BIOSENSORS MEETING UPDATE

IMPLANTABLE GLUCOSE SENSOR EXPECTED SOON

GÖHREN, G.D.R.—For patients afflicted with insulin-dependent diabetes mellitus (IDDM), controlling blood glucose at near-normal levels can best reduce the disease's long-term, life-threatening cardiovascular side effects. An implantable glucose sensor would greatly aid in controlling insulin delivery to IDDM patients. At the International Society of Artificial Organs Workshop on Intracorporal Sensors held here last September, 70 scientists, clinicians, and engineers from 11 countries were briefed on the latest achievements toward development of a research prototype needle-type sensor. Also discussed were the problems associated with short- and long-term implantation in tissue, and possibilities for *in situ* recalibration of an implanted glucose sensor.

Over the past 10 years, experimenters have been attempting to devise a sensor of suitable selectivity and stability that can be implanted in an appropriate site in the body. Now, it appears that the first such sensor, using subcutaneous needle placement, should be available soon for 24- to 48-hour test monitoring of glucose levels in hospitalized patients.

Both enzymatic and nonenzymatic approaches for constructing an *in vivo* sensor have been under study. Within the next 6–12 months, needle-type prototypes based on the enzymatic approach should be available for initial clinical studies in Europe. These first sensors will be from groups headed by E. Pfeiffer (University of Ulm Medical Clinic, Ulm, F.R.G.) and Uwe Fisher (Central Institute of Diabetes, Karlsburg, G.D.R.), who chaired the meeting.

In the U.S., Food and Drug Administration investigational device exemption approval will be needed before commencing initial clinical studies. Extensive animal testing most likely will continue throughout the clinicals to work out any material or design problems—especially difficulties in the stability of the tissue-prosthesis interface, particularly for longer-term implants.

In the enzymatic prototype, glucose oxidase provides the selectivity, with electrochemical or optical determination of oxygen consumption or hydrogen peroxide production as the output. Test results with the enzyme sensor placed subcutaneously in animals show the enzyme to be stable for at least several days. (Its stability over longer time periods is yet to be determined.) Restricting glucose diffusion to the sensor circumvents problems of oxygen deprivation. And subcutaneous—as opposed to intravenous—sensor placement circumvents clot formation.

Nonenzymatic clinical prototype sensors should follow a year later. Here, the glucose is directly oxidized electrochemically, with selectivity achieved through a complex transient potential applied to a plain platinum electrode. The current is sampled at selected applied potentials and related to the glucose concentration. The transient waveform can be designed to exclude current resulting from the oxidation of other endogenous compounds or therapeutic drugs.

This approach is undergoing animal testing at the Joslin Diabetes Center (Boston, MA), the University of Pittsburgh (PA), and Siemens AG (Erlangen, F.R.G.). Although free of the stability problems associated with the enzymatic approach, the practical degree of selectivity attainable over long-term use concerns researchers.

The consensus among conference attendees was that the problems associated with both short- and long-term sensor implantation in tissue are turning out to be the most difficult to solve. The acute inflammatory response of the subcutaneous tissue to the inserted needle sensor appears to alter its response time and possibly the interstitial glucose concentration over time. Sensor placement also is critical.

Lemuel Wingard (University of Pittsburgh) and Manuel Alvarez-Igaza at Cranfield Institute of Technology (Cranfield, U.K.) are experimenting with alternative stabilized-enzyme-based approaches to solve these problems of selectivity and long-term stability, using immobilized mediators or structures to give direct electron transfer without the use of oxygen or the formation of hydrogen peroxide.

Further research breakthroughs are needed, however, to reduce these alternatives to practice. These include devising methods to obtain direct electron transfer from the glucose-oxidase enzyme-cofactor complex to an electrode surface without the need for mediators, and the synthesis of less labile oxidation-reduction catalysts that retain a high selectivity for glucose. Crystallization and X-ray diffraction studies of deglycosylated oxidase to obtain evidence for the active site three-dimensional structure of the enzyme-cofactor complex should aid progress on newer glucose catalysts.

Also, to devise a longer-term implant, the problem of tissue encapsulation—which can alter response time—must be addressed. Edmund Spaeth (Baxter Technology and Ventures division of Baxter Healthcare, Irvine, CA) presented promising animal data on minimizing and stabilizing tissue capsule formation by means of sensor membrane surface texturing.

In many of the studies under discussion, special membrane coatings were used for the interface between the sensor and body fluids or tissues. Nearly all of the polymer formulations were highly empirical and not easily reproducible; more solid work is required.

And most worrisome, perhaps, to the conference attendees was the practicality of *in situ* recalibration to account for electrode drift. Clinically used sensors likely will require at least one-point *in situ* recalibrations, but technical flaws were identified in each single-point procedure described.

—Lemuel B. Wingard, Jr. and Edmund E. Spaeth