

A Continuous Glucose Sensor Based on Wired Enzyme™ Technology—Results from a 3-Day Trial in Patients with Type 1 Diabetes

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ABSTRACT

Wired Enzyme™ (Therasense, Alameda, CA) sensing technology for continuous measurement of *in vivo* glucose concentrations offers the benefits of (1) excellent sensor stability, (2) reduced susceptibility to variations of *in vivo* oxygen concentration, and (3) minimized response to common electroactive interferents. This study describes the response of 48 sensors (25 in the upper arm, 23 in the abdomen) implanted for 3 days in patients with Type 1 diabetes. Prospective calibration was performed using capillary blood; results were compared with venous plasma glucose values obtained at 15-min intervals. Ninety-eight percent of readings fell in the clinically accurate Clarke error grid zone A or clinically acceptable zone B. Choice of the site of the implanted sensor (upper arm vs. abdomen) or the capillary blood calibration site (arm vs. finger) did not affect system accuracy.

INTRODUCTION

EVIDENCE SUGGESTS THAT improved glycemic control can minimize many of the complications associated with Type 1 diabetes.¹ Frequent self-monitoring of blood glucose, in concert with intensive insulin therapy, greatly improves glycemic control. Continuous glucose sensing offers all the advantages of high-frequency discrete testing, coupled with valuable additional information about the rate and direction of glucose change. In addition, glucose information is obtained at times when testing does not usually occur (e.g., postprandial glucose peaks, sleep), resulting in the potential

for sensitive alarms for hypo- and hyperglycemia.

The TheraSense FreeStyle Navigator™ (Alameda, CA) Continuous Glucose Sensor (CGS) is a subcutaneous, electrochemical sensor, which operates for 3 days implanted at a site in the body. It is based on Wired Enzyme™ (Thera-sense) sensing technology,² a mediated glucose-sensing technology that offers a number of advantages over conventional oxygen-dependent electrochemical glucose-sensing technologies, which utilize hydrogen peroxide (H₂O₂) detection at high [~500 mV vs. a silver/silver chloride (Ag/AgCl) reference electrode] applied potential.

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In contrast, Wired Enzyme technology works at a relatively gentle oxidizing potential of +40 mV, using an osmium (Os)-based mediator molecule specifically designed for low potential operation and stably anchored in a polymeric film for *in vivo* use. The sensing element is a redox active gel, consisting of (1) Os-based mediator molecules attached by stable (bidentate) anchors to a polymeric backbone film and (2) glucose oxidase (GOx) enzyme molecules. These two constituents are permanently coupled together via chemical cross-linking. The result is a glucose-sensing gel, which accurately transduces glucose concentrations to a measured current over the glucose range 20–500 mg/dL.

The Wired Enzyme sensing technology offers three primary advantages over conventional H_2O_2 -based detection systems:

1. The electrochemical response is extremely stable. Many *in vivo* glucose sensors have struggled with sensitivity (output per unit glucose concentration) that drifts substantially over the life of the implant.^{3,4} This drift causes the

sensors to require frequent and/or retrospective calibration. Wired Enzyme sensors have, after the initial break-in period, an extremely stable *in vivo* sensitivity, typically losing no more than 0.1% sensitivity/h.

2. The Wired Enzyme technology does not rely on oxygen for signal generation, unlike conventional sensors. Although oxygen can compete for electrons with the Os-based mediator molecules, and thereby modestly reduce the sensor output, the overall effect is much smaller than exists in conventional H_2O_2 -measuring systems, which can generate no signal in the absence of oxygen. This reduced oxygen dependency results in minimal sensitivity to *in vivo* oxygen variations and good linearity at high glucose concentrations.
3. The CGS operates at an applied potential of only +40 mV, much gentler than the ~500 mV required by H_2O_2 -sensing systems. Oxidation (and subsequent false high glucose readings) of many interferents (acetaminophen, uric acid, etc.) is minimized by this low operating potential.

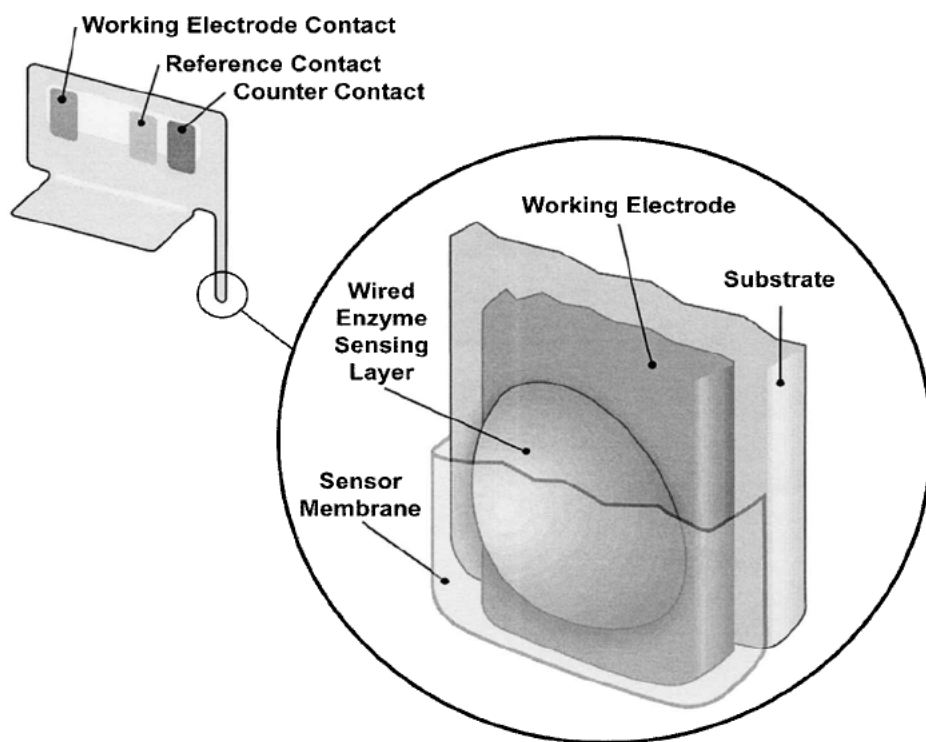


FIG. 1. Schematic diagram of the TheraSense CGS, showing contact pads for the three sensor electrodes. Detail (not to scale) shows the working electrode surface, with attached Wired Enzyme sensing layer, and overlying glucose-limiting membrane.

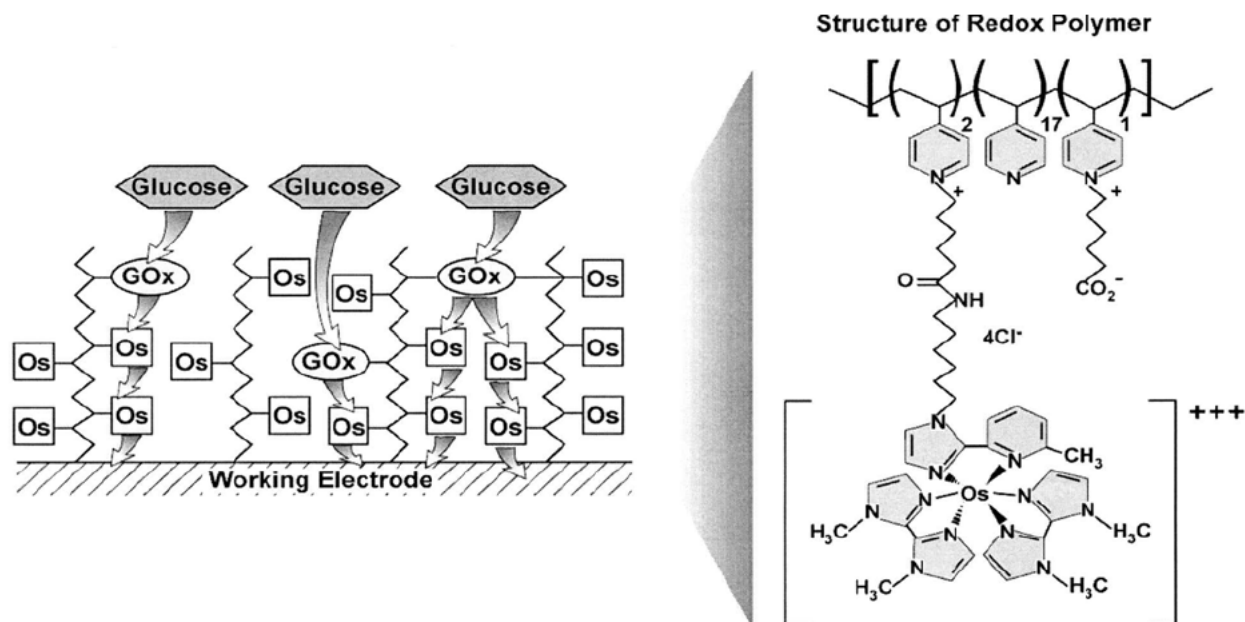


FIG. 2. Schematic diagram of the Wired Enzyme sensing layer, showing redox polymer, incorporated enzyme (GOx), and path of electron flow from glucose to the working electrode. Detail shows the actual structure of the redox polymer.

This paper presents preliminary results from an accuracy study conducted in 30 patients with Type 1 diabetes, using frequent (15-min intervals for 3 days) venous blood glucose measurements as reference values. This study was performed with a corded system; evaluation of a wireless system is underway and will be described in future publications.

SUBJECTS AND METHODS

Sensor description

The TheraSense CGS is a three-electrode, amperometric sensor, pictured schematically in Figure 1. Working and counter electrodes are fabricated from carbon; the reference electrode is Ag/AgCl. The dimensions of the subcutaneous portion of the sensor are ~5 mm long × 0.6 mm wide × 0.25 mm thick.

The working electrode has an active area of ~0.15 mm², which is coated with the Wired Enzyme sensing layer. This cross-linked glucose-transducing gel is formed from three components: (1) a high-molecular-weight mediating redox polymer, consisting of a modified poly(vinylpyridine) backbone loaded with poly(biimidazolyl) Os complexes securely anchored

through a bidentate linkage (Fig. 2), (2) GOx, and (3) a bifunctional short-chain epoxide cross-linker. The Wired Enzyme sensing layer has a mass of 300 ng (dry thickness ~2 μm), and is ~35% (by weight) redox polymer, 40% GOx, and 25% cross-linker. The resulting glucose-sensing gel can efficiently capture and transport electrons from glucose molecules, which are free to diffuse within its relatively hydrophilic interior. A schematic diagram of the Wired Enzyme is shown in Figure 2, showing the flow of electrons from glucose to the working electrode.

A glucose-restricting membrane (Fig. 1), consisting of a high-molecular-weight poly(vinylpyridine)-poly(ethylene glycol) copolymer cross-linked using a trifunctional short-chain epoxide, overlays the sensing layer. This membrane is ~50 μm thick, and serves to reduce glucose diffusion to the active sensing layer by a factor of ~50, leading to an *in vivo* sensitivity of ~0.1 nA/(mg/dL), and a linear response over the concentration range 20–500 mg/dL. The sensor's response time to an instantaneous change in glucose concentration was ~3 min. In addition, the hydrophilic membrane presents a biocompatible surface to the body, reducing irritation.

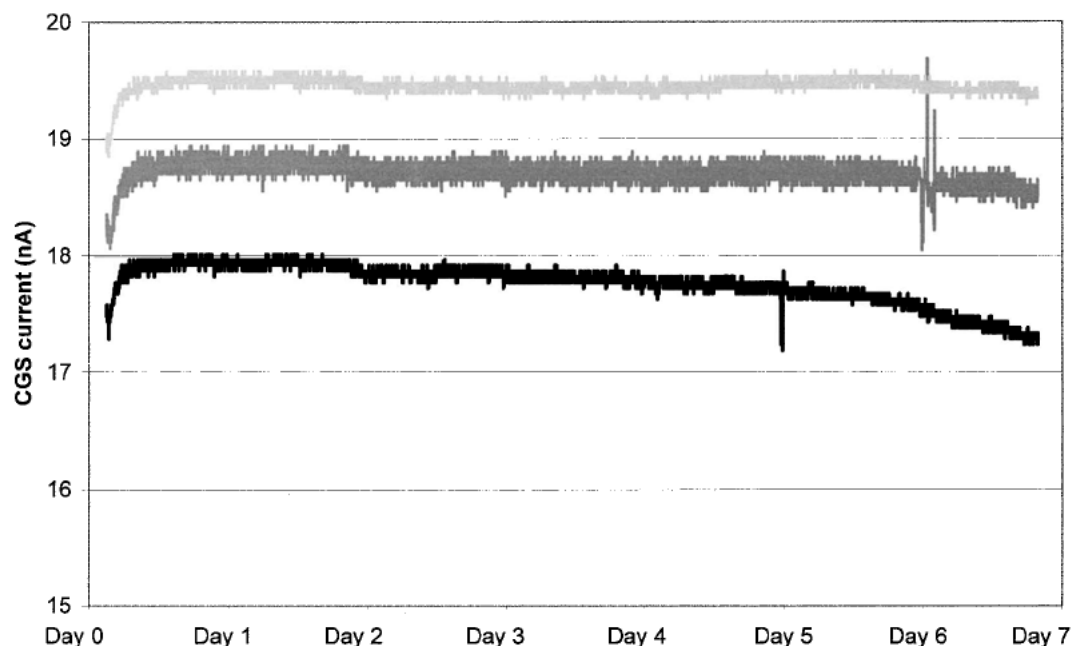


FIG. 3. *In vitro* stability test of three CGSs in 500 mg/dL glucose, 0.1 M PBS buffer, at 37°C. Mean current decay rate is 0.011%/h.

Sensor electronics

The sensor was placed into the subcutaneous tissue of the upper arm or abdomen using a spring-actuated insertion mechanism. The sensor was connected via cord to a portable potentiostat–data logger device, which maintained the glucose-sensing working electrode at a potential of +40 mV versus the Ag/AgCl reference electrode, while obtaining and storing instantaneous current values at 10-s intervals. Subjects were also fitted with small (~1-cm²), insulated, transdermal skin temperature sensors, which were applied in the immediate vicinity of the continuous glucose sensor.

In vitro CGS evaluations

These were carried out at 37°C in 0.1 M phosphate-buffered saline (PBS) contained in a 2-L jacketed beaker with gentle stirring. Oxygen dependence experiments were conducted under two gas mixtures: 95% N₂/5% O₂ and 98% N₂/2% O₂. Interferent evaluations were conducted in separate experiments using 0.2 mM acetaminophen, 0.085 mM ascorbate, and 0.5 mM uric acid. Proclin 500 (Supelco, Bellefonte, PA) was added at 5 µL/L to retard bacterial growth in long-term stability experiments (Fig. 3).

Biocompatibility testing

Testing was performed on large-scale assemblies consisting of all sensor components (substrate, electrode inks, membrane, and sensing layer formulations) in proportions corresponding exactly to actual sensor composition. Cytotoxicity was assessed by ISO elution test (minimum essential medium extract) *in vitro*. Sensitization was assessed with a maximization test (Magnusson Kligman method) in guinea pigs. Irritation was assessed with an ISO intracutaneous reactivity test in rabbits. Systemic toxicity was assessed by a USP systemic injection test in rabbits. Subchronic sensitization was assessed by a 30-day implantation test in rabbits. Genotoxicity was assessed by Ames mutagenicity test *in vitro*. Hemocompatibility was assessed by a hemolysis test (extract method) *in vitro*. All tests were passed.

Clinical trial procedure

Subjects were fitted with one or two CGSs and corresponding transdermal skin temperature sensors, as described above. Sensor implant depth was ~5 mm. Subjects were also fitted with a heparin lock for obtaining venous blood samples. Glucose and temperature data

were obtained at 10-s intervals over the 3-day trial period, while venous blood samples were obtained at 15-min intervals. Venous plasma blood glucose values were measured on a YSI 2300 (Yellow Springs Instruments, Yellow Springs, OH). Capillary blood measurements were also made using the TheraSense Free Style® Blood Glucose System to enable development of a prospective calibration algorithm. Arm capillary blood was obtained hourly at hours 0–12, 24–30, and 48–54 for all 30 subjects. Finger capillary blood was also obtained at the same times for 10 subjects wearing 19 CGSs.

Glycemic challenges were performed daily for all subjects. Subjects were given intravenous insulin once (0.15 U/kg, followed by 0.10 U/kg if necessary to achieve hypoglycemia), and oral glucose (75 g) on two separate occasions. Vital signs were monitored at 15-min intervals during administration of intravenous insulin.

An institutional review board approved the trial protocol. Inclusion criteria for the study were (1) Type 1 diabetes, (2) C-peptide less than 0.5 ng/mL, and (3) age 18 or older. Thirty subjects were enrolled at three clinical trial sites (Renton, WA; San Antonio, TX; and Walnut Creek, CA). Subjects ranged in age from 20 to 85 years, with a mean of 40 years. There were eight females and 22 males, comprising three African Americans, 26 Caucasians, and one Hispanic.

Calibration procedure

A prospective calibration algorithm was developed in an earlier study, consisting of 20 sensors (15 arm, five abdominal) implanted into subjects with Type 1 diabetes. The 48 sensors, whose performance is described here, were implanted in a separate study conducted sequentially following the calibration development set. *Therefore, none of the data sets described in the present study was used in development of the calibration algorithm.* For each implant, three FreeStyle capillary blood glucose measurements were used as calibrants subject to the following exclusion criteria:

1. *Time.* Calibration point 1 occurred a minimum of 1 h after insertion. Calibration point 2 occurred a minimum of 2 h after a suc-

cessful calibration point 1. Calibration point 3 occurred a minimum of 21 h after a successful calibration point 2.

2. *Glucose range.* Calibration was allowed within the capillary blood glucose range 60–350 mg/dL.
3. *Rate of glucose change.* Calibration was restricted to glucose rates of change of 2 mg/dL/min or less. [A separate study in 20 patients with Type 1 diabetes performing normal daily routines (i.e., not performing daily glucose challenges) showed that the rate of 2 (mg/dL)/min was exceeded only 4% of the time, consistent with other published data.^{5]}
4. *Sensitivity.* Calibration was allowed only if the resulting nominal sensitivity (in nA/mM glucose) was within a preset range as determined by a code assigned to each CGS production lot.
5. *Temperature.* Calibration was allowed over the skin temperature interval 28–37°C.

The operating sensitivity for the first 2 h of operation was based entirely on calibration point 1. However, subsequent operating sensitivities (after the second calibration point was obtained) were based on a weighted average of all previously obtained calibration points. This had the effect of refining, and increasing the accuracy of, the calibration as the implant proceeded. This refinement process was made possible by the near-negligible drift of the CGS sensitivity with time.

The calibration process also involved a correction for changes in skin temperature underneath the insulated skin temperature probe. An adjustment of 7%/°C, relative to the skin temperature at the time of the operative calibration point, was performed.

One sensor (of 49 implanted) did not achieve calibration, because of violation of point #4, the sensitivity restriction, above. That sensor is excluded from the statistical analysis.

RESULTS

The excellent *in vitro* stability of the CGS is demonstrated in Figure 3, a plot of three separate sensor responses (in nA) versus time in 500

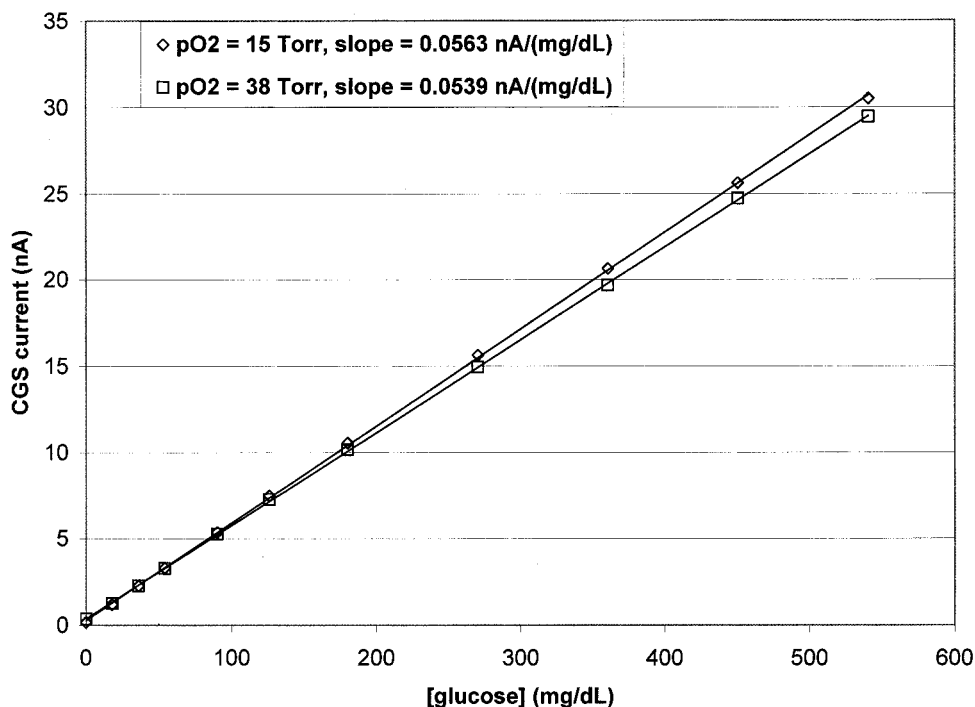


FIG. 4. Oxygen dependence of CGS over the glucose concentration range 20–500 mg/dL. The averaged response of eight sensors in 0.1 M PBS at 37°C is shown: (◇) $pO_2 = 15$ torr, (□) $pO_2 = 38$ torr.

mg/dL glucose (in PBS at 37°C) over a period of 7 days. The average *total* decay in glucose signal over the 7-day test period was 1.7%. The mean hourly rate of decay is insignificant, at 0.011%/h. Similar stabilities are observed *in vivo* (*vide infra*).

In vitro testing was also performed to determine the effect of oxygen on the sensor's linearity. These results are shown in Figure 4, a plot of current versus glucose concentration for CGS maintained under oxygen tensions of 15 and 38 torr, respectively. (These lowered O_2 levels reflect the reduced levels found in subcutaneous tissue.⁶) Both high and low oxygen curves exhibit excellent linearity ($R^2 = 0.9999$ for both curves) over the glucose range from 18 to 540 mg/dL. The difference in slope is only 4%, with differences varying from 0.4% at 36 mg/dL to 3.5% at 540 mg/dL, indicating minimal oxygen dependence for the continuous sensor.

Finally, *in vitro* interference testing was performed with acetaminophen, ascorbate, and uric acid. These three interferents were tested at the top of their normal physiological or therapeutic range (0.2 mM, 0.085 mM, and 0.5 mM,

respectively).⁶ The glucose-equivalent interferences were 3 mg/dL for acetaminophen, 19 mg/dL for ascorbate, and 3 mg/dL for uric acid tested at these levels. The interferences due to uric acid and acetaminophen are inconsequential, which can be attributed largely to the low operating potential of +40 mV versus Ag/AgCl.

Next, *in vivo* testing with actual implanted sensors was performed. A representative data set showing implanted CGS data (from an abdominal sensor) *overlaid* with venous plasma glucose values is shown in Figure 5. Note that these are raw data; CGS currents (left-hand axis) are uncalibrated and uncorrected for temperature, while venous plasma glucose values are shown on the right-hand axis. *No time shifting of data has been performed.*

There are two noteworthy aspects to these data. First, there is obviously an excellent correlation between the CGS raw current values and venous plasma glucose concentrations. No substantial lag between subcutaneous and venous glucose concentrations is evident. Second, the sensitivity of the implanted CGS is essentially unchanged over the 3-day implantation

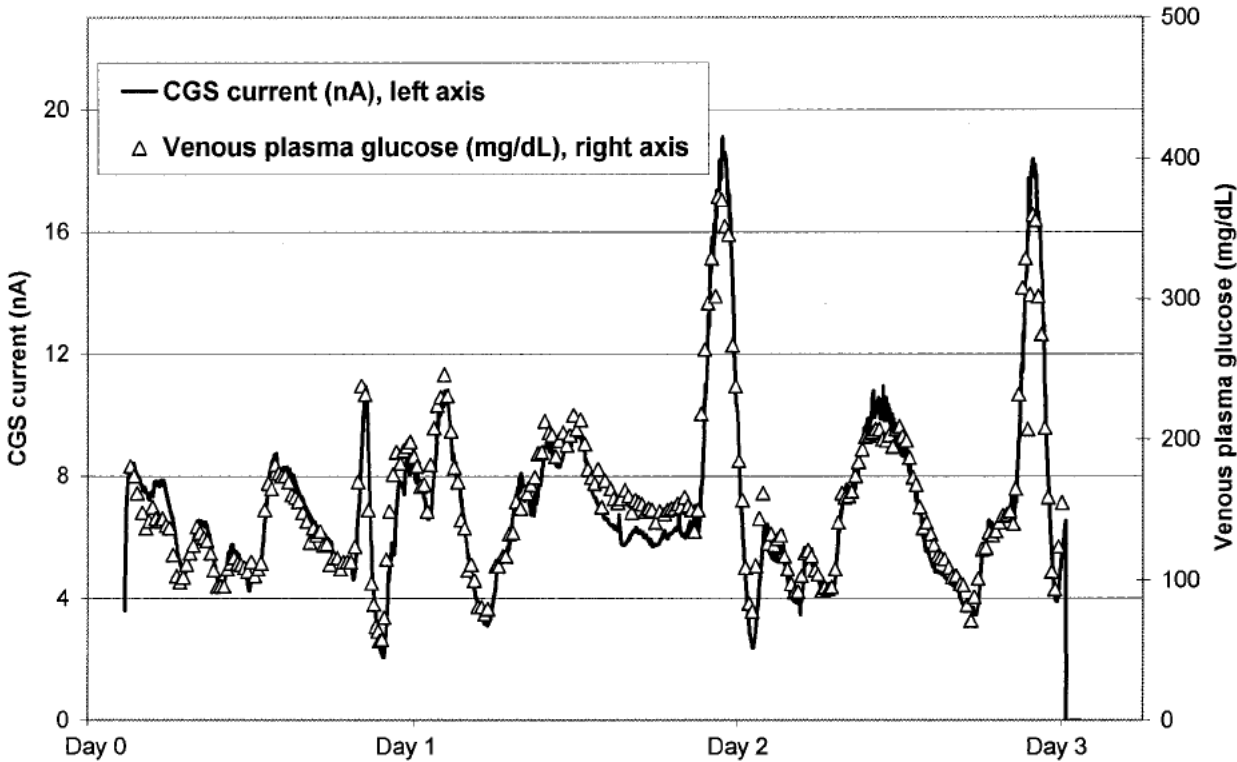


FIG. 5. Overlay plot of implanted (abdominal) sensor raw current compared with venous plasma glucose: (—, left axis) CGS raw current, in nA; (Δ , right axis) venous plasma glucose, in mg/dL.

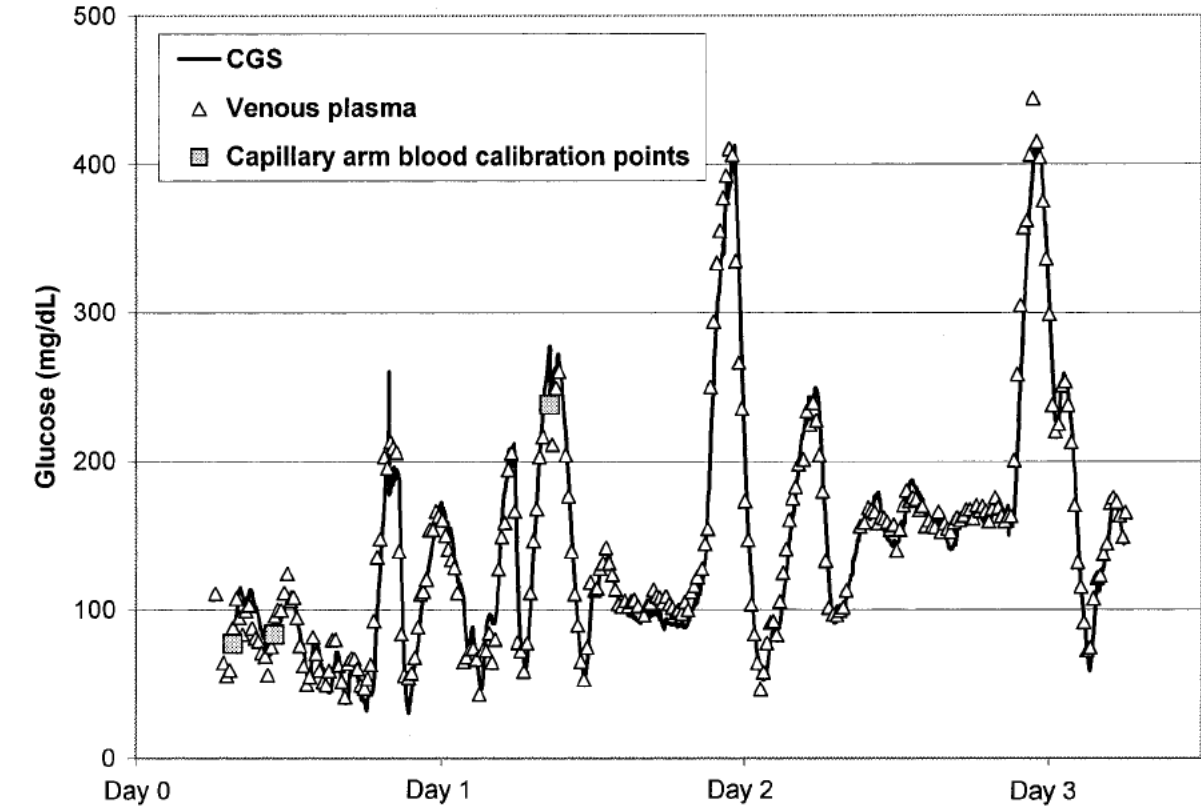


FIG. 6. Calibrated continuous glucose data for sensor implanted in arm: (—) CGS glucose; (Δ) venous plasma glucose; ($\blacksquare$) FreeStyle arm stick capillary blood calibration points.

period. This signal stability makes it possible to schedule the three calibration points in the first 24 h of the implantation, with no additional calibration points during the final 48 h. Since sensor drift is nearly negligible, operating sensitivities can become a weighted average of multiple calibration points; this is helpful for reducing any error inherent in the calibrating capillary blood glucose measurement.

A similar data set is shown in Figure 6, a representative example of the output from one of the 48 calibrated sensors. Here, a prospective calibration based on the indicated FreeStyle arm capillary blood measurements (as described in Subjects and Methods, above) has been applied to the subcutaneous current data to convert them to glucose concentration data. Again, no time shifting of data has been performed.

There is an excellent correlation between subcutaneous and venous plasma glucose values, indicative of both reliable sensor function

and an accurate calibration. The data set of Figure 6 (and all other data sets shown) was calibrated using FreeStyle arm capillary blood. However, no significant change in accuracy was found (*vide infra*) when finger capillary blood was used as a calibrant.

Data sets were also obtained for sensors simultaneously implanted in the abdomen and arm of a single subject. An example of such data is shown in Figure 7.

There is a good agreement between the glucose values measured at arm and abdomen subcutaneous sites, as well as with venous plasma values. Some deviations from the venous plasma values are observed on the night of the first implant, when subcutaneous values fall intermittently below the venous plasma values. Based on data (not shown) for spatially adjacent sensors implanted at a single site, we believe these deviations result from interactions between the sensor and the insertion site, not from systematic differences between venous and subcutaneous glucose. These devia-

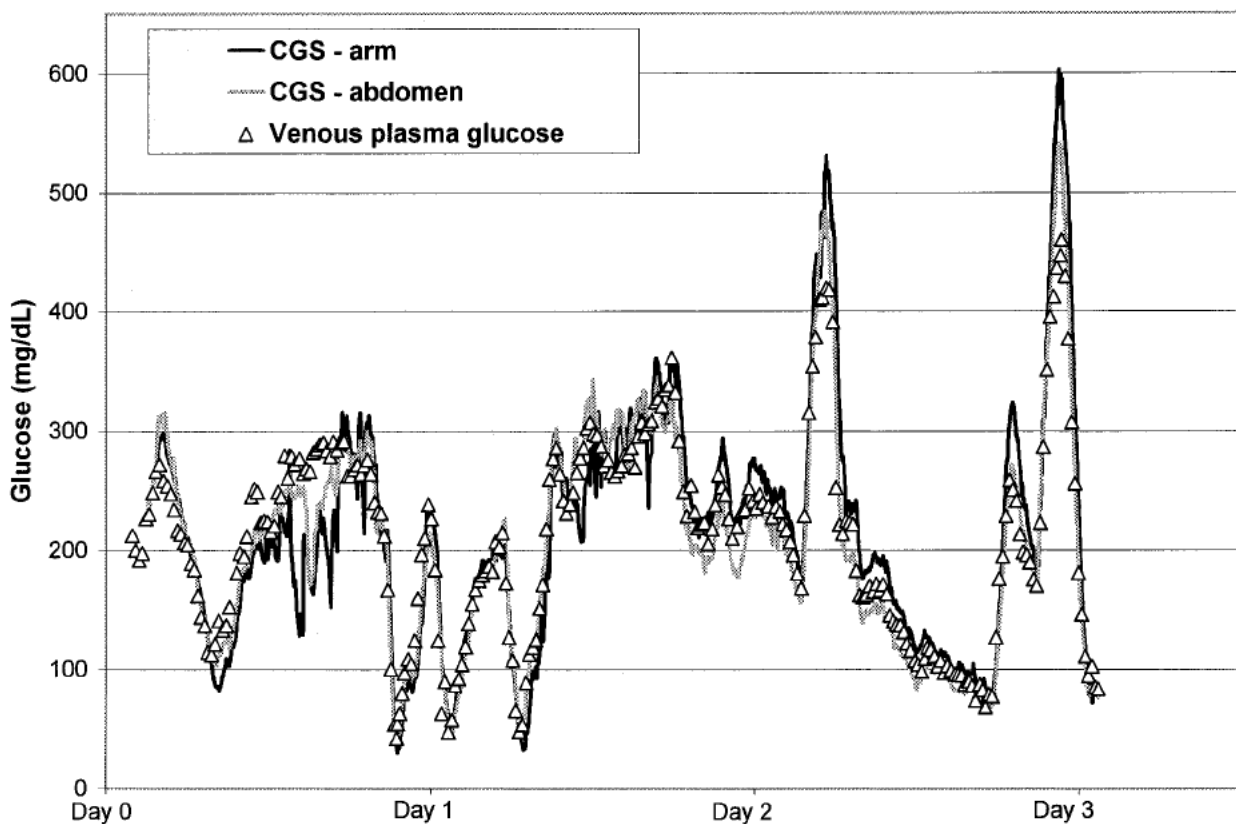


FIG. 7. Comparison of two calibrated, simultaneously implanted CGSs located in arm (—) and abdomen (---). Venous plasma glucose is also shown (Δ).

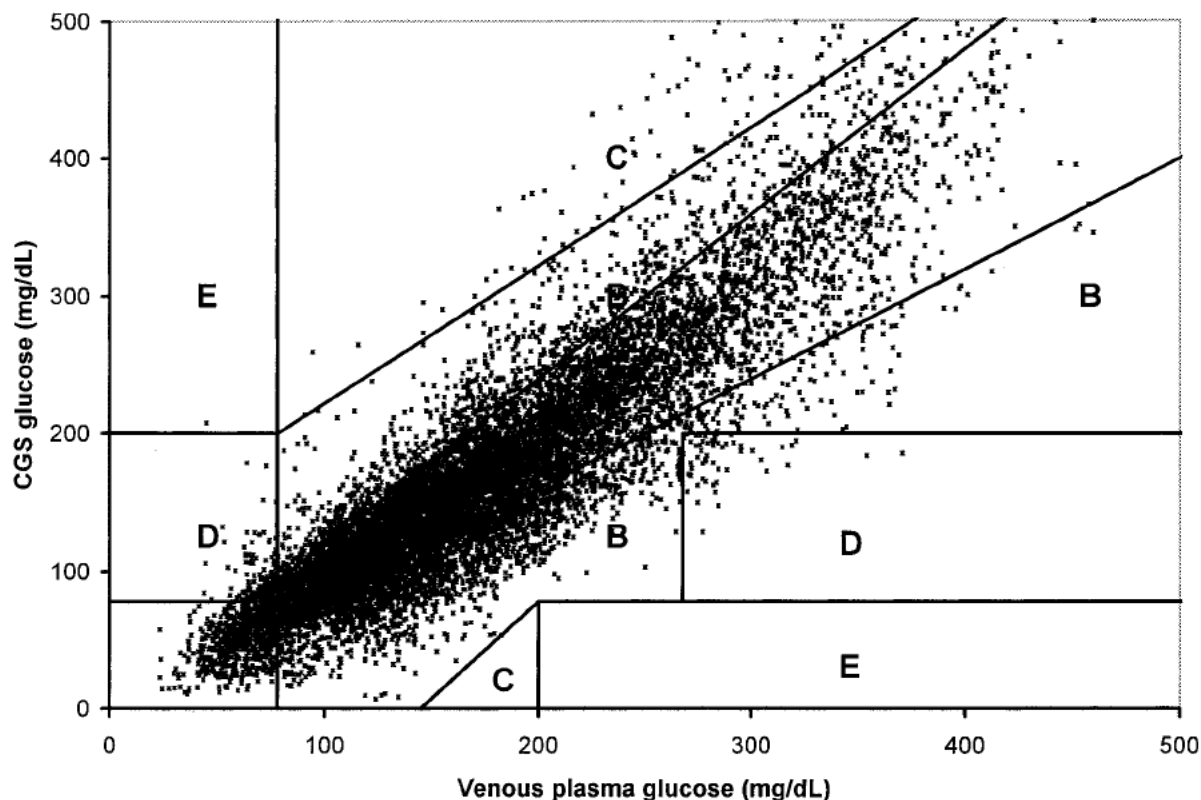


FIG. 8. Clarke error grid for 48 CGSs (25 in arm, 23 in abdomen), comprising 12,667 data pairs, calibrated using arm stick capillary blood: %A = 67.9, %B = 29.7, %C = 1.2, %D = 1.1, %E = 0.0.

tions are virtually always negative (the sensor value reads lower than the venous glucose value), and tend to occur (a) at night and (b) early in the course of the 3-day implantation. The cause of the negative deviations is unknown, but some possibilities are as follows: (1) Cells or other subcutaneous structures may adhere to the sensor surface, blocking glucose ingress. (2) Blood clots formed upon sensor insertion may exert a similar glucose-blocking effect (blood clots were not observed to adhere to the active areas of explanted sensors, but that does not preclude their presence prior to explantation). (3) Constriction of local blood vessels, due to external pressure effects, may restrict glucose delivery to the sensor site.

These deviations are not frequent. Sensitivity was reduced by 40% or more for only 4% of the roughly 3,500 sensor-hours represented by this study. Overall, the system performed well, as demonstrated in Figure 8, a Clarke error grid for all 48 sensors (25 in the arm and 23 in the abdomen) inserted in the 30 subjects. As before,

these data are prospectively calibrated, with no time shifting, using arm capillary blood.

This graph represents 12,667 data pairs. Approximately 98% of the data fall within the clinically accurate "A" region, or the clinically acceptable "B" region of the Clarke error grid. Other methods of parsing the data are also possible, as shown in Table 1. Here data are divided according to the implant site (arm or abdomen), and/or according to the capillary blood calibration site (arm or finger).

CONCLUSIONS

All of the continuous glucose data presented above (with the exception of the raw data overlay of Fig. 5) were derived using a prospective calibration based on nominal calibration times of 1, 3, and 24 h after implantation. The calibration algorithm was developed using a separate data set of 20 similar implanted sensors. None of the data reported here was used in

TABLE 1. SUMMARY OF CLARKE ERROR GRID AND STATISTICAL DATA FOR IMPLANTED CGSs, BASED ON CALIBRATION AND IMPLANT SITE

Subset	Description	Calibration site	n ^a	Clarke error grid					MAD (%)
				%A	%B	%C	%D	%E	
A	All (25 arm, 23 abdominal) sensors	Arm	12,667	67.9	29.7	1.2	1.1	0.0	17.3
B ^b	19 sensors with arm, finger calibration available	Arm	4,987	67.7	29.3	1.8	1.1	0.0	17.4
C ^b	19 sensors with arm, finger calibration available	Finger	4,922	68.2	29.8	1.1	0.8	0.0	17.0
D	25 arm sensors	Arm	6,656	67.0	30.3	1.8	1.0	0.0	17.7
E	23 abdominal sensors	Arm	6,011	69.0	29.1	0.6	1.3	0.0	17.2

^aNumber of continuous sensor/venous plasma data pairs.

^bSubsets B and C have slightly different *n* values, since there were small variations in the time at which calibrated operation (and hence meaningful venous/subcutaneous glucose pairs) began.

development of the calibration algorithm. The TheraSense CGS has an extremely stable *in vivo* sensitivity after a modest acclimation process (during which sensitivity may *rise* by a few percent) that is generally complete in a few hours. Since the sensor output is so stable, it is advantageous (1) to concentrate the calibration points in the first 24 h of use, and (2) to continuously refine the calibration (rather than basing sensitivity *only* on the most recent calibration point), as multiple calibration points are obtained. No calibration is required for the final 48 h of the 72-h implant. These strategies allow a minimization of calibration error.

No time shifting [used frequently in the literature to compensate for any error due to (1) physiological time lags between the subcutaneous and reference glucose measurements, or (2) slow system response times] has been applied to any of the data presented here. All data are real-time. We believe that time shifting of glucose values and prospective calibration are incompatible concepts. Based on the complete accuracy study data set described in Figure 8 (12,667 data pairs) the *average* physiological time lag (subcutaneous–venous) was found to be ~8 min for our system. This value was determined by the theoretical exercise of finding the minimum in mean absolute deviation (MAD) as reference and subcutaneous values were time-shifted. Of this 8-min lag, ~3 min can be attributed to the response time of the

sensor, with 5 min due to physiology. A recent review³ of various subcutaneous glucose measurement strategies reported lag times ranging from 2 to 30 min, with an average lag of 8–10 min, in good agreement with our preliminary findings. A more complete study of physiological glucose lags based on the raw data of this study will be the subject of a future publication.

The data of Figures 5–7 demonstrate excellent linearity at both high and low glucose values (induced by glycemic challenges); the sensor faithfully tracks glucose values over the physiologically relevant range *in vivo*. Overall, for the complete data set, 98% of readings fall within the clinically accurate Clarke error grid zone “A” and the clinically acceptable zone “B.” This is excellent performance, and does not take into account the extra diagnostic value conferred by the directional trend information inherent to continuous monitoring.

As outlined in Table 1, no significant difference was found between arm capillary blood calibration (MAD = 17.4%) and finger capillary blood calibration (MAD = 17.0%). Thus, arm capillary blood served as an equally accurate, and less painful, calibrant compared with finger blood. Studies⁷ under extreme conditions (glucose loading followed by intravenous insulin) have claimed a large possible variation between arm and finger capillary blood. (The recommended⁸ rubbing of the alternate site

was also omitted in these studies.) In fact, under normal use conditions, these differences are not significant unless glucose is changing very rapidly.⁹ Restriction of calibration to rates less than 2 (mg/dL)/min virtually eliminates this possible error source. Finally, using arm capillary blood calibration, no significant difference was found between an insertion site in the arm (25 sensors, MAD = 17.7%) and abdominal insertion (23 sensors, MAD = 17.2%).

The data presented here are for a cabled system with attached potentiostat logger. Home-use studies are currently underway with a wireless system utilizing a pager-sized, handheld informational display module (FreeStyle NavigatorTM). This system is capable of providing real-time glucose information at 1-min intervals. In addition, glucose trending rate information will be available, with a visual rate indicator allowing users to discriminate among glucose rate changes of less than 1 (mg/dL)/min, 1–2 (mg/dL)/min (moderate change), and greater than 2 (mg/dL)/min (rapid change). We believe this feature will add substantial predictive utility that is not reflected in the Clarke error grid statistics. The system is also designed to provide hypo- and hyperglycemic alarms with user-settable thresholds. Studies utilizing this wireless system, particularly the utility of trend and alarm information, will be the subject of future publications.

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REFERENCES

1. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986.
2. Csoregi E, Schmidtke DW, Heller A: Design and optimization of a selective subcutaneously implantable glucose electrode based on “wired” glucose oxidase. *Anal Chem* 1995;67:1240–1244.
3. Roe JN, Smoller BR: Bloodless glucose measurements. *Crit Rev Ther Drug Carrier Syst* 1998;15:199–241.
4. Wisniewsky N, Moussy F, Reichert WM: Characterization of implantable biosensor membrane biofouling. *Fresenius J Anal Chem* 2000;366:611–621.
5. Jungheim K, Kapitza C, Djurhuus CB, Wientjes KJ, Koschinsky T: How rapid does glucose concentration change in daily-life of patients with type 1 diabetes? [abstract]. Presented at the Second Annual Diabetes Technology Meeting, Diabetes Technology Society, Atlanta, November 2002.
6. Burtis CA, Ashwood ER, eds: *Tietz Textbook of Clinical Chemistry*. Philadelphia: W.B. Saunders Co., 1999.
7. Koschinsky T, Jungheim K: Risk detection delay of fast glucose changes by glucose monitoring at the arm. *Diabetes Care* 2001;24:1303–1304.
8. FreeStyle[®] blood glucose testing system [test strip package insert]. Alameda, CA: TheraSense, 2000.
9. Bennion N, Christensen NK, McGarraugh G: Alternate site glucose testing: a crossover design. *Diabetes Technol Ther* 2002;4:25–33.

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