Feasibility of Continuous Long-Term Glucose Monitoring from a Subcutaneous Glucose Sensor in Humans

BARBARA J. GILLIGAN, D.V.M.,1,2 MARK C. SHULTS, M.S.,1,2 RATHBUN K. RHODES, Ph.D.,1,2 PETER G. JACOBS, M.S.,1,2 JAMES H. BRAUKER, Ph.D.,2 THOMAS J. PINTAR, M.D.,3 and STUART J. UPDIKE, M.D.1

ABSTRACT

The feasibility of continuous long-term glucose monitoring in humans has not yet been demonstrated. Enzyme-based electrochemical glucose sensors with telemetric output were subcutaneously implanted and evaluated in five human subjects with type I diabetes. Subject-worn radio-receiver data-loggers stored sensor outputs. Every 1–4 weeks the subject’s glucose levels were manipulated through the full clinical range of interest using standard protocols. Reference blood glucose samples were obtained every 5–10 min and analyzed in our hospital clinical laboratory and/or on glucose meters. The sensor data were evaluated versus the reference data by linear least squares regression and by the Clarke Error Grid method. After surgical explantation and device inspection, the tissue–sensor interface was evaluated histologically. The remaining sensor-membranes were also recalibrated for comparison with pre-implant performance. Four of the five glucose sensors tracked glucose in vivo. One sensor responded to manipulated glucose changes for 6.2 months with clinically useful performance (≥90% of sensor glucose values within the A and B regions of the Clarke Error Grid). For this sensor, recalibration was required every 1–4 weeks. The other three transiently responding sensors had electronic problems associated with packaging failure. The remaining sensor never tracked glucose because of failure to form any sustained connection to adjacent subcutaneous tissue. Thus, stable, clinically useful sensor performance was demonstrated in one of five subjects with diabetes for a sustained interval of greater than 6 months. While this glucose sensor implant technology shows promise in humans, it needs to be made more reliable and robust with respect to device packaging and sensor–tissue connection.

INTRODUCTION

Tight control of glucose is now well known to reduce the risk of complications from diabetes.1,2 However, to safely achieve tight control a reliable, painless, continuous method is needed to monitor blood glucose long term. Our approach to developing this technology is to implant a sensor based on the enzyme electrode principle into subcutaneous tissue.3–6 To be clinically useful and practical the sensor must be easy and safe to implant, provide reliable real-time blood glucose levels long term, and provide the trend information...
inherent in a continuous sensor. A major limitation to effective glucose sensing with a subcutaneously implanted sensor has been the development of scar tissue by the foreign body response to implanted materials. We previously reported the use of angiogenic membranes that stimulate a local capillary bed at the sensor head, resulting in successful continuous glucose sensing in canines for as long as 5 months with one sensor working effectively for over 1 year (authors’ unpublished data). In this brief report we document the initial feasibility trial in humans in which we demonstrate that the foreign body response barrier to glucose transport can be overcome in humans for up to 7 months. This clinical feasibility study was conducted in 1999–2000.

RESEARCH DESIGN AND METHODS

The sensor implants were designed and fabricated by Markwell Medical, Racine, WI. This sensor’s characteristics and glucose monitoring performance were previously described in a dog model and discussed in a review article. The sensor responds linearly from 40 to 400 mg/dL glucose even when oxygen is at a low physiological tension of 40 mm Hg. Sensors were constructed as previously described. Briefly, the glucose sensor consists of a sensing membrane with entrapped glucose oxidase placed over a polarographic H$_2$O$_2$ anodic electrode sensor. This sensing membrane is further covered by a proprietary bilayer angiogenic and bioprotective membrane similar to that in our dog model, which provides bioprotective and angiogenic functions. The bioprotective function is needed to prevent “environmental stress cracking” by tissue macrophages and the destructive oxidative species they release from gaining close proximity to the enzyme active membrane. The angiogenic function is needed to stimulate macrophages to release factors that initiate angiogenesis.

Pre-implant testing and sterilization

The sensor is calibrated in vitro prior to implantation. The sensor must perform linearly to glucose from 0 to 400 mg/dL at low partial pressure of O$_2$ (30 mm Hg) with <5% average error to qualify for implant. Stability of sensor calibration must then be maintained within ±15% for a week after the addition of the bilayer angiogenic membrane. Sterilization was performed using glutaraldehyde as described previously. Sterilant residue was removed by four consecutive 5-min rinses in copious sterile saline on a horizontal shaker in the operating room just prior to surgical implantation.

Human subjects

Five human subjects with type 1 diabetes, three men and two women with a mean age of 27.8 years (range 18–45 years) with a mean of 9.2 years (range 3–17 years) of insulin dependence, all reliable insulin pump users, were recruited using a research protocol and informed consent approved by the University of Wisconsin Human Subjects Committee and the Food and Drug Administration. Patients with a history of keloid formation were excluded. With the patient under local anesthesia in the University of Wisconsin Hospital Ambulatory Surgery Facility (Madison), each sensor unit (1.2 × 3.2 × 7 cm) was placed in a pocket created by blunt dissection in the subcutaneous tissue of the abdomen above the rectus muscle lateral to the midline, inferior to the umbilicus with the sensor head facing inward and residing in the deep subcutaneous tissue.

In vivo evaluation and calibration

Each subject wore a prototype radio-receiver data-logger that recorded the sensor glucose values every 128 s. The radiotelemetry system was based on principles and a design previously described, but reduced in size (19 × 10 × 6 cm) to be worn on a belt or shoulder strap. The sensor was studied intensively every 1–4 weeks with a Glucose Tracking Study (GTS) protocol consisting of glucose loading by the oral or intravenous route after fasting and/or subcutaneous insulin (lispro bolus via insulin pump) as needed to manipulate blood glucose through the clinical range of interest. Reference blood glucose samples were obtained every 5–10 min. Venous blood plasma samples were stored on ice and analyzed the same day in our hospital clinical laboratory.
Samples obtained by finger prick were run simultaneously on One Touch Profile™ (Life-Scan, Johnson & Johnson, Milpitas, CA) and LNX (San Diego, CA) In Charge™ glucose reagent strip meters. The glucose sensor data were evaluated by linear least squares regression (LLSR) analysis. The sensor lag time was determined by optimized LLSR analysis and used to calculate calibration factors. The clinical utility of the sensor response was determined by the Clarke Error Grid method and by evaluating the correlation coefficient.

**Oxygen limitation**

Glucose sensors based on the enzyme electrode principle require at least a minimal tissue O$_2$ tension at the sensor implant site in order to respond to glucose. When first implanted these sensors report zero or very low glucose levels due to oxygen limitation. Only after neovascularization occurs at the subcutaneous tissue-sensor interface within the foreign body capsule (FBC) that forms around the implant does the sensor start to respond to glucose. This angiogenesis-dependent start-up phase can be demonstrated as early as 6 days or be delayed 2 or 3 months for reasons not yet entirely clear to us, but possibly related to the large size, high mass (27 g), and high density (1.23 g/mL) of this early-model glucose sensor. It is widely known that glucose oxidase enzyme requires an excess of oxygen in order to function as a glucose sensor. When a sensor implant is reporting erroneously low glucose values, “oxygen limitation” is suspected. The presence of oxygen limitation was confirmed by having the human subject breathe 100% oxygen for 10–20 min. If the sensor response markedly increased to match reference glucose blood levels, only to fall well below these levels when the subject returned to breathing room air, then we concluded the sensor was oxygen limited. Eleven oxygenation studies were performed in four of the subjects when oxygen limitation was suspected.

**Evaluation of sensor explant**

Sensors were surgically explanted under local anesthesia in the University of Wisconsin Hospital Ambulatory Surgery Facility after a mean of 179 days (Table 1). The quality and extent of FBC formation at the sensor/tissue interface and the extent and quality of the fibrous tissue ingrowth into the surgical polyester fabric jacket (IMPRA 6108, Bard, Tempe, AZ) were examined grossly and studied histologically. The seal of the electronics package was inspected for leaks. An attempt was made to recalibrate the sensor using the pre-implant sensor qualification protocol. When the sensor packaging had failed causing failure of the electronics, the enzyme active membrane was removed and applied over a new functional electrode sensor assembly for testing.

**RESULTS**

**Safety**

This study found no safety problems related to the implant device in any of the human subjects. Adverse events consisted of the anticipated postsurgical discomfort, and mild seroma formation surrounding the implant in two of five subjects. Subjects elected to use analgesic medication for postoperative pain, as needed, for 2–8 days post-implant. The seromas resolved without intervention within 14 days.

**In vivo performance**

Four of the five glucose sensors tracked glucose *in vivo* at least transiently. One sensor responded to changes in glucose with clinically useful performance for 6.2 months (185 days). A total of 92 GTS were performed on the four functional sensors. Forty-two of the GTS (46%) showed evidence of sensor responsiveness to changes in glucose levels *in vivo* (Table 1).

The best sensor performance occurred in the second subject enrolled in the study. This sensor was initially oxygen limited and unable to track glucose levels, as confirmed during five oxygen inhalation studies between days 25 and 49. The exact mechanism of the oxygen limitation is not known but is thought to be due to inadequate vascularization of the sensor/tissue interface, perhaps caused by motion causing shear forces due to the large size and mass of the sensor. This sensor began tracking blood
glucose with excellent linear correlation to blood glucose values throughout the clinical range of interest during GTS beginning on day 81 and for an additional 185 days (6.2 months) thereafter. Figure 1 shows a typical GTS, demonstrating that sensor glucose correlated with the clinical laboratory values and the reagent strip meters typically used by people thereafter.

### Table 1. Summary of Glucose Tracking Studies (GTS) by Subject

<table>
<thead>
<tr>
<th>Study subject</th>
<th>Total number of GTS</th>
<th>% responsive&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% clinically useful&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Onset (days) of electronic problems&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Sensor duration (days implanted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>33</td>
<td>75.8</td>
<td>69.7</td>
<td>272</td>
<td>298</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>25</td>
<td>0</td>
<td>29</td>
<td>152</td>
</tr>
<tr>
<td>4</td>
<td>22</td>
<td>50</td>
<td>13.6</td>
<td>70</td>
<td>175</td>
</tr>
<tr>
<td>5</td>
<td>21</td>
<td>9.5</td>
<td>0</td>
<td>10</td>
<td>174</td>
</tr>
</tbody>
</table>

NA, not applicable.

<sup>a</sup>Sensor responsiveness was defined as any definite response to change in blood glucose from the sensor, including erratic responses (correlation coefficient < 0.8) or those with limited linear range due to oxygen limitation.

<sup>b</sup>Clinically useful responses are defined as having ≥90% of the sensor glucose values within the A and B regions of the Clarke Error Grid.

<sup>c</sup>The number of days post-implant before a definite or abrupt shift in sensor baseline occurred that identified onset of a major electronic problem.

### FIG. 1. Example of a Glucose Tracking Study from the sensor in Subject 2 at 103 days post-implant. Sensor glucose values (connected closed circles) were calculated from regression analysis against the Clinical Laboratory reference glucose (closed diamonds). Simultaneous finger stick blood glucose values are displayed as open triangles (LXN meter) and open squares (One Touch meter). The correlation coefficient of sensor glucose to clinical laboratory glucose was optimized (0.9945) with an 8-min lag time. An open arrow indicates postural changes at end of study.
with diabetes to monitor their blood glucose. Most of the GTS were designed to reach a blood glucose of approximately 300–350 mg/dL as seen in Figure 1. The linear range of the sensor was further tested on Day 110 when blood glucose was raised to 550 mg/dL with multiple oral glucose loads. The sensor successfully tracked the glucose throughout the full range, with a correlation coefficient of 0.983 (y-intercept = 0). The sensor continued to have excellent linear correlation with the reference blood glucose values during GTS through post-implant day 243. Day 266 was the last day glucose tracking could be demonstrated. During the functional lifetime of the sensor, the sensitivity to glucose (measured by the slope of the regression line of sensor output vs. reference values) declined gradually from a maximum on day 103 of 82% of the pre-implant slope to a minimum of 3% on day 250. The lag time of the sensor gradually increased from a minimum of 2 min to 20 min.

The Clarke Error Grid method was used to determine if the sensor implant could be used to provide clinically useful glucose values. Clinically useful was defined as >90% of the study data falling within the A and B regions of a Clarke Error Grid. The Error Grid data shown in Table 2 and Figure 2 were generated using the retrospectively determined same-day calibration factors. Clinically acceptable sensor values were demonstrated in all GTS from day 81 through day 266 (Fig. 2).

The calibration factors determined from the same-day analysis were also used to calculate sensor glucose values of subsequent studies to determine the interval in days before recalibration was necessary, using the same Clarke Error Grid criteria as above. From day 81 through day 180 no recalibration interval was less than 14 days. The calibration values from day 88 to day 125 produced clinically useful glucose values for 30 days or more before recalibration was necessary.

This, our best-performing sensor, consistently and reliably tracked blood glucose changes when the subject was in a sitting position but was less reliable when the subject

<table>
<thead>
<tr>
<th>Day post-implant</th>
<th>Correlation coefficient</th>
<th>% A and B</th>
<th>% A</th>
<th>% B</th>
<th>% C</th>
<th>% D</th>
<th>% E</th>
</tr>
</thead>
<tbody>
<tr>
<td>81</td>
<td>0.988</td>
<td>100</td>
<td>94</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>88</td>
<td>0.981</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>95</td>
<td>0.948</td>
<td>100</td>
<td>87</td>
<td>13</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>103</td>
<td>0.974</td>
<td>100</td>
<td>94</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>110</td>
<td>0.983</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>125</td>
<td>0.954</td>
<td>100</td>
<td>93</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>130</td>
<td>0.911</td>
<td>100</td>
<td>93</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>136</td>
<td>0.907</td>
<td>100</td>
<td>89</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>147</td>
<td>0.950</td>
<td>100</td>
<td>95</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>151</td>
<td>0.976</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>158</td>
<td>0.897</td>
<td>100</td>
<td>76</td>
<td>24</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>165</td>
<td>0.977</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>180</td>
<td>0.945</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>193</td>
<td>0.863</td>
<td>100</td>
<td>86</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>208</td>
<td>0.962</td>
<td>100</td>
<td>85</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>215</td>
<td>0.991</td>
<td>100</td>
<td>90</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>222</td>
<td>0.938</td>
<td>100</td>
<td>86</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>229</td>
<td>0.984</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>236</td>
<td>0.937</td>
<td>100</td>
<td>82</td>
<td>18</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>243</td>
<td>0.965</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>250</td>
<td>0.716</td>
<td>100</td>
<td>65</td>
<td>35</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>256</td>
<td>0.890</td>
<td>100</td>
<td>78</td>
<td>22</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>266</td>
<td>0.966</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Correlation coefficient calculation and Clarke Error Grid analysis of sensor versus reference glucose values were done using the optimized LLSR same-day calibration. Clinically acceptable sensor values are defined as >90% of the sensor values with Regions A and B.
stood or lay down. This postural effect was attributed to compression of the blood supply in the tissues around the sensor producing a blood perfusion and/or oxygen limited response. The posture effect can be seen in Figure 1 (open arrow) at the very end of the study.

**Failure of packaging and electronics**

Three of the sensors developed early significant problems in the device electronics due to moisture penetration of the packaging. The polyethylene packaging used in this prototype device is known not to provide a true water-resistant seal. This failure mode has an unpredictable onset and was also seen in our earlier canine studies. The packaging/electronic problems appear in the sensor baseline (zero glucose value or intercept) as baseline increases or abrupt shifts during the implant period (Table 1). Yet these sensors were still able to respond to changes in blood glucose for brief periods of up to several days. The sensor in subject 4 produced oxygen-limited responses between days 13 and 91 and clinically useful results during three GTS on days 87, 100, and 108 before the electronics failed completely. Two other sensors (subjects 3 and 5) had electronic problems very early and showed only oxygen-limited or very slow (lag time >20 min) responses during the GTS.

**Explant histology**

The first subject enrolled in the study failed to form any tissue connection to the implant, and the sensor was completely isolated from the surrounding viable tissues by a thin fluid layer inside a FBC. All four of the other implants were well anchored within the subcutaneous FBC that always forms. The FBC recruits its own blood supply and is made up of living

![Figure 2](image-url)  
**FIG. 2.** Clarke Error Grid plot of all Glucose Tracking Studies in Subject 2 from day 81 to day 266. Sensor glucose values were calculated from the same-day optimized LLSR calibration factors.
cells that consume oxygen and glucose. Likewise, the sensor also both samples and consumes oxygen and glucose continuously in order to function. Ingrowth of mixed fibrous and fatty connective tissues and neovasculature was observed in the fabric of the device. Histology of the sensor/tissue interface revealed a mild local inflammatory response and a macrophage cell layer adjacent to and within the angiogenic layer causing structural disruption of the angiogenic layer. We believe this disruption of the angiogenic layer with associated inflammatory response may have acted as a biologically active barrier to diffusion of glucose and/or oxygen to the sensing membranes as well as increasing the length of the diffusion path between the vasculature and enzyme active layer of the sensor.

**Explant in vitro test results**

The sensors were tested *in vitro* after explant for comparison with pre-implant values. The sensors from Subjects 1 and 5 performed with sensitivity and response times comparable to pre-implant values. The sensors from Subjects 2 and 4 had stopped transmitting prior to explant, so the sensing membranes were transferred to functional sensor units for testing. The sensor membrane from subject 2 had 10% of the pre-implant sensitivity and twofold the response time, suggesting a membrane permeability change to explain the *in vivo* sensitivity loss. However, such explant studies are subject to error due to the difficulty matching the *in vivo* stretch of the membrane over the replacement sensor electrode. Loss of enzyme activity is considered less likely but cannot be ruled out. The sensing membrane from Subject 4 retained 60% of the pre-implant responsiveness. The sensor from Subject 3 failed to respond to glucose *in vitro* because of electronic problems with the device. The sensing membrane when tested on a functional unit was comparable to pre-implant.

**Failure modes**

There were several failure modes seen in this feasibility study: (1) Three of the five implants suffered water leakage into the package, causing problems with the electronics. (2) An inflammatory response within the angiogenic layer in four of the five sensors eventually caused distortion of the biointerface material. We suspect that this response may have limited the diffusion of glucose and/or oxygen to the enzyme layer of the sensor and impaired sensor function. (3) The first sensor implanted had a complete failure of tissue growth into the implant fabric so that no neovascular interface formed over the sensor. This sensor never tracked glucose. This was the first subject studied, and no limitations were placed on activity after surgical implant. The subject’s high activity levels may have generated shear forces that prevented the anchoring necessary for sustained angiogenesis to occur at the sensor–tissue interface. This subject also had slow healing of the implant incision and developed a hypertrophic scar after the device was explanted, indicating that this subject may have had a healing abnormality that was not identified prior to the study. Based on the observations in this subject, the next four subjects were all instructed to limit their activity for 2 weeks following surgical implantation of the sensor.

**DISCUSSION AND CONCLUSIONS**

Over the last 35 years, progress has been made towards achieving a clinically useful, continuous, implantable glucose sensor for tracking glucose in patients with diabetes. We have previously reported long-term function of glucose oxidase-containing sensor membranes. Membrane polymers have been developed that alter the transport ratio of glucose and oxygen so that oxygen is delivered in excess, a condition necessary for proper sensor function in the low oxygen tension environment of the subcutaneous tissue. Some of the success and promise of our sensor to function long term within an FBC can be attributed to the sturdy multilayer polyurethane sensing membrane. This membrane is engineered to be non-biodegradable and physically stable, allowing the sensor to stay in calibration long term.

The current challenge in developing an implantable glucose sensor with long-term function is to apply tissue-engineering principles to orchestrate within a subcutaneous FBC the
long-term delivery of both oxygen and glucose needed to support sensor function. Strategies to establish long-term vascularization within the FBC while simultaneously preventing tissue formation that blocks transport of oxygen and glucose must be used. The outer angiogenic layer used in this study was designed to interact with tissue macrophages to stimulate and maintain a vascular response while preventing the formation of a classic foreign body response. The gradual increase in the lag time seen in subject 2 may have resulted from both changes in the permeability of the sensing membrane (explant in vitro test) and disruption of the angiogenic membrane by a macrophage layer. The lag time of 20 min seen in the last GTS may not be clinically acceptable; however, with continuous readout, trend information, and alarms available, a lag time of up to 10–15 min is likely to be acceptable.

This initial clinical feasibility study was designed to see if a university laboratory prototype sensor, based on the enzyme electrode principle and implanted in subcutaneous tissue, could track glucose long term in a human with diabetes in a clinically useful manner. The sensor had shown sufficiently promising performance in a dog model to merit human trial. Feasibility was defined as showing sufficient glucose tracking performance to pass the Clarke Error grid criteria over an extended length of time. We achieved this in one of the five subjects with diabetes. In this subject stable clinically useful glucose sensor performance was demonstrated for >6 months. During the first 4 months of this time the stability was remarkable, requiring recalibration at most every 14 days. Three of the other sensors suffered early electronic problems from leakage of water and tracked glucose only transiently.

The successful demonstration of feasibility in this one subject was tempered by indications of inflammatory cells penetrating into and distorting the membranes. This and other observations lead us to believe that considerably more refinement of the sensor is needed, including improving the robustness of the membrane system.

Reducing the size and mass of the sensor to prevent motion of the device should reduce the time for sensor start-up by minimizing the disruption of the fragile new capillaries necessary to supply oxygen and glucose to the sensor. Miniaturization is also anticipated to resolve the vascular compression/postural effects seen in subject 2. The motion of this large prototype may also have been the source of the local inflammatory response that disrupted the membranes.

This glucose sensor implant technology shows promise in humans but needs to be miniaturized, better sealed against water penetration, and made more robust and reliable. Importantly, the long-term transport of glucose and oxygen across the sensor–tissue interface of a glucose sensor implanted in the subcutaneous tissue of humans appears feasible.

**ACKNOWLEDGMENTS**

This trial was supported through SBIR grant DK40657 from the NIH and by DexCom, Inc., San Diego, CA. Special thanks to Marjorie Wallrath, R.N. for assistance with the GTS; Dr. Thomas Warner for pathology; Drs. David Dibbell, Hans Sollinger, and Munci Kalayoglu for surgery; Jason McClure for device sterilization; and the study participants for their exemplary cooperation and dedication.

**REFERENCES**


Address reprint requests to:
Stuart J. Updike, M.D.
Biomedical Engineering Laboratory
University of Wisconsin, Madison
B-3058 VA Hospital
2500 Overlook Terrace
Madison, WI 53705

E-mail: sju@medicine.wisc.edu