relatively high oxygen solubility may be helpful to minimize the steady-state oxygen deficit (10,11,13), but this sensor design provides no means to account for the effects of local oxygen variations on the signal. Membranes have been proposed (16,17) that may partially counter the problem of electrochemical interference, which is substantial with this sensor design (14,18). However, peroxide-mediated enzyme inactivation (15) is inevitable with this design. Frequent recalibration may be necessary to account for interference and enzyme inactivation. Commercial in vitro versions of this sensor have provisions for automatic rinsing and recalibration between samples, but there is no assurance that a stable continuous implantable sensor can be achieved by this approach. Given these inherent characteristics, this sensor design may be limited to short-term applications at best.

An alternative is the *oxygen-based enzyme electrode sensor* (3,13), which has a membrane containing immobilized glucose oxidase coupled to a membrane-covered electrochemical oxygen sensor. Glucose and oxygen diffuse into the membrane and react, resulting in a reduction of the amount of oxygen that would otherwise be detected by the oxygen sensor. The signal current is subtracted from that of a similar reference oxygen sensor without the enzyme, and a glucose-dependent difference current results.

This approach has several important advantages (19). First, catalase can be co-immobilized in excess within the membrane to forestall peroxide-mediated glucose oxidase inactivation. This is obviously not possible with the peroxide-based sensor. Second, a confluent nonporous hydrophobic membrane is used between the enzyme layer and electrode surface to prevent access of polar molecules to the electrode surface. This vastly reduces electrochemical interference compared with the peroxide-based sensors, which must use porous membranes. The hydrophobic membrane also completely retains the current within the sensor. Third, the use of the reference oxygen sensor in conjunction with an appropriate glucose sensor design can eliminate the oxygen deficit and render glucose determination transparent to oxygen. The nominal disadvantage of this approach is that

the sensor has more components and may therefore be more difficult to fabricate.

Recent innovations in this sensor design include a two-dimensional cylindrical configuration in which oxygen enters the enzyme region from the end and side, while glucose enters from only the end, allowing adequate oxygen availability even at substantial concentration mismatches (20), and development of a three-electrode potentiostatic oxygen sensor (21), which is much more stable than the well-known two-electrode Clark oxygen sensor. In addition to new design features, there is now a better understanding of factors that affect the stability of the immobilized glucose oxidase: The immobilized enzyme is remarkably stable under certain conditions but can decay rapidly in the presence of hydrogen peroxide (15). Sensor designs that incorporate an enzyme reserve, include co-immobilized catalase, and promote relatively low catalytic generation of peroxide are advantageous (22).

Another sensor design is the *mediator-based enzyme electrode sensor* (23–25), in which electron exchange molecules included in the enzyme region take the place of oxygen to shuttle electrons between the enzyme and electrode surface. This feature is intended to avoid the oxygen limitation. There is a reduction in sensitivity to oxygen with this design. However, the problem of electrochemical interference remains, and there is a potential for mediator washout. A successful sensor for in vitro glucose determination has been developed by this approach, but is difficult to adapt to in vivo applications.

Continuous *microdialysis* is also being considered as a basis for glucose sensing (26,27). The concept involves the use of a small hollow fiber inserted under the skin through which a buffer is circulated and returned to an external glucose analyzer. Extracellular glucose is detectable in this manner, but there are often significant response lags due to glucose equilibration. A possibility exists for development of this type of device for short-term applications, but convenient long-term applications are unlikely because of the obtrusiveness of the apparatus.

Membrane-covered catalytic electrodes have been studied extensively for glucose sensing (28,29), but problems with selectivity to glucose and electrochemical interference remain substantial.

Noninvasive optical glucose sensor concepts have received considerable attention in recent years. The premise is that light in the near-infrared or other region of the spectrum that has some sensitivity to glucose is beamed on a relatively transparent region of tissue such as the finger web (30). The transmitted or reflected light signal is processed by mathematical filtering techniques to maximize any aspects of the signal that may show some correlation with blood glucose samples obtained at the time of the observation. The overwhelming problem with this approach is the lack of adequate selectivity for glucose. There is substantial chemical interference from many biological molecules, as well as physical interference from tissue structures, temporal and spatial variations in perfusion, and several optical effects. In addition, there is a fundamental reservation about calibration of the device: The retrospective correlations between signal and blood glucose concentration described above change with time and are not useful for real-time monitoring. These issues must be resolved by systematic mechanistic studies before further development by industry can be justified. The

best hope for this approach may be to establish a separate qualitative relationship for each user that detects large glucose changes. However, even this degree of response will be very difficult to validate at best and may lead to a sensor that is of minimal clinical value. Despite substantial industrial investment, media attention, and considerable enthusiasm on the part of proponents, prospects for implementation of a noninvasive glucose sensor in the near future are not encouraging.

A variety of *other sensor concepts* have been explored, including glucose oxidase coupled to thermal sensors (31), osmotically active gels (32), and fiber-optic sensors with glucose-sensitive ligands (33,34). Some of these approaches have been the basis of devices that can respond to glucose in buffer under ideal conditions, but there should be little expectation that these devices can function as implantable sensors.

Other types of sensors are sensitive to certain *physiological effects of glucose*. Simple bare electrodes or other sensors responsive to local microvascular perfusion, temperature, or potassium fluxes can often register a change in signal immediately after a glucose injection because of the effects of glucose on a variety of physiological phenomena. This has led to the hope that monitoring these phenomena might reliably indicate glucose concentration. In reality, the signals are only weakly related to glucose and are not specific. Moreover, this approach requires independent prior knowledge of glucose challenges and is not effective for detection of spontaneous glucose changes. In our view, it is unlikely that reliable glucose sensing can be achieved by this route.

IMPLANT STUDIES

Short-term subcutaneous implants. The short-term subcutaneous sensor is the most difficult application. The peroxide-based sensor has been fabricated in the form of a needle and implanted in dogs (35,36), rats (8,12), and pigs (24). The sensors typically remained in place for several days and signals were recorded in response to intravenous glucose challenges. The sensitivity and baseline of each sensor's output were independently adjusted after each experiment. Anesthesia was used during testing in most cases. The most common experimental protocol was to determine how closely statistical averages of signals at discrete times from various sensors correlated with statistical averages of blood glucose concentration. Responses of sensors that did not meet expectations were often ignored. Because of the emphasis on statistical correlation, there was no attempt to interpret the signals of individual sensors, although an interpretation of this kind is necessary for actual application of the sensor. Little understanding of the factors that affect glucose transport to implanted sensors was revealed. These studies show that subcutaneous sensors can sometimes produce a response to blood glucose challenges under ideal conditions, but it remains unclear whether the response can be useful for glucose monitoring.

There has also been an attempt to use the peroxide-based sensor as a long-term implant in dog subcutaneous tissue (11). The sensor and a telemetry unit (37) were implanted for periods of up to 90 days. The sensor signal decayed continuously over the implant period, and the sensor required recalibration before each recording session. No determina-

tion was made of the maximal period the sensor could operate accurately without recalibration, although this was apparently only a few days at most. Thus, even though the implant remained in place for up to 90 days, it could not be considered a reliable, functioning sensor for that period. It would not be feasible for such a sensor to accurately indicate spontaneous glucose fluctuations or be used for purposes of continuous control. The authors reported that the range of sensitivity to glucose decreased significantly over the implant period because of an increasing oxygen limitation, even after recalibration. This may have been caused by enzyme inactivation, progressive electrochemical interference, or an advancing tissue reaction. The important question of whether the limitations were due to sensor design, tissue remodeling, or local physiological phenomena was not considered. The many questions raised by this study remain to be addressed.

The peroxide-based sensor in the form of a fine needle has been used as a short-term subcutaneous implant in humans (7,10,38–40). In these studies, sensors were connected by percutaneous leads to wearable instrumentation and there was no need for local anesthesia. Statistical correlations were reported between groups of sensor responses, and averaged blood glucose concentrations were determined by a standard method. As judged by *in vitro* characterization before implantation, sensors typically had a rapid response to concentration changes and were linear over clinically useful ranges. Most studies noted a substantial decay in signal over the several-day implant period, but the sensor responses were typically adjusted after the experiment to correspond to actual blood glucose values. One group (40) used a rapid recalibration device that adjusted readings during use based on glucose values determined by frequent blood sampling. Extensive histological studies of the sensor environment were not feasible in humans.

Although most investigators interpreted these results as highly promising, in our view, there are a number of reservations. First, there is the problem of decay in sensitivity over the implant period. This has led to the use of retrospective calibration, in which the sensor sensitivity is adjusted after the experiment to match independently determined steady-state blood glucose values. In addition, the actual values of the signal without recalibration are not often reported, making it difficult to compare actual rates of signal decay. The correlation between steady-state blood glucose and retrospectively adjusted signal conveys the impression that the sensor can be useful in real time, but in fact, monitoring in real time cannot be based on retrospective calibration unless there is a highly reproducible pattern of signal decay, which has yet to be established. Improved means of calibration must be developed.

Other reservations pertain to the tissue structure around the sensor. The technique of sensor insertion may be of crucial importance, and there must be a means of knowing whether a functional placement has been achieved. Trauma associated with sensor placement leads to tissue inflammation and the wound-healing process, which may interfere with stabilization of the sensor signal. The insertion must not cause significant bleeding or lead to the formation of a reservoir of tissue fluid around the sensor. The resulting local hyperemia must stabilize rapidly after insertion and give rise to a stationary mass transfer field if reliable readings are to be expected. Given these considerations, it is unlikely

that the sensor can be inserted and used shortly thereafter to confidently administer medication. There is a need for better understanding of the effects, time course, and reproducibility of trauma associated with sensor insertion.

Data selection in these studies is also problematic. Because it is not possible to present all results, representative results must be selected. However, results selected with the intent of demonstrating that the sensor is working often do not indicate the range of responses typically obtained, which would be useful for a deeper understanding. Furthermore, reports of the percentage of apparently functional sensor implants do not convey the troubling inability to predict if a specific sensor that is functional *in vitro* will give meaningful signals when implanted subcutaneously. Data selection practices and incomplete description of results may unintentionally convey the impression that favorable results are more common than is actually the case.

In addition to issues of calibration, tissue stabilization, and data selection, it is our view that there is inadequate definition of the relationship between the signal of a sensor implanted in tissues and actual blood glucose values. A simple, stable proportionality that applies with confidence in all situations probably does not exist. If a generally useful relationship is found, it will be more complicated than presently appreciated. The glucose signal is affected substantially by dynamic physiological aspects of the sensor environment and changes in the environment with time. For example, microvascular perfusion of the site and therefore delivery of glucose to the sensor may be strongly influenced by transient events such as sympathetic stimulation, thermal effects, and hydrostatic variations due to posture, movement, etc. Unfortunately, most research to date has been directed at finding a simple statistical correlation between the signal and blood glucose concentration, rather than understanding the role of relevant physiological phenomena and developing a deterministic model of glucose transport in living tissue that can be used in a predictive fashion. Moreover, in many cases blood sampling has not been sufficiently frequent to clearly define blood glucose fluctuations. More carefully conceived research is needed to establish the generality of signal–blood glucose relationships.

There is likely to be no consensus on the ultimate promise of short-term tissue implant applications until these controversies are resolved. These questions have led to the most important difference of opinion—whether human trials of short-term subcutaneous sensors are presently justified. Early studies in humans have emphasized correlative, trial-and-error observations, rather than mechanistic research. Many questions can be more effectively addressed at present with animal studies. There is an urgent need for directed basic studies that lead to a better understanding of the sensor response in the tissue environment before the results of clinical trials can be interpreted. It will not be possible to effectively address deficiencies in response without a better basic understanding. Support for basic studies of this type does not fall in the domain of industrial research and must come from public sources. In all, there is much to be learned before the subcutaneous sensor can be operated confidently.

Short-term intravenous sensor. Technically, the short-term intravenous sensor for inpatient use is much more straightforward. The sensor could be coupled to an intravenous fluid flush system and may have no greater propensity for complications than the intravenous catheters presently in

use. Both the oxygen-based and the peroxide-based sensors have been operated intravenously in animals (8,41). No further basic research is needed, and this is the most direct route to clinical application of an implantable sensor, although the demand may be small relative to other potential applications.

Long-term intravenous sensor. The oxygen-based sensor has been implanted intravenously in six dogs for periods of 7–108 days (19). The glucose sensor was at the tip of a cylinder with a 2-mm outer diameter and a total length of ~30 cm. The sensor and a similar oxygen reference sensor were advanced into the jugular vein so that the tips were positioned in the center of the superior vena cava several centimeters above the entrance of the right atrium. The sensor leads were connected to a telemeter and instrumentation unit (42) implanted subcutaneously. No systemic anticoagulation was needed. The sensitivity to glucose, determined before implantation, during use, and after explantation, was not substantially altered by long-term implantation (19), and there was no need for recalibration during the entire period of the implantation. The experiments were not limited by immobilized enzyme lifetime, oxygen deficit, oxygen sensor instability, chemical interference, or biological incompatibility. These results demonstrate that this glucose sensor can function when implanted in the bloodstream of a dog for a period of several months and has the potential of operating for longer periods.

The success of the sensor as an intravenous implant in animals and the apparent biocompatibility suggest the possibility of use of this site for chronic implantation in humans. A catheter-like sensor that can be easily introduced into the vena cava, retrieved, and replaced every 3–6 months with a nonsurgical procedure may be clinically useful. This application raises a concern about patient safety: there is the possibility of clot formation or vascular wall damage. However, it is well documented that similar pacemaker leads and chronic drug delivery catheters implanted in the superior vena cava in humans can be biocompatible and are relatively innocuous (43,44). This sensor is ready for development by industry, and implementation in humans may be relatively easily justified. Lag-free intravenous blood glucose recording may become the gold standard and the most useful approach for control of insulin pumps.

OTHER ISSUES AND CONCLUSIONS

Development of an implantable sensor is not a trivial task. The fact that research has been under way for decades in this area should be no more surprising than the fact that research in any area takes time. However, the need for the implantable glucose sensor is now clearer than ever. Although there has been considerable progress on certain sensor concepts, disparate investigative approaches and development goals have led to some confusion.

Priority must now be given to consummation of the most advanced sensor approaches. There are no fundamental technical barriers to the use of oxygen-based sensors for short- and long-term intravenous applications, and given appropriate industrial commitment, these applications could be available within a few years. The peroxide-based sensor also has some promise, mainly for short-term applications. Both the oxygen-based and the peroxide-based sensors may eventually be useful in some capacity as subcutaneous

implants, but more focused research is needed on the physiology of sensor-tissue interactions. Certain long-term and intravenous sensor applications may actually be closer to clinical introduction and should be addressed more aggressively. Other sensor concepts are much farther behind. It is naive to expect that a significant new solution or breakthrough will come from a serendipitous discovery of the proverbial isolated inventor working with minimal resources.

A more meaningful industrial involvement is needed. At present, industrial attention is focused on subcutaneous applications, but advances must await the resolution of certain questions about sensor operation in vivo. The answers will come from targeted research supported by public sources. In addition, more emphasis is needed by industry on long-term applications. Some investigators have pointed out that large-scale manufacturing of reproducible and reliable sensors may also pose technical difficulties (10). This may be true if the cost of manufacture is a crucial factor, as it is for disposable short-term sensors.

It is now time to reach a consensus of investigators, funding agencies, and industrial partners so that implementation of the implantable glucose sensor can move ahead decisively.

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