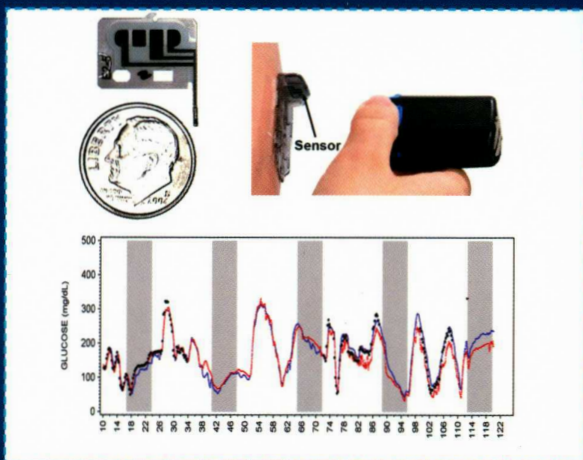


*Chemical Analysis: A Series of Monographs on
Analytical Chemistry and Its Applications*
J. D. Winefordner, Series Editor

In Vivo Glucose Sensing



Edited by
David D. Cunningham
Julie A. Stenken

IN VIVO GLUCOSE SENSING

Edited by

DAVID D. CUNNINGHAM

JULIE A. STENKEN



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CHAPTER 5

COMMERCIALLY AVAILABLE CONTINUOUS GLUCOSE MONITORING SYSTEMS

Timothy Henning

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5.1 INTRODUCTION

5.1.1 Why Do We Need Continuous Glucose Monitoring?

This chapter will explain the technology used in the three commercially available continuous glucose monitoring (CGM) systems that are approved by the FDA in 2008. The history of how the technology was developed, the technical hurdles that had to be overcome, and the performance of these technologies will be covered. The future development and uses of the technology will also be discussed. Although the technology will undoubtedly evolve in the coming years, the underlying principles of how the technology works and the challenging problems that were overcome in developing the technology will serve as a foundation for future technological developments of CGM.

People with types 1 and 2 diabetes face the daily challenge of maintaining a stable glucose level in their body. Home glucose testing has allowed people with diabetes to frequently test their blood and obtain an accurate reading of their blood glucose at that point in time. The person with diabetes can then act on the glucose reading by injecting insulin if their glucose reading is too high or by eating if their glucose level is too low. Although home glucose testing is very valuable, it can only provide the person with diabetes a glucose reading at that specific moment in time. Because of the inconvenience and cost of pricking your finger and making a glucose measurement, the person with diabetes often performs testing less than twice per day. The glucose levels of people with diabetes are however very labile and periodic testing cannot provide them enough information to properly control their glucose level. A clinical study was done where the diabetic subject performed on average nine blood glucose measurements per day.¹ Despite the great number of tests that were performed daily, the subjects still spent on average 4.8 h per day in hyperglycemia (blood glucose above 180 mg/dL) and 2.1 h in hypoglycemia (blood glucose below 70 mg/dL). Hyperglycemia is known to contribute to long-term vascular damage and hypoglycemia can lead to mental confusion and ultimately death. The time spent outside euglycemia by people with diabetes should not be blamed on the person because they cannot measure frequently enough with home glucose testing to maintain control. Maintaining euglycemia during sleep is beyond the control of the person with diabetes. The only solution to this problem is a device that can provide an almost continuous measurement of blood glucose, so that person with diabetes can obtain glucose values frequently enough to adjust their treatment accordingly to maintain euglycemia. CGM can also provide alarms to alert the person with diabetes while they are sleeping. The technology is being developed that will allow the CGM to work with an insulin pump and provide an automated system to maintain euglycemia.

Home glucose test strips were able to reach the market two decades before the first continuous glucose monitors. This points to the tremendous challenges faced in the development of CGM. Following the long and colorful development of the technology will make it easier to understand the present systems.

5.1.2 Why Electrochemical and Not Optical Systems?

Glucose is a monosaccharide that provides the fuel for all the cells in the body. Nature has evolved enzymes that react with glucose producing by-products that can be used

to generate an analytical signal. The details of the enzyme reaction are covered in the subsequent section. The enzyme glucose oxidase is used in the current CGM systems and was used for the home glucose test strips. The home glucose test strips have now evolved and use the enzyme glucose dehydrogenase that does not require oxygen as a coreactant. YSI, formerly Yellow Springs Instruments, introduced a blood analyzer in 1972 that used an immobilized glucose oxidase membrane on top of an electrode to generate hydrogen peroxide. The same YSI glucose electrode is used to measure many blood samples, which differentiates the electrode from single-use glucose strips. Hydrogen peroxide is electrochemically active and can be oxidized at a precious metal electrode to produce a current that is proportional to glucose. This instrument is still in production today and serves as the reference method for most of the clinical trials involving CGM. The YSI instrument has many properties that make the technology ideal for use in CGM: glucose oxidase is inexpensive and relatively stable and is very selective for glucose, the enzyme is easily immobilized, the electrochemical detection of the hydrogen peroxide produced from the glucose oxidase reaction can be done with inexpensive electronics, and the electronics can be located far away from the electrodes requiring only small wires to transmit the current.

Optical systems have certainly been constructed that can measure the reaction of glucose with glucose oxidase. The term optical systems refers to systems that measure a change in an optical property of a reaction zone, for example, change in color, in response to a reaction of glucose with another chemical or biological agent not normally present in the body. The first home use glucose test strips were based on color changes that resulted from the glucose oxidase reaction (for a review of how home glucose test strips work, see Ref. 2). The color change requires a dye that is irreversibly changed in the reaction. A reservoir of fresh dye would be needed to run the reaction continuously as would be needed for a continuous glucose sensor. The optical means of measuring glucose must be located in proximity to the color formation. This would require that the optical reader be placed inside the body or possibly outside the skin just above a color-forming reaction that is located just underneath the skin. As with most optical systems, alignment of the instrument with the reaction center is critical. The optical system based on enzymes would, therefore, have the following disadvantages over electrochemical systems: requires a reservoir of dye, the optical reading system needs to be near the color change, optical readers need to be aligned with color change, and optical readers are typically more expensive than electrochemical circuits. To get around the problem of consuming reagent, these systems have found other means of reacting with glucose. Inorganic boronate compounds that can reversibly bind glucose and naturally occurring glucose binding proteins have been discovered.³⁻⁸ These binding events between glucose and the binding molecule can be used to trigger an optical signal. The details of these reactions are not the subject of this chapter, so the reader should refer to the reference for further details. Because of the many technical challenges facing optical systems for continuous glucose monitoring, their progress has been slow but deliberate. Several companies have shown results in animals that look promising and the author expects that commercial continuous glucose monitors based on optical systems will be available in the next decade.⁹

Much research has been done on the direct detection of glucose in the body using electromagnetic radiation with no chemicals placed inside the body.^{10,11} Light impinges on the body and the reflected or transmitted light is changed based on the interaction of the body with the light and that change possibly contains information about glucose levels in the body. This technique is called noninvasive glucose monitoring, but since electromagnetic radiation does enter the body, the measurement is not truly noninvasive. Several companies are actively working on continuously shining light into the body so that a continuous measurement of glucose can be made. None of these systems are commercially available, so they will not be covered in this chapter except for the preceding comments.

5.1.3 Operation of Electrochemical Systems

5.1.3.1 Enzyme Reactions at Electrodes The reaction of glucose oxidase with glucose is explained in many sources. An elementary understanding of this reaction, discussed in the following sections, is necessary to comprehend the various generations of biosensor technology. Since the current commercial CGMs encompass two generations of biosensor technology, it is necessary to provide a broader understanding of these key fundamental points. This and the following sections are particularly relevant because most of the differences between the commercial systems arise from the distinction in generations of biosensor to which they belong.

Glucose oxidase belongs to a class of enzymes that has an electroactive FAD site at which their specific reaction occurs. Glucose reacts with the FAD site in glucose oxidase and two electrons are transferred from glucose to the FAD site. Glucose is oxidized to gluconic acid. The reduced FAD site must be oxidized before the enzyme can oxidize another glucose molecule. In nature, the FAD site is oxidized by oxygen dissolved in the sample and the oxygen is reduced to hydrogen peroxide (a description of the glucose reaction can be found in Section 1.2.1). Hydrogen peroxide is electroactive and can be oxidized at an electrode. The current produced by the hydrogen peroxide will be related back to the amount of glucose in the sample that reacts with glucose oxidase. The hydrogen peroxide generated from the naturally occurring oxygen allows the reaction of the enzyme and substrate to be sensed at the electrode and can be characterized as a mediator between the enzyme reaction and the electrode. The discovery was made that electroactive molecules could be added to the reaction that would perform the same function as oxygen.¹² Unlike oxygen that is naturally present in most samples, these compounds would need to be added to a sample because they are not naturally occurring compounds. The electroactive molecules also function to mediate the reaction between the enzyme reaction and the electrode, hence they are called mediators. Replacing oxygen with a mediator has many advantages, which will be described in greater detail in the following sections.

5.1.3.2 Electrode Configurations The term “electrode” has different meanings depending on the context of the use of the term. Electrode could mean a single piece of metal at which one reaction occurs. Electrode also has the meaning

of a device that senses a specific compound, such as a “combination pH electrode.” In reality, a combination pH electrode is a pH sensor that is composed of a pH electrode and a reference electrode. In this chapter, the complete device for detecting glucose will be referred to as a glucose sensor. The glucose sensor is composed of at least two electrodes, which will be explained in this section.

Electrochemical detection of glucose requires that an enzyme that reacts with glucose produce a change in the oxidation state of a reactant: oxygen or a mediator. The change in oxidation state must then be sensed at a metal surface by an exchange of electrons between the reactant and the metal surface. The electrode where this occurs is called the working electrode. The working electrode then must contain at a minimum the enzyme needed for the reaction and a metal surface for the exchange of electrons. The major characteristic required for a good working electrode is that the reaction with the reactant should be fast and should remain so for the whole duration of the measurement. Metal surfaces have a tendency to adsorb other molecules that may physically block the exchange of electrons, which results in a “poisoning” or “fouling” of the working electrode, as described in Section 1.6.1. Many designs of working electrodes contain a membrane that prevents the poisoning of the metal surface.

At a minimum, the working electrode must be electrically coupled to a second electrode that “completes the circuit.” The second electrode must allow a current to flow into or out of it that is directly opposite to the current flowing through the working electrode. A battery will not work if only one end of it is attached to the device that it is intended to power. Both ends of the battery are required to be attached so that a current can flow out from one end of the battery into the other end. The electrode that performs this function is called the counter electrode. The main requirement for the counter electrode is that it must always pass a current that is larger than the working electrode so that the current at the working electrode is not limited by the current output at the counter electrode.

A third electrode function, called the reference electrode, also needs to be performed for a reliable electrochemical measurement of glucose. The reference electrode serves the purpose of providing a known electrochemical potential for the sensor. A reference electrode has associated with it a chemical reaction that occurs at a known potential. At this point, the concept of potential will be explained in a manner as simple as possible to fully comprehend how the various electrodes operate. All CGM systems use a silver/silver chloride reference electrode. The reduction of silver chloride to silver occurs at a known potential. The potential is the energy of the electrons in the metal part of the electrode. The potential of the silver/silver chloride reaction is known and constant as long as the chloride level in the sample is known and constant. The chloride level in the body varies over a narrow range, 98–108 mM, and so it is relatively constant for each person. The importance of having a defined and stable reference electrode cannot be underestimated. The electronics that control the sensor apply a potential difference between the working electrode and the reference electrode. Since the potential of the reference electrode is fixed, the potential to which the working electrode is driven by the electronics is also known and fixed. When an oxidation occurs at an electrode, the electrochemical potential of the electrons in the reactant can find a lower electrochemical potential in the metal electrode, so they

transfer to the electrode. The potential of the working electrode *must* be at such a level where the reactant will react when it arrives at the metal surface, so that a current is produced that is proportional to the amount of glucose in the sample (for a basic explanation of electrochemical reactions, see Chapter 1 of Ref. 13). In some commercial CGM systems, the function of the counter electrode and the reference electrode are combined into one electrode. Sensors that have only one working electrode and one reference/counter electrode are called “two-electrode” sensors, and sensors with separate working, counter, and reference electrodes are called “three-electrode” sensors. The advantages and disadvantages of each type will be discussed in Section 5.5.

5.1.3.3 First/Second/Third-Generation Sensors The technology of electrochemical sensors can be described in terms of first-, second-, and third-generation sensors.^{14,15} The term generation does not mean that one generation was developed prior to the other, but rather it is strictly used to identify the chemical reaction used to make the glucose measurement. The commercially available CGM systems are either the first- or the second-generation sensors, and future systems are likely to be third-generation sensors. A first-generation glucose sensor uses oxygen to react with glucose oxidase and produce hydrogen peroxide (Figure 5.1). Hydrogen peroxide is then oxidized at the metal surface of the working electrode. The potential at which the metal surface must be maintained to enable the oxidation of hydrogen peroxide to occur is 600–700 mV when using a silver/silver chloride reference electrode. First-generation sensors must find a way to cope with the large concentration difference between oxygen and glucose. In people with diabetes, glucose is 2–30 mM and the oxygen concentration is typically 0.1–0.3 mM. The desire is to have the enzyme reaction be limited by the concentration of glucose and not by the concentration of oxygen, so all first-generation systems face this problem.

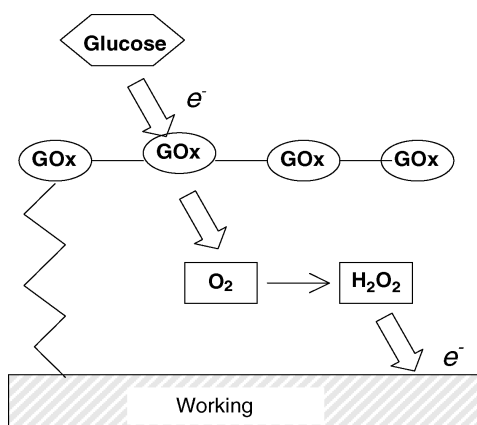


Figure 5.1 Electrochemical reaction of glucose with glucose oxidase immobilized on a working electrode. Copyright 2008 Abbott. Used with permission.

First-generation systems require that a diffusion barrier be used that slows down the diffusion of glucose more than that of oxygen so that the oxygen concentration is not rate limiting. Polymers with high oxygen solubility, such as polyurethanes and polysiloxanes, are good choices (for further discussion of membrane properties, see Section 1.2.2). Necessarily, when the glucose diffusion is restricted, the current generated is also reduced, which can make the miniaturization of such systems problematic. Another solution to the oxygen limitation is to dilute the sample containing glucose, which lowers the glucose concentration but not the oxygen level. The YSI glucose analyzer was the first electrochemical glucose analyzer to be sold and it relied on dilution of samples. Of course, sensors implanted in the body cannot rely on diluted samples.

A second-generation sensor uses an exogenous mediator (i.e., a mediator other than hydrogen peroxide) to react with glucose oxidase instead of oxygen (Figure 5.2). The mediator can be added at a higher concentration than oxygen to eliminate the problem of low oxygen concentrations. All single-use electrochemical test strips sold today are second-generation sensors. The potential at which the mediator can react at the metal surface of the working electrode can be manipulated based on the chemical structure of the mediator. The commercially available CGM system based on second-generation technology uses a potential of approximately 40 mV versus a Ag/AgCl reference electrode. The second-generation sensor does not require as restrictive a membrane as the first-generation sensor to slow down the diffusion of glucose, so the currents can be higher. The challenge of using a second-generation system inside the body is that the mediator must remain attached to the sensor. The mediator must also maintain its ability to react with the enzyme after it is coupled to the working electrode. Attempts were made to physically entrap the mediator over the electrode using a semipermeable membrane, but the mediator can leak out and the construction of this type of sensor is complex.^{16–18} Immobilization of the mediator in a “redox polymer” has been more successful.¹⁹ Development of a second-generation glucose sensor that can be used inside the body has been challenging and only recently it has been approved by the FDA and commercialized.

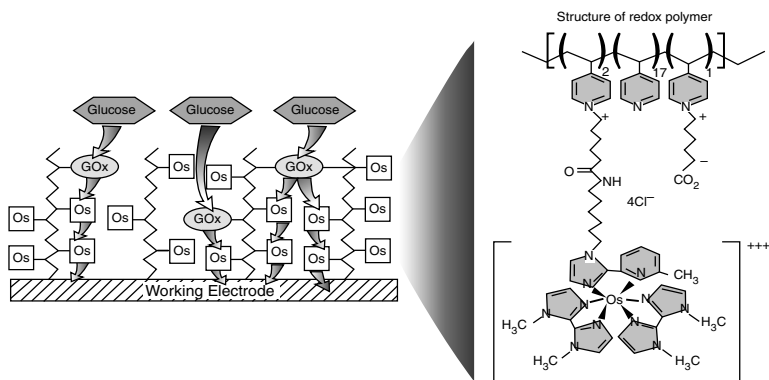


Figure 5.2 Electrochemical reaction of glucose with glucose oxidase immobilized within a redox polymer on a working electrode. Copyright 2008 Abbott. Used with permission.

Home use glucose test strips do not require that the mediator be confined to the working electrode. As a result, the single-use, second-generation home use glucose test strips have been commercially available for 20 years prior to the implanted second-generation glucose sensor being approved.

A third-generation sensor will not require oxygen or a mediator to react with the enzyme. In a third-generation sensor, the enzyme itself is in electrical communication with the metal surface of the electrode. Electrons can be transferred back and forth between the metal surface and the enzyme. Making such an electrical connection has proven difficult, but some recent success has been reported.^{20–23} The active site of the enzyme is typically buried inside the enzyme so that exchange of electrons with the metal surface is difficult. If such a system is developed, it would have the advantages of second-generation system because it would not be oxygen dependent and would have the simplicity of a first-generation sensor because it would not require a mediator. The third-generation systems developed to date show a sluggish electron exchange with the enzyme.²⁴ The electron exchange can be increased by applying a larger potential to the metal surface, but applying a larger potential makes the electrode more susceptible to electrochemical interferences that can be found inside the body.

5.2 HISTORY OF CGM

5.2.1 Doctor Updike and Generation 1 (Dexcom)

One of the first researchers in the field of continuous glucose monitoring and enzyme electrodes is Dr. Stuart Updike of the University of Wisconsin. Dr. Updike published an article in 1967 on the electrochemical detection of glucose based on the depletion of oxygen from the reaction of glucose with immobilized glucose oxidase.²⁵ As a practicing nephrologist, Dr. Updike noted the utility of such a sensor to provide continuous glucose results for the care of patients with diabetes. In 1980, Dr. Updike was granted a patent for a system that would automatically extract blood out of a patient, mix the blood with a diluent, and then read the glucose concentration using a sensor.²⁶ The sensor had glucose oxidase immobilized on the surface that reacted with glucose and caused a local reduction in the oxygen concentration. The blood samples were oxygenated to a constant level. The patent proposed that samples could be extracted as often as every 2 min. Overall, the device is large and contains a pump, multiple valves, diluent solution, calibration solution, heparin solution, as well as the glucose sensor and electronics. The device could be used in a hospital setting but would not be practical for everyday use by a person with diabetes. In 1982, Dr. Updike and colleagues recognized that hydrophobic membranes would restrict glucose diffusion much more than oxygen diffusion.²⁷ If the membrane was effective, the reaction of glucose and glucose oxidase would not be limited by oxygen but by glucose. Using this special membrane, the sample did not need to be diluted, which raised the possibility of making a measurement directly in the body and the possibility of making an artificial pancreas was raised. The membrane was also found to stabilize glucose oxidase, which would be required for a glucose sensor to operate in the body.

The Updike group applied for a patent in 1985 for a glucose meter with a reusable glucose oxidase membrane that could measure glucose directly in blood.²⁸ The meter was eventually sold commercially by Eli Lilly under the name Direct 30/30.²⁹ The meter was different from all the other glucose meters designed for home use because the glucose sensor was reusable. It remains the only commercially available home use glucose monitoring system that was based on the detection of hydrogen peroxide, generation 1, rather than an exogenous mediator, generation 2. The glucose sensor could be used by a person with diabetes to run as many whole-blood fingerstick samples as they wished in a 30 day period. The membrane had to be kept wet between samples and calibrated once per day by the user using an aqueous calibrator. The analytical performance of the meter was good. The device was recalled because the user interface was not robust enough, but the Direct 30/30 demonstrated a significant improvement in glucose membrane technology. Previous membranes were often a series of very porous materials, for example, nylon netting. Updike's new membrane was a polyurethane membrane derivatized with anionic carboxylate groups and hydrophilic polyether segments.²⁸ This membrane had no defined pores and relied on the solubility of glucose and oxygen in the membrane to control the reactant flux to the enzyme. This new approach was able to slow down glucose diffusion much more than oxygen, so undiluted whole-blood samples could be analyzed. This membrane technology would also make it possible to operate a glucose sensor inside the body. At this same time, John Mastrototaro worked for Lilly on glucose sensors.³⁰ Mastrototaro moved to MiniMed and started their continuous glucose monitoring program.

Dr. Updike founded a company, Markwell Medical, which used the membrane technology to implant continuous glucose sensors in dogs.^{31–33} The implants contained all the sensor electronics, telemetry, and batteries to use the devices for many months. Dr. Updike pioneered the use of different materials to promote the regrowth of blood capillaries around the implanted device. The body naturally tries to wall off any implanted device because the body sees it as a foreign body. Using Velcro-like materials, Updike's group claimed to be able to promote the ingrowth of blood capillaries. The fully implanted sensor was rather large, 7 cm long and 1.2 cm high, because of the state of electronics miniaturization at that time. The device for its size was not attractive for human implantation and the company received very little funding for many years. In 1999, Markwell Medical received substantial funding and it was renamed DexCom. The objective of DexCom was to further develop the totally implanted continuous glucose sensors that Markwell Medical was using. Eventually, they were able to run a human clinical trial with mixed success.³⁴

5.2.2 Professor Heller and Generation 2 (Abbott)

The typical electrochemical glucose sensor has a problem with the low level of oxygen found in biological samples compared to the high level of glucose. The earliest electrochemical glucose analyzers diluted the sample to decrease the glucose concentration. The problem of low oxygen concentration was overcome in generation 2 sensors by the use of exogenous mediators that take the place of oxygen in the enzyme reaction. These mediators are soluble in blood, which makes them ideal for use in blood sampled from the body but would not be appropriate for use inside the

body. In the early 1990s, Dr. Adam Heller at the University of Texas developed polymers that contained mediators and enzymes chemically attached to the polymers.^{19,35} “Redox Polymers” could then react with glucose and did not require oxygen. Electrons are exchanged between the mediator on the polymer and the enzyme. The mediator is then able to exchange its electrons with the other mediators in the polymer until the electrons are eventually exchanged with the metal surface of the electrode. Because the process does not require oxygen, the need to decrease the glucose concentration is much less, so higher signals or smaller electrodes are possible. Exogenous mediators are also typically oxidized at lower potential than the endogenous mediator hydrogen peroxide, which is an advantage because fewer oxidizable interferences can be oxidized at low potentials. Although the theory is simple, the practical challenges of designing such a membrane are formidable. The mediator must be able to rapidly exchange electrons with the enzyme. Some home use glucose strips use mediators that do not exchange very rapidly with the enzyme, but they can overcome this limitation by using a large excess of mediator. There are limited attachment sites in a typical polymer, so large excesses of mediator cannot be created. If the mediator is too loosely attached to the polymer, the mediator will be lost and if the mediator is too tightly attached to the polymer, it may not be loose enough to react with the enzyme.

Dr. Heller and his son licensed the redox polymer technology from the University of Texas in 1991 and formed the company E. Heller and Company. The company became TheraSense in 1997 and was bought by Abbott Laboratories in 2004. Along the way of developing a subcutaneous implanted glucose sensor, TheraSense decided to also develop a glucose test strip for use outside the body. TheraSense’s glucose test strip business was very successful and it continued the development of an implanted sensor. The long time required to commercialize a product is an indicator of the tremendous challenges that had to be overcome to commercialize a second-generation sensor.

5.3 PERFORMANCE REQUIREMENT OF CGM

5.3.1 Performance Measures

5.3.1.1 Clinical Use of CGM CGM systems are at present used by doctors and patients in one of the two ways that are described in this section and some of the future applications of the technology are covered in Section 5.7. The systems are approved to be worn for short periods, 3–7 days. The goal of these short wear sessions is to provide insight into the glucose patterns found within a person’s day. These patterns can be interpreted by a doctor to change the treatment regime of a person with diabetes. The first Medtronic CGM system approved did not even provide a live glucose result to the user. The data had to be downloaded at the doctor’s office and were viewed only retrospectively. The data, however, are still very valuable for the adjustment of insulin dosage and insulin type. One of the unique aspects of diabetes is that the person with diabetes has the control through the use of insulin, diet, and exercise to make a significant difference in their disease. Even with a live continuous display, the results

may need to be interpreted by a trained professional to see the correct pattern. Custom software is also expected to improve this interpretation by at a minimum speeding up the analysis. As the number of people with diabetes increases, the workload on primary care physicians and endocrinologist will become worse. Technologies like CGM are needed to allow doctors to make correct treatment decisions and more effectively use their time with the patient. Although the ability to see trends and adjust insulin dosing is important, the next use of CGM is as the lifesaver. If a person with diabetes chooses to wear a CGM device essentially everyday, then the information can be used by the person with diabetes in their everyday treatment of their disease. Again, the person with diabetes, especially those using insulin, decides how to treat their disease several times a day. The more information they have that can be easily interpreted, the better they can treat themselves. Using conventional blood glucose meters, they know what their glucose level is at the time when they made a glucose measurement. However, they neither know what their glucose level was 10 min before they made the blood glucose measurement nor do they have any means of estimating what it will be 10 min after. CGM devices enable them to know their glucose level every minute of the day. The CGM device can be used to set alarm levels to warn the person with diabetes when they reach a dangerous glucose level. Two of the devices will also project ahead and warn a user that they are heading for a potentially dangerous glucose level. The alarm features, however, are only important if the CGM device is accurate. An inaccurate device will lead to many false alarms and the user will eventually turn off the alarms because they are annoying. One CGM device that was not commercially successful suffered from this problem.³⁶

5.3.1.2 Accuracy Accuracy is the most important criteria used to judge the performance of an analytical measurement. A measurement of a body component, however, is judged differently than your typical laboratory analysis. Accuracy will not only be defined in terms that a scientists is normally accustomed to, but it will also be defined by the diagnostic requirements of the disease that the measurement is directed at. Accuracy can then become a curious mix of both analytical performance and medical necessity. The methods used to judge the accuracy of blood glucose meters are well established and have been applied to CGM systems. The accuracy methods used for glucose meters will be described along with the limitations of these methods when they are applied to CGM as well as the new methods that have been developed just for CGM.

The accuracy of home glucose meters can be measured like any other analytical technique by comparing the results of samples run on both a blood glucose meter and a reference instrument. The paired points are plotted with goals of a slope of one, intercept of zero, and minimal scatter about the unity line as measured by the correlation coefficient (r). The International Standards Organization (ISO) has chosen to define accuracy using a plot of paired points, but in a way that includes precision and takes into account the diagnostic significance of the points. Because glucose varies over such a wide range, the accuracy is defined differently for two different glucose ranges. Above 75 mg/dL glucose, 95% of the blood glucose measurements must be within $\pm 20\%$ of the reference instrument. Below 75 mg/dL glucose, 95% of the blood glucose measurement must be within ± 15 mg/dL of the reference

instrument. If the specification for above 75 mg/dL was applied to lower glucose levels, then the accuracy, absolute difference between blood glucose meter and reference instrument, of the measurement would have to improve so that at 20 mg/dL the allowed error would be ± 4 mg/dL. Such accuracy would be hard to obtain with the reference instrument and impossible with an inexpensive and disposable blood glucose strip. Using a range of ± 15 mg/dL is clinically acceptable at low glucose levels because the treatment is the same once a low level is reached, so the absolute accuracy is not needed. If the criteria of ± 15 mg/dL were applied to high glucose levels, the accuracy of the whole-blood glucose would have to be very good. This 15 mg/dL is only 5% of 300 mg/dL, which is significantly tighter than the 20% allowed. The treatment decision would be the same if the glucose value is within 20%, so this level of accuracy is acceptable at higher glucose levels. This method of defining accuracy inherently includes a measurement of precision. If a glucose meter was not precise, then 95% of the values would not fall within their ranges. The ISO method can be applied to the evaluation of continuous glucose meters by comparing the continuous blood glucose measurement to a blood sample taken at the same time and measured on a reference instrument. No ISO standards have been developed for CGM.

Dr. William Clarke wanted to know if his patients could accurately predict their glucose level based solely on how they felt.^{37,38} He asked patients to predict their glucose level based on how they felt and then measured their blood glucose level. Their predictions were not very accurate, but Dr. Clarke looked for a method of determining accuracy from relatively poor data. He decided to look at the data from the standpoint of whether the glucose prediction would be so far off so as to cause the patient harm or was it close enough to not to harm the patient. He developed what is known today as the Clarke error grid. The grid has several zones with different results for the patient depending on which zone the data are located. The grid is used by plotting data pairs from the device being evaluated and a reference instrument (see Figure 1.7). The grid has many of the same constraints as the ISO standard discussed above. Above 75 mg/dL, the results are good if they fall within $\pm 20\%$ of the reference value. Below 75 mg/dL, the grid is more tolerant than the ISO standard, which reflects the clinical reality that any low glucose value needs to be treated. The ISO standard requires 95% of the paired points to be within certain limits, but does not comment on the 5% of the points that can fall outside those limits. The grid seeks to classify these points in terms of the hazard to the patient, so it looks at the clinical significance of all the points. The grid became so popular that several variations have been debated to possibly improve the grid. The consensus error grid sought to fix some of the deficiencies of the Clarke error grid. Similar to the ISO standard, the grid measures both accuracy and precision.

The Clarke error grid and subsequent variations are better suited for the determination of the accuracy of new techniques like CGM than the ISO standard. The grid does not require the high degree of analytical accuracy that is necessary to pass the ISO standard. Many companies developing noninvasive glucose measurements have relied solely on the grid. The statistics from the grid can however be deceiving. A high percentage of data in the A and B zones of the grid does not mean the device being tested is accurate. Data in the B zone represent those data that are not

analytically very accurate but would also not harm the patient. In the opinion of the author, use of the ISO standard, possibly with relaxed requirements, and the grid together are the best ways to judge new technology.

Another parameter commonly used to measure the accuracy of glucose measurements is to report the differences between the CGM device and the reference instrument. The mean or median difference can be reported for all values. The median difference tends to be lower than the mean if there are any large outlier values. The sign of the difference measurement will show if there is any bias to the measurement. However, positive and negative deviations will cancel each other out, so this is not the standard parameter used. Taking the absolute value of all the differences eliminates the problem of differences canceling each other out. The difference will have the units of mg/dL. Because of the wide physiological range of glucose, a 20 mg/dL difference at high glucose level would be of no concern, while the same difference at low glucose level would be a concern. Since there is such a wide range of glucose values, the differences can be normalized by dividing it by the reference value. The new statistic is dimensionless and is often expressed as a percentage. The median absolute relative difference (MARD-median) and mean absolute relative difference (MARD-mean) are probably the most reported number for accuracy (equation (5.1)). Because the number is based on the absolute value of the difference, the MARD does not tell you if any bias is present.

$$\begin{aligned} \text{MARD}(\text{mean}) &= \left(\left(\sum \frac{|[\text{Glucose}]_{\text{sensor}} - [\text{Glucose}]_{\text{reference}}|}{[\text{Glucose}]_{\text{reference}}} \right) / n \right) \times 100\% \\ \text{MARD}(\text{median}) &= \text{MEDIAN} \left(\frac{|[\text{Glucose}]_{\text{sensor}} - [\text{Glucose}]_{\text{reference}}|}{[\text{Glucose}]_{\text{reference}}} \right) \times 100\% \end{aligned} \quad (5.1)$$

The following provides a practical example of how the different statistical parameters used to judge the accuracy of glucose monitoring relate to each other. A person with type 2 diabetes using insulin to control the disease performed 176 glucose measurements using a blood glucose meter over a 23 day period. The average of all the glucose values was 205.6 mg/dL, which is a higher average than would be desirable, but this subject may be representative of a large number of the population with diabetes who are not in good control of their glucose. Each of the 176 glucose values was randomly assigned an offset that would result in a specified standard deviation for the whole data set. The various statistical parameters were then calculated for the encoded level of variation in the glucose values. If the process were repeated on the same data set, the results would have been slightly different because of the random assignment of the deviations. The results are summarized in Table 5.1 and a series of Clarke error grids are shown in Figure 5.3. The mean absolute difference (MAD) tends to change proportionally with increasing error while the Clarke error grid zones exhibit a more unusual behavior. The Clarke error grid zones change significantly when the errors cause certain boundaries in the grid to be crossed, as can be best seen in Figure 5.3. There is no deliberate offset of the slope or Y-intercept encoded into the results. If errors were introduced into the slope and intercept, some of

TABLE 5.1 Simulated Error in Glucose Measurements

(a)

Error at 1 SD mg/dL	Slope	Intercept mg/dL	<i>r</i>	MAD mg/dL	MARD	SE mg/dL	SRE
10	1.002	0.4	0.99	8.7	4.2%	10.7	5.2%
20	1.004	0.8	0.96	17.4	8.5%	21.4	10.4%
40	1.008	1.6	0.85	34.8	16.9%	42.8	20.8%
60	1.011	2.4	0.74	52.1	25.4%	64.2	31.2%
80	1.015	3.2	0.63	69.5	33.8%	85.6	41.7%

(b)

Error at 1 SD mg/dL	Distribution of data points in error grid					
	A	B	C	D	E	Outside
10	99.4%	0.1%	0.0%	0.6%	0.0%	0.0%
20	96.0%	3.4%	0.0%	0.6%	0.0%	0.1%
40	76.8%	21.8%	0.1%	1.0%	0.0%	0.3%
60	58.5%	36.0%	1.8%	2.2%	0.6%	1.0%
80	46.5%	40.0%	5.7%	3.5%	1.5%	2.6%

MAD, mean absolute difference; MARD, mean absolute relative difference; SD, standard deviation; SE, standard error; SRE standard relative error.

the parameters would be affected and others would not. The standard error is not normally reported for CGM, but is a popular metric for noninvasive glucose monitoring systems. The standard error and mean absolute difference are very similar for measurements without significant outliers. The standard error is significantly higher than the mean absolute difference when significant outliers are present in the data set.

The different methods of measuring accuracy were all developed for blood glucose meters that provide a reliable glucose measurement at one point in time. Since CGM provides a continuous stream of glucose results, are the same accuracy measures appropriate for CGM? Any single glucose result reported by a CGM device is preceded by many glucose measurements and followed by many more glucose measurements. Does the wealth of data provided by CGM devices mean that they do not need to meet the same accuracy requirements of glucose meters? This question is still being debated. In the near future, the common accuracy metrics used for blood glucose meters will be applied to CGM devices because no other methods have been established as industry standards. When are the CGM results good enough so that the person with diabetes does not need to use blood glucose fingerstick measurements and can rely solely on the CGM results? This is still an unanswered question because no CGM device has been approved that does not require calibration with blood glucose measurements.

CGM devices have the ability to alarm the patient if their blood glucose level is beyond the preset limits or even if the device projects that the patient’s blood glucose level will be beyond the preset limits. The accuracy of the alarms can be measured based on the number of true alarms given, false alarms given, and alarms that should

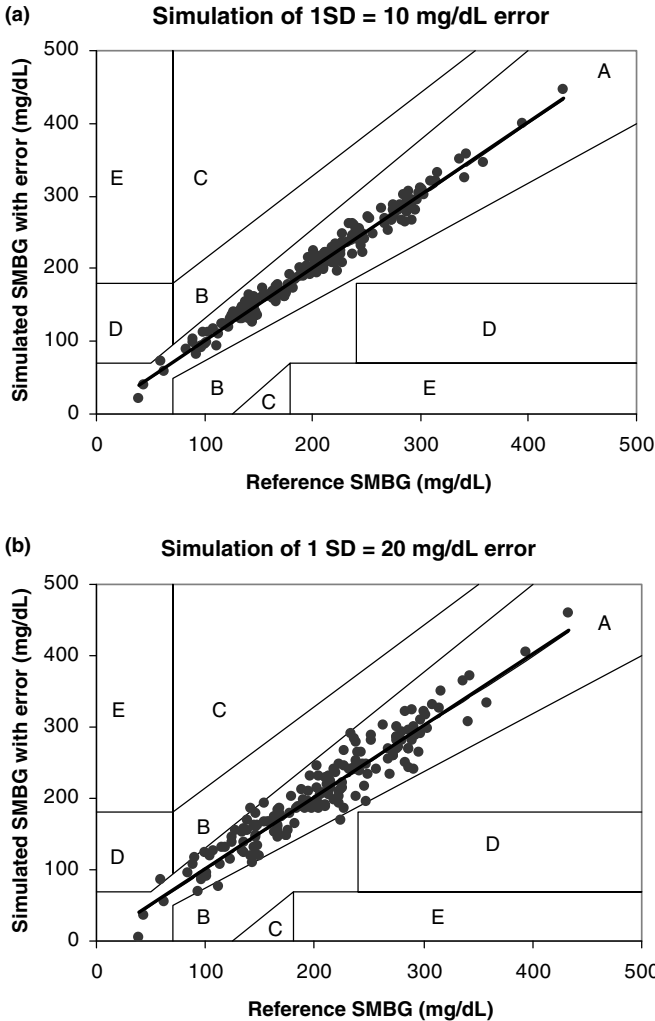


Figure 5.3 Simulation of the incorporation of different amounts of error into self-monitoring blood glucose (SMBG) readings: (a) -10 mg/dL, (b) -20 mg/dL, (c) -40 mg/dL, and (d) -80 mg/dL. Copyright 2008 Abbott. Used with permission.

have been given but were missed. The subject is so complicated that another chapter would be needed just to cover this subject (see additional information in Section 1.3.2.1). Since blood glucose meters do not alarm, they do not provide any history to establish acceptable criteria. Does a false alarm in the middle of the day matter less than a false alarm in the middle of the night that wakes the person up? If the CGM reads 79 mg/dL and alarms and the blood glucose is 80 mg/dL, above the alarm threshold of 79 mg/dL, is that a false alarm? Everyone would agree that the CGM is

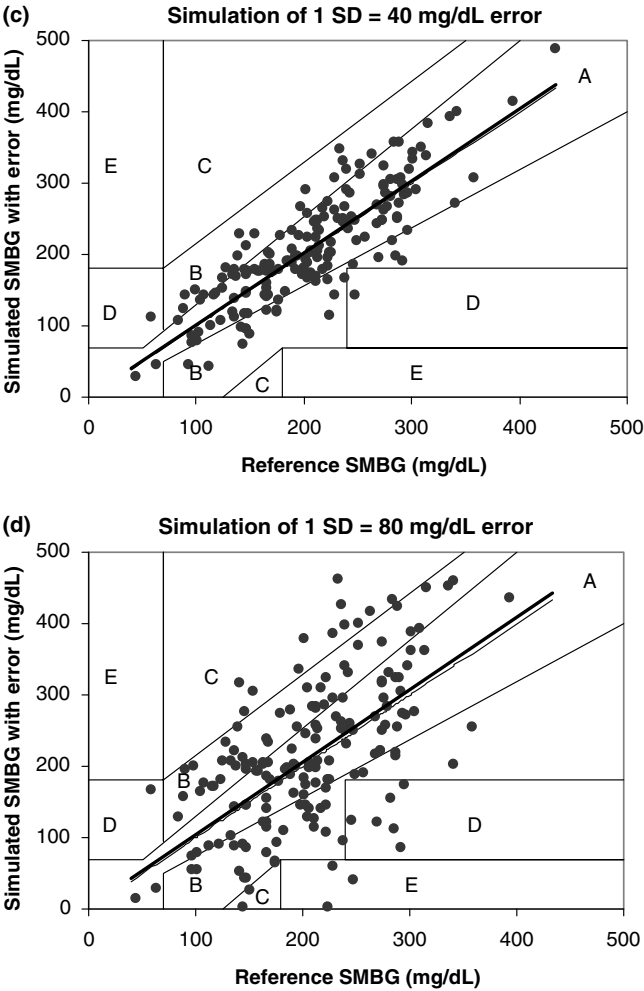


Figure 5.3 (Continued)

giving an accurate reading when it reads 79 mg/dL because it is so close to the blood reading of 80 mg/dL. Several methods of reporting alarm accuracy have been proposed, but no consensus exists today on which method is correct.

5.3.1.3 Precision Measuring the precision of blood glucose strips is very easy and involves testing a number of strips with the same sample with a fixed glucose level. The standard deviation and relative standard deviation (also called percent coefficient of variation) can then be easily calculated for the strips. There is no such easy precision measurement for CGM devices. The manufacturers have placed two CGM devices in a person and then compared the glucose readings made by each

device at the same point in time. Because the device measures glucose as frequently as every minute and can be worn for several days, a comparison of two devices can yield thousands of paired data points. The differences between the paired points can be calculated and a standard deviation of the differences calculated to indicate the precision. However, the precision only compare two devices. It would not be practical to put 20–30 devices in one person to get a better indication of the device to device variability. Two devices could be worn by a number of people, which adds the person to person variability to the device to device variability. Precision is, therefore, a rarely quoted statistic for CGM devices. As mentioned in Section 5.3.1.2, precision is a component of most of the accuracy measurements, so it is not totally neglected.

5.3.2 User Requirements

5.3.2.1 Short-Term Versus Long-Term Systems All the CGM devices on the market are at present approved for either 3, 5, or 7 days of wear. These short-term systems fulfill the needs of the person with diabetes for the monitoring of glucose patterns, as described in Section 5.3.1.1. These systems can also be worn continuously by changing the systems every 3–7 days. A long-term system, greater than 6 months, would at a minimum have a device implanted in the body and a display outside the body. Such systems are being developed and will be discussed in Section 5.7. Both types of systems require some type of calibration using a fingerstick blood glucose measurement. The frequency of calibration of the short-term systems is approximately daily, while the frequency of calibration of the long-term systems has not been determined but is likely to be less frequent than short-term systems.

The short-term systems are the only systems on the market. Because the devices are inserted by the user at home, they allow a user to choose how often and at what times they want to wear the device. The person with diabetes may not want to wear the device at times for personal reasons. Short-term devices are flexible and the diabetic can ease into the use of the device. Long-term systems require a long-term commitment to the use of the device. Inserting the long-term device and retrieving it from the body will likely be done in a physician's office and some of the larger devices require surgical procedures. The long-term devices do eliminate the need to change the device every few days as is required for the short-term devices. The long-term devices will also be more discrete than short-term devices because a transmitter or wires will not have to be worn by the diabetic on the skin. Long-term systems, however, are years away from reaching the market.

On-market CGM devices are limited to 3–7 day. There are several technical reasons that will make extending the lifetime beyond 7 days very difficult. The most daunting task is to get the devices to stick to the skin for more than 7 days. The skin continually expels dead cells, so its surface is not stable. The lifetime can be extended by placing bandages over the device to help it adhere, but this secondary bandage will still have many of the same limitations of the primary adhesive used to stick the devices. The longer the device remains in the skin, the greater the chance of an infection developing around the site. Bacteria can grow along transcutaneous devices and form biofilms that can lead to infection. No serious infections have been reported with the current 3–7 day devices. The longer the device remains in the body, the greater

the chance that it will evoke an immune system response that could alter the system performance. The recommendation is to replace insulin cannulas every 3 days, but this may be because of the irritating effect of the insulin on the local tissue provoking an inflammation response. The CGM sensors seem to evoke much less tissue irritation. A final technical challenge will be sensor lifetime for extended periods of time. The robustness of the sensors for extended insertion times has not been reported.

5.3.2.2 Types 1 and 2 Diabetes The term diabetes covers a wide range of conditions and each of these conditions has different needs for CGM. Type 1 diabetes is defined as a complete loss of insulin secretion that typically happens at a young age. People with type 1 diabetes depend completely on the injection of insulin to live. These people must pay attention to the glucose level throughout each day or risk serious short- and long-term health consequences. A major threat to the life of a person with type 1 diabetes is to pass out while operating machinery such as driving a car because of low glucose (hypoglycemia). The consequences of low glucose are threatening enough that the person with type 1 diabetes will spend large portions of the day with high glucose levels (hyperglycemia) to protect themselves from passing out. High glucose levels over a long period of time will damage the eyes, kidneys, and nerves as well as cause cardiovascular disease. The type 1 diabetic, therefore, will be a key user of CGM devices. The person with type 1 diabetes has already shown a desire to seek new technology to treat their disease by adopting insulin pumps. The CGM device needs to protect the diabetic by setting of alarms if their glucose is low or high. The alarm feature is especially important during sleep when the person with diabetes is not aware of the typical physiological clues that warn them of problems. The CGM device will also allow tighter glucose control by allowing the person with diabetes to safely maintain a glucose level that is not too high. A distinct subset of type 1 diabetics is younger children where the parents are primarily responsible for the patient's treatment. This small population will likely be one of the firsts to adopt CGM because the parents need information to manage their child's disease as the child may not be capable of communicating effectively.

Type 2 diabetes is a very complex disease where the cells of the body are not able to utilize the insulin produced by the body. The disease is usually associated with aging and obesity. Describing the disease as the body has too many cells (fat) for the amount of insulin produced is a gross simplification. Losing weight no doubt typically helps the type 2 diabetic regain glucose control but the disease is progressive. The disease is treated by weight loss, better nutrition, and drugs that help the body better utilize the insulin present. Patients at this stage of the disease do not suffer from the extreme glucose levels as seen in type 1 diabetes and would not need the advantages of CGM. The loss of glucose control becomes worse with time and eventually some people with type 2 diabetes start using insulin injections to help maintain glucose control. The person with type 2 diabetes at this stage has not completely lost their insulin production, but the loss is bad enough to require insulin injections. At this point in the disease, measuring glucose levels more frequently is required. The injection of too much insulin can produce hypoglycemia and hyperglycemia becomes more prevalent. The disease begins to resemble type 1 diabetes but the patients are typically older. Because of their age, these people with type 2 diabetes may not be as

technologically savvy as the typical person with type 1 diabetes and therefore less able to handle CGM devices. However, the large aging population in the United States, known as “baby boomers,” now facing type 2 diabetes is much better prepared to handle technology than previous generations. A paradigm shift is possible where aging baby boomers will adopt some of these newer technologies to achieve a better quality of life. The baby boomers are also more likely to be able to afford the new technology than past generations.

5.3.2.3 Ease of Use The use of a CGM device involves a number of skills that may not be present in all people with diabetes. A patch is applied to the skin and a sensor inserted across the skin. The procedure is similar to inserting an insulin catheter for an insulin pump, so it should be simple enough for any insulin pump user to do. Applying the adhesive patch is similar to applying a Band-Aid and should be simple enough for most people with diabetes to accomplish. The sensor insertion needs to be simple because it will be done on the outer part of the forearm or on the stomach. Performing the insertion on the arm means that it will have to be done with one hand. The insertion should not involve any complicated twisting, turning, or pulling. Adults certainly have enough available skin space to wear the devices on a continuous basis, which would involve rotating to different sites as the previous wear site heals. Small children who wear the devices continuously may have to use alternate body sites such as the buttocks. One of the on-market devices is at present approved for use by children.

The CGM devices will be used by patients at home on a regular basis, so the process of using the device should be simple to learn and simple to do. Placement on the body and insertion of the device were discussed and another potentially complex operation is the calibration of the device. Once the devices are placed on the body, they all require a minimum of one blood glucose value for calibration. Ideally, the blood glucose value would be automatically read by the CGM device and used for calibration. Requiring a separate blood glucose meter for calibration requires that the data be transferred in some manner from the blood glucose meter to the CGM device. The transfer can involve cables and additional steps that make the process more complex. One manufacturer has placed a blood glucose meter inside their display device, so the transfer of information is done automatically for the user. In this case, the display device can also be used to perform blood glucose measurements to check the accuracy of the CGM device and a separate blood glucose meter does not have to be carried around by the user. The device that displays the glucose results should be easy to read in different lighting conditions and have buttons and menus that are easy to navigate. Because of the proliferation of handheld electronics such as cell phones, the design of user interfaces is a well-known skill and most devices are intuitive to operate.

5.4 HOW TO MAKE A MEASUREMENT

5.4.1 Components

All the on-market CGM devices have similar components and the details of each manufacturer’s device will be explained in the subsequent section. An adhesive holds

a patch to the skin. The sensor is inserted across the skin using a sharp device to make a cut into the skin and the sharp device is then retracted leaving the sensor in the skin. The sensor has a glucose-oxidase-based working electrode located under the skin and electrical contacts located above the skin. Electrical contact is made from the sensor to an electrical measuring apparatus, the potentiostat. The electrical measuring apparatus is powered by batteries. The electrical measuring apparatus is reusable and may be integrated into the sensor patch or separately attached to the skin and connected to the sensor patch using wires. The electrical measuring apparatus communicates with a device that displays the glucose results using telemetry. The display device is also used to input calibration information. Besides displaying the most current glucose value, the display device will also show plots of the glucose values over time, alarm settings, and various software menus. The display device will have a large memory typically capable of recording glucose results of months.

5.4.2 The Signal

The working electrode of the sensor contains the enzyme glucose oxidase. The enzyme reacts with glucose and the enzyme is reduced. The reduced enzyme then reacts with either oxygen, the first-generation sensor (Figure 5.1), or exogenous mediator, the second-generation sensor (Figure 5.2). The hydrogen peroxide produced by the reaction with oxygen or the reduced exogenous mediator is oxidized at the metal surface of the working electrode that is poised by the potentiostat at a potential sufficient to cause the oxidation of the hydrogen peroxide or the mediator. Electrons flow into the metal surface and an equal number of electrons flow out of the counter electrode (or combination counter and reference electrode if the system is two electrode). The technique of measuring the current while the potential is held constant is called chronoamperometry. More sophisticated potential profiles, such as sweeping the potential over a fixed range, are often used in electrochemical measurements. However, since the current measurement will be made continuously for several days, keeping a constant potential is an advantage because it allows a constant glucose diffusion profile to be established across the enzyme-containing membrane that covers the metal conductor. The flux of reactant to the metal surface then becomes a function of the flux of glucose across the membrane. The concentration of glucose at the metal surface is assumed to be zero because sufficient enzyme is present to oxidize all the glucose. The concentration of glucose at the membrane surface in contact with the body is assumed to be the concentration inside the body. The change in glucose concentration from the surface in contact with the body to the surface in contact with the metal conductor is the concentration gradient that drives glucose diffusion into the membrane. Over a defined period of time, the amount of glucose diffusing into the membrane is the flux of glucose. If the glucose concentration in the body increases, the flux of glucose entering the membrane will be higher and the amount of reactant reaching the metal surface will be higher leading to a higher current. The thicker the membrane, the longer it will take for the change in flux outside the membrane to affect the flux inside the membrane. As a generalization, thicker membranes will react more slowly than thinner membranes. The diffusion coefficient of the glucose in the membrane will also affect how quickly the current changes. The change in response

is often called the “response time” of the electrode and can be reported as the time for the current to change 90% of the final change.

An important consideration in the design of the electrode is the thickness of the enzyme membrane. The membrane needs to contain an excess of glucose oxidase so that all the glucose arriving at the membrane will be oxidized within the membrane. The amount of enzyme in the membrane will be determined by both the concentration of the enzyme in the membrane and the thickness of the membrane. The membrane controls the flux of glucose and oxygen into the membrane. Because it plays a pivotal role in determining the current, any changes in the solubility or diffusion rate of the reactants will affect the current. Changing membrane properties can be partially compensated for by the calibration process that will be explained in the subsequent section. An ideal electrode would require very few calibrations. A sensor that does not require calibration has not been commercialized. The membrane will also play a key role in determining how sensitive the sensor is to motion within the body. An ideal sensor would consume so little glucose that there would not be any glucose gradient in the body outside the membrane surface. If such a gradient existed, then it could be disturbed by movement of the sensor or by movement of the fluid around the sensor. The generation 1 sensor produces hydrogen peroxide that is not naturally present in the body. The hydrogen peroxide will diffuse not only to the metal surface of the electrode but also into the body. The generation 2 sensor has immobilized mediator, so the reactant does not diffuse into the body.

The current flows continuously through the electronics but is typically digitized at a fixed frequency. A number of digitized current measurements can be averaged to provide a single current value or converted to a single glucose value that will be displayed to the person with diabetes using the device. The method of converting the current to a glucose value is called “calibration” and is explained in the following section.

5.4.3 Calibration

The current produced by the continuous glucose sensor must be converted into a glucose value in order for it to be useful to the user. A device that comes precalibrated, such as is done with glucose test strips, would be ideal because it would not need any calibration. This has challenges because each insertion of the sensor into the body produces a unique response. Calibration requires that the current produced at a point in time is matched to a blood glucose measurement made with a glucose strip. The current can be divided by the glucose level determined by the glucose strip to produce a glucose sensitivity factor. This simplified explanation assumes the current is zero when the glucose concentration is zero or is predictable. Future glucose levels can be calculated by dividing the current by the sensitivity factor. This method of calibration looks to be very straightforward and should not be a cause for concern. In reality, a number of factors make calibration a challenging process that requires a detailed discussion to understand all the possible implications. This section will briefly review some of the more interesting challenges; however, a whole chapter could be devoted just to the calibration of CGM devices.

The calibration is done with one or more blood glucose measurements using blood glucose strips. The blood measurement will then set the glucose sensitivity

factor and affect the accuracy of all future sensor results until another calibration is accomplished. Blood glucose strips do not have the accuracy of the more sophisticated glucose analyzers used in central laboratories (see Section 5.3.1.2 for glucose strip accuracy). It would not be practical for people with diabetes to carry around with them large clinical analyzers, so glucose strips are the only possibility for calibration. The inaccuracies of the blood glucose strips will then affect the accuracy of the CGM results and in essence CGM measurements can be no more accurate than the technique used to calibrate them. Once the CGM sensor is calibrated, the question becomes when does it need to be recalibrated? The manufacturers of on-market CGM systems all employ different recalibration schemes, which points to the complexity of the question. An empirical approach involves calculating accuracy based on using different numbers of calibration points and at different frequencies. With the increase in the number of calibration points and the frequency of calibration, the accuracy will reach a level at which additional calibrations do not measurably improve the accuracy. The frequency of calibration must also be tolerable to the user otherwise the device would not be used, so a compromise is struck between increasing the number of calibration points and making a device that can be used. It is also a matter of fact that a user would not want to do calibrations in the middle of the night.

Some researchers have suggested that CGM sensors need to be calibrated by taking blood glucose measurements at two points in time when the blood glucose measurements are very different. By pairing the two blood glucose measurements to two current readings of the sensors, the two data pairs can be used to calculate a line that describes the response of the sensor. This approach is important if at zero glucose the current is not zero or is not predictable. If at zero glucose the current is zero or a known stable value, then this can be used as one point for defining the calibration line and a blood glucose measurement, or measurements taken substantially at the same time can be used as a second point to define the calibration line. Since all the on-market CGM systems do not require a pair of glucose values with differing values, they either have zero current at zero glucose or assume or predict what the current is at zero glucose. The calibration can also be limited by the blood glucose reading. The manufacturers limit the range of acceptable blood glucose values so that low glucose and high glucose values cannot be used for calibration. The manufacturers presumably do this because they have found that extreme blood glucose values are not as reliable for calibration as more moderate glucose values. Calibration when glucose is rapidly rising, such as immediately after eating, is not recommended. The limitations applied to calibration would seem to be related to the dynamics of equilibration between the blood and the interstitial space where the sensor is placed in. As mentioned previously, the subject of calibration is both complex and controversial and is one of the continuing challenges to improve the accuracy of CGM sensors.

5.5 COMMERCIALY AVAILABLE CGM DEVICES

5.5.1 Medtronic

MiniMed obtained the first FDA approval for a CGM device in 1998 and was purchased by Medtronic in 2001. The first CGM devices from MiniMed did not

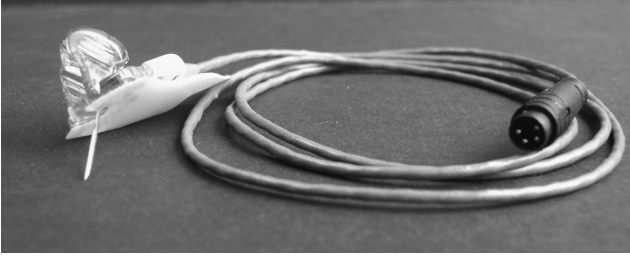


Figure 5.4 Medtronic glucose sensor with cable. Copyright 2008 Abbott. Used with permission.

display the glucose reading to the user. The sensor was inserted in a doctor's office and the patient carried a device that recorded the output of the sensor. When the patient returned to the doctor's office after 3 days, the data were downloaded into a computer along with a minimum of four blood glucose measurements per day that were used to calibrate the output of the sensor. The system made a glucose measurement every 10 s and every 5 min it stored the glucose data in its memory. This type of nondisplay device did not allow the user to manage their diabetes while wearing the device. The results were used by the doctor to observe the normal daily variations in glucose of the user and recommend insulin adjustments and possible lifestyle changes to the user. Improvements were made to the sensor performance and a discontinuity in the calibration algorithm that occurred at midnight was fixed. The device was sold under the name CGMS[®] System Gold.[™] As shown in Figure 5.4, the sensor is attached to a cable and the cable would be attached to a monitor that could be worn on a belt. Since the glucose result is not displayed on the device, the monitor could also be hidden under clothing.

Medtronic has now developed a system that displays the glucose results to the user in real time. The system is called Guardian[®] REAL-Time. The sensor is again placed in the skin but now a MiniLink[™] Real-Time transmitter is also attached to the sensor (Figure 5.5). The transmitter wirelessly sends the glucose information to a monitor that displays the glucose result. The system requires a blood glucose measurement every 12 h for calibration. The monitor can also display arrows showing the direction of change in glucose and the number of arrows displayed indicates how rapidly the glucose is changing. In addition, the user can program in warnings that will project future glucose readings and warn the user if their glucose is projected to be dangerously high or low. Alternatively, the monitor can be a Medtronic insulin pump that is equipped with the correct technology to receive and display the signal. This system is called the Paradigm[®] REAL-Time 522 or 722 pump.

The sensor that attaches to the skin is shown in Figure 5.6. A needle containing a slot is used to insert the sensor (Figure 5.7). The slot holds part of the sensor and allows the needle to be withdrawn but leaves the sensor in the body. The sensor is inserted at an approximately 45° angle and the length of the sensor in the body is 12 mm. The sensor consists of a plastic housing that contains within it a thin flexible substrate that contains working, counter, and reference electrodes (Figure 5.8). The sensor is a three-electrode sensor that does not require a large reference electrode because

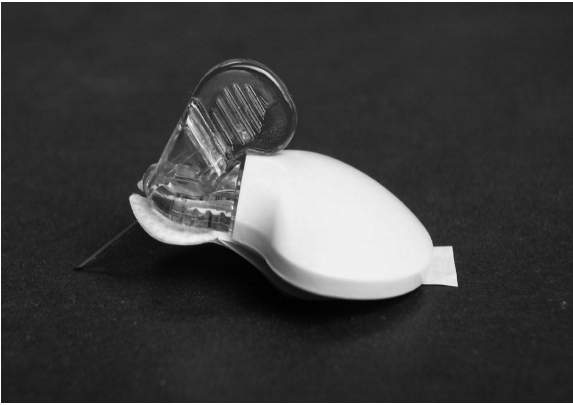


Figure 5.5 Medtronic transmitter and glucose sensor. Copyright 2008 Abbott. Used with permission.

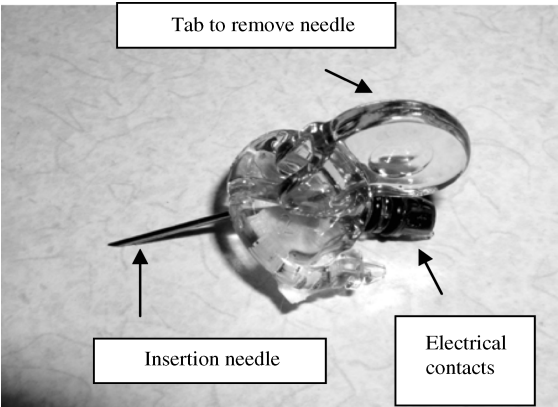


Figure 5.6 Medtronic continuous glucose sensor. Copyright 2008 Abbott. Used with permission.

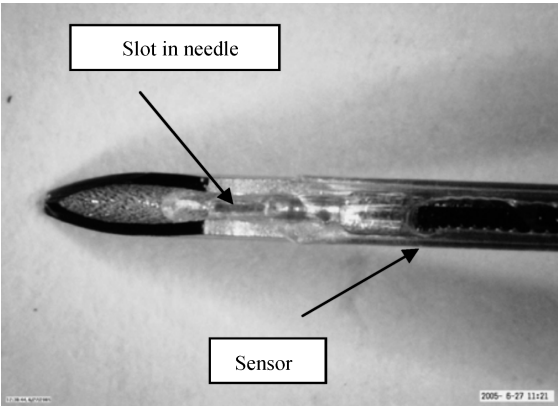


Figure 5.7 Close-up view of the metal needle with a slot where the Medtronic sensor sits within. Copyright 2008 Abbott. Used with permission.

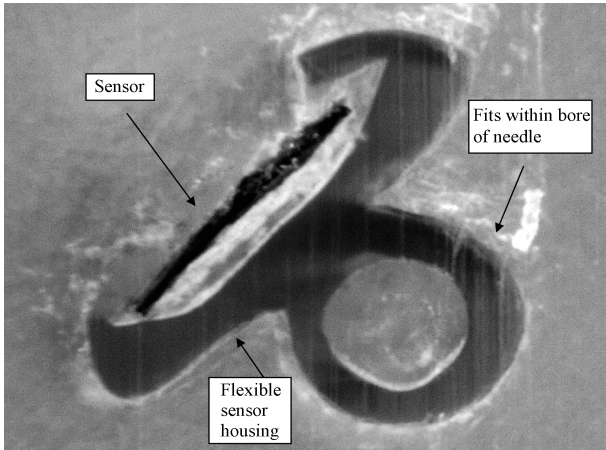


Figure 5.8 Cross section of the thin Medtronic sensor contained within a plastic housing and also showing the portion of the housing that fits within the bore of the needle used for the insertion. Copyright 2008 Abbott. Used with permission.

current does not flow through the reference electrode. A glucose oxidase membrane is applied to the working electrode. The membrane will react with glucose to produce hydrogen peroxide that is oxidized at the working electrode to produce a current. The sensor is, therefore, a first-generation sensor because it uses oxygen to react with the glucose oxidase. The construction of the sensor is proprietary, but some general observations can be made. The electrodes are formed on a thin plastic substrate using what appears to be a thin film process used in the semiconductor industry for patterning metals (Figure 5.9). Platinum is plated on the surface of the working electrode and gives the electrode a black appearance. The outer plastic housing appears to protect the thin flexible plastic piece that the electrodes are printed on during the insertion process into the body. The thin plastic piece with the printed electrodes has a wider portion that resides outside the body (Figure 5.10). The wider portion acts as points of electrical contact to a cable leading to the CGMS System Gold

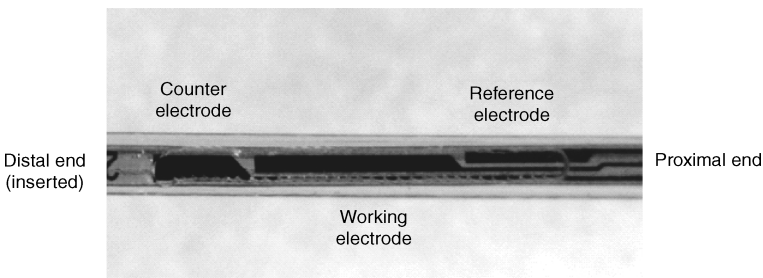


Figure 5.9 Close-up view of the Medtronic sensor showing the working, counter, and reference electrodes. Copyright 2008 Abbott. Used with permission. (See the color version of this figure in Color Plates section.)

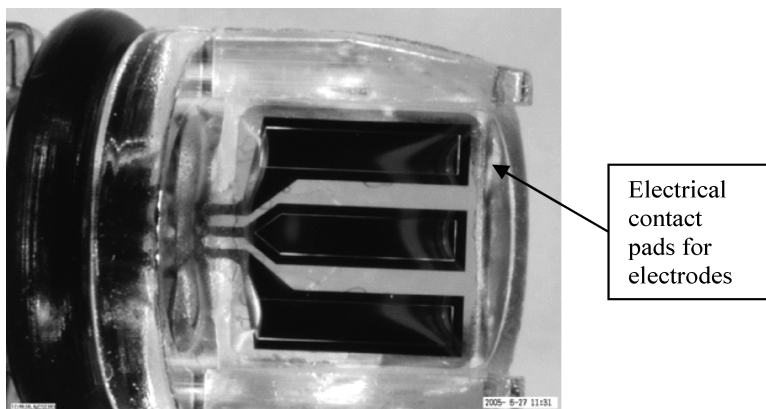


Figure 5.10 Close-up view of the Medtronic sensor's electrical contact pads for the working, counter, and reference electrodes. Copyright 2008 Abbott. Used with permission.

monitor or to the Guardian REAL-Time transmitter. Adhesive patches keep the sensor attached to the body for 3 days.

5.5.2 Dexcom

The company developed by Stuart Updike at the University of Wisconsin and under the name of Markwell Medical became DexCom in 1999. Although the company was originally started to commercialize a long-term implanted continuous glucose sensor, it later became focused on a subcutaneous sensor. Dexcom received FDA approval in 2006 to sell their 3-day continuous glucose monitoring system and in 2007 to sell their 7-day sensor. The 3-day device is named the DexCom short-term continuous glucose monitoring system (STS™) to differentiate it from the long-term system (LTS™) and the 7-day device is named the SEVEN™ STS®. The device was approved to be used with blood glucose strips, so the users do not solely rely on the STS glucose result for their treatment. This is referred to as an adjunctive use of the device. The device requires a prescription.

The general use of the system will be described and then a more detailed description of the sensor and how it is inserted into the skin will be provided. The sensor comes to the patient in a sterile package that contains a patch for adhering the STS sensor and STS transmitter to the skin and a sensor insertion device, STS applicator (Figure 5.11). The patch is applied to the skin by removing plastic tabs that cover the adhesive in a manner similar to an adhesive bandage. The user then pushes on the inserter and then pulls on the inserter, thus driving an approximately 24 gauge needle into the skin with the sensor contained within the needle and then removing the needle leaving the sensor in the skin. The used inserter is removed from the patch and discarded (Figure 5.12). The STS transmitter is inserted into the patch that causes it to make electrical contact with the sensor (Figure 5.13). The transmitter is powered by a nonreplaceable battery. The transmitter is in radio frequency

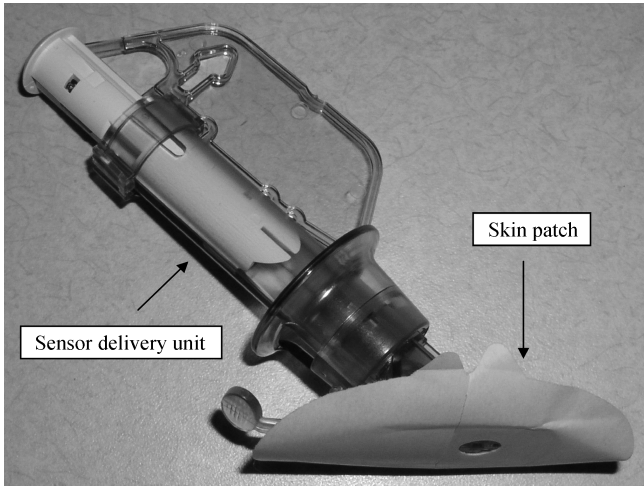


Figure 5.11 Dexcom skin patch with sensor delivery unit attached. Copyright 2008 Abbott. Used with permission.

communication with the STS receiver (Figure 5.14). The glucose results are displayed on the receiver.

Once the sensor is inserted, the user is instructed to wait 2 h before they are prompted to calibrate the sensor. The user must run duplicate blood glucose measurements using a specific brand of glucose meter and download the fingerstick data into the receiver. The calibrated sensor will transmit data from the transmitter to the receiver every 5 min. The data are stored inside the receiver and can be displayed

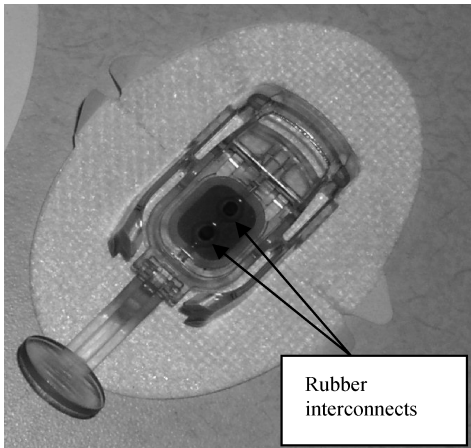


Figure 5.12 Top view of the Dexcom skin patch with the sensor delivery unit removed. Copyright 2008 Abbott. Used with permission.

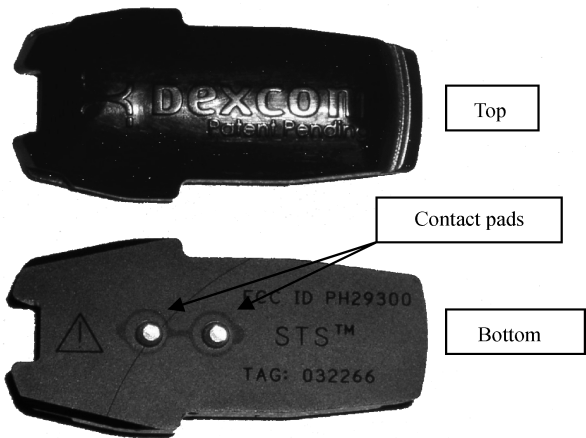


Figure 5.13 Top and bottom views of the Dexcom transmitter that is inserted into the skin patch. Copyright 2008 Abbott. Used with permission.

on the receiver’s screen in a number of ways. The sensor must be recalibrated using a blood glucose measurement at least every 12 h. After 3 or 7 days depending on the version of the product, the sensor and patch are removed and discarded but the transmitter is saved and used for the next insertion.

The electrodes inserted under the skin consist of a thin platinum wire and a silver wire with a silver chloride coating on the outside (Figure 5.15). The end of the platinum wire that is inserted under the skin is coated with an insulating coating except at the tip. At the tip of the wire some of the insulating coating has been removed and a membrane is visible. The exposed membrane contains glucose oxidase and is the site where the reaction occurs with glucose. The exact composition of the membrane is proprietary. A small distance further up the insulated platinum wire, the silver wire is wrapped around the platinum wire. The ends opposite to those in the skin of the platinum and silver wires do not go into the skin. At this end, the platinum wire does

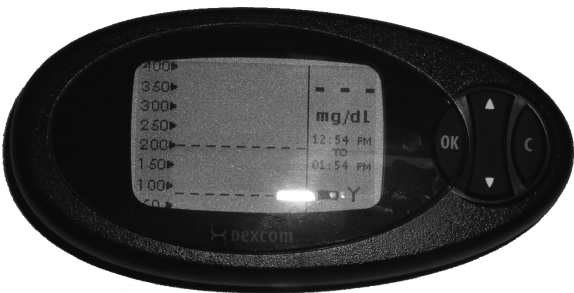


Figure 5.14 Top view of the Dexcom receiver unit. Copyright 2008 Abbott. Used with permission.

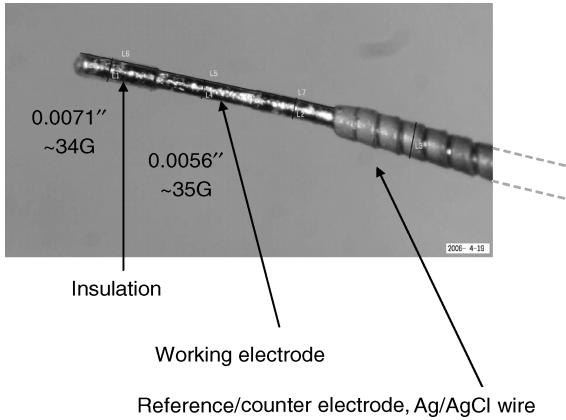


Figure 5.15 Close-up view of the tip of the Dexcom sensor that is inserted under the skin. Copyright 2008 Abbott. Used with permission.

not have an insulating coating and the silver wire does not have a silver chloride coating (Figure 5.16). The ends of these wires are used to make electrical contact with the STS transmitter.

The STS inserter places the platinum and silver electrodes into the skin and makes electrical contact between the electrodes and the adhesive patch. A detailed explanation is required to understand how the STS inserter works (Figure 5.17). In the unused inserter, the two electrodes are inside the barrel of the needle. When the user presses on the inserter, the needle, with electrode inside, first pierces through two conductive rubber pads housed in the patch. The insertion occurs at an approximately 45° angle to the skin and the conductive rubber pads are also angled at 45° . The needle continues to pierce through the skin to a depth of approximately 1.2 cm. The user then pulls back the inserter that withdraws the needle. The electrodes remain in the skin when the needle is withdrawn because a cylinder fills the bore of the needle upon retraction preventing the electrodes from retracting with the needle. Finally, the cylinder is also fully removed. When the needles and cylinder are removed, the conductive rubber pads that were pierced by the needle collapse around the ends of the electrodes. The ends of the electrodes have different lengths so that each end makes electrical contact with only one of the conductive

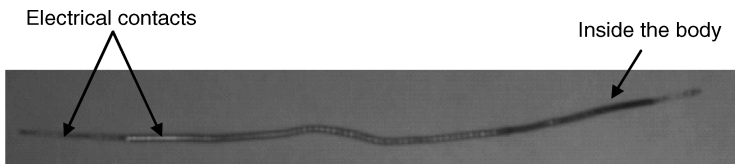


Figure 5.16 Complete view of the Dexcom sensor. Copyright 2008 Abbott. Used with permission.

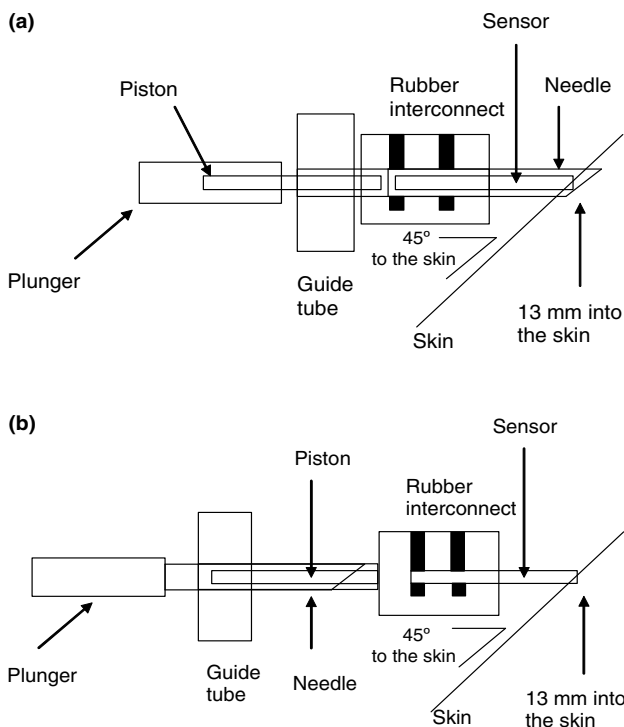


Figure 5.17 Schematic representation of the Dexcom inserter. (a) Inserting the sensor into the skin within the needle. (b) Retracting the needle leaving the sensor in the skin and in contact with rubber interconnects. Copyright 2008 Abbott. Used with permission.

rubber pads. The inserter is removed from the patch and the conductive rubber pads move to a position horizontal to the skin. Since the electrodes are thin wires, they easily bend to accommodate the movement of the pads and are not pulled out of the skin. When the transmitter is placed into the patch, it makes electrical contact with the rubber pads, which means the electrodes are now in electrical contact with the transmitter (Figure 5.18).

The DexCom membrane contains glucose oxidase that reacts with glucose in the presence of oxygen to produce hydrogen peroxide. The hydrogen peroxide is oxidized at the metal surface of the working electrode, which means it is a first-generation sensor. The transmitter applies a potential that is generally 0.5–0.7 V between the working electrode and the silver/silver chloride wire. An equal number of electrons flowing into the working electrode flow out of the silver/silver chloride wire and cause the reduction of silver chloride to silver. The electrode measurement is a two-electrode system. Because the silver chloride coating is consumed, there must be enough silver chloride to react with all the electrons being produced at the working electrode for the lifetime of the sensor. This necessitates the use of a large surface area

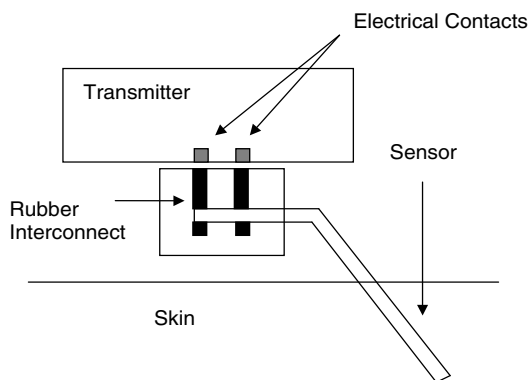


Figure 5.18 Schematic representation of the Dexcom sensor and transmitter mounted on the skin. Copyright 2008 Abbott. Used with permission.

silver chloride coating when compared to the surface area of the working electrode. Depletion of the silver chloride layer would mean that the reference counter electrode would not have a defined potential and would then not act as a proper reference electrode for the system. The Dexcom system carries a warning about the use of acetaminophen (active ingredient in Tylenol) when using the device. This seems to indicate that the system operates at a potential where acetaminophen can be oxidized at the working electrode and that the working electrode cannot prevent acetaminophen from reaching the metal surface of the working electrode. Preventing acetaminophen from reaching the metal surface is difficult because acetaminophen is uncharged and so it cannot be stopped by ionic membranes. Cation exchange membranes are often used in glucose electrodes because the fixed anionic sites of the membrane repel anionic interferents found in the body, primarily urate and ascorbate, but will not stop acetaminophen.

5.5.3 Abbott

TheraSense was founded in 1996 to develop the glucose monitoring technology invented by Dr. Adam Heller at the University of Texas. TheraSense was purchased by Abbott Laboratories in 2004 and combined with their MediSense business unit to form Abbott Diabetes Care Inc. The FreeStyle Navigator® continuous glucose monitoring system was approved by the FDA in 2008. The FreeStyle Navigator system is available by prescription to display glucose values for up to 5 days. The FreeStyle Navigator receiver continuously displays a glucose result, which with fingerstick blood glucose measurements can be used by people with diabetes to guide their treatment.

The sensor comes to the patient in a sterile package that contains a sensor support mount for adhering the sensor and transmitter to the skin and a sensor insertion device. The mount is applied to the skin in a similar manner to apply an

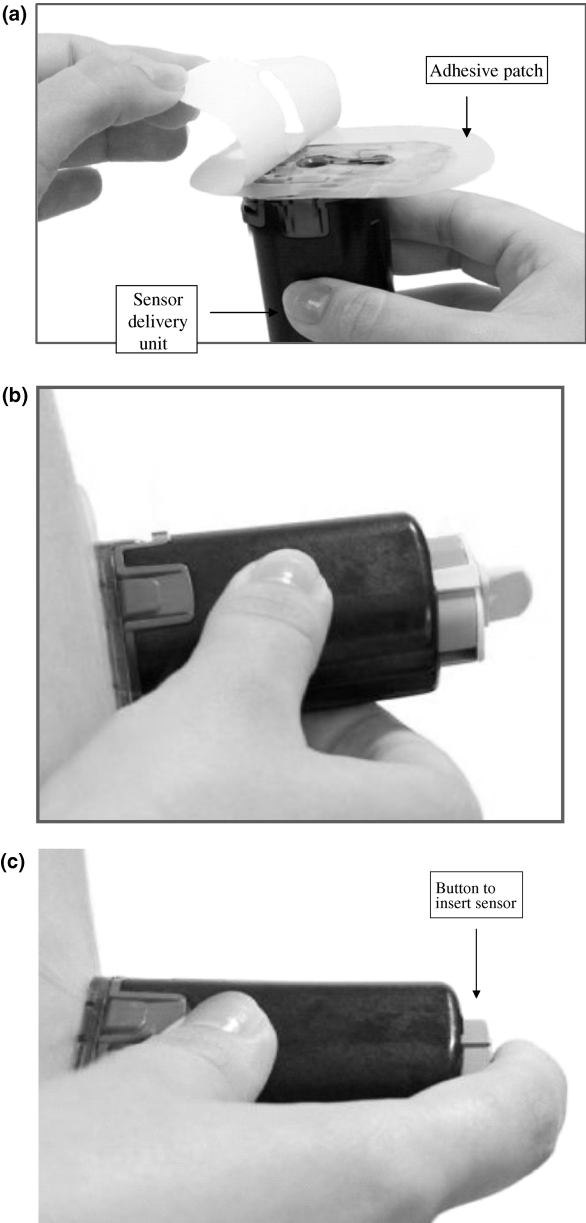


Figure 5.19 Application of the Abbott system to the body. (a) Removing adhesive from patch. (b) Applying patch and sensor delivery unit to the skin. (c) Pressing button to insert sensor. (d) Removing sensor delivery unit. (e) applying transmitter. Copyright 2008 Abbott. Used with permission.

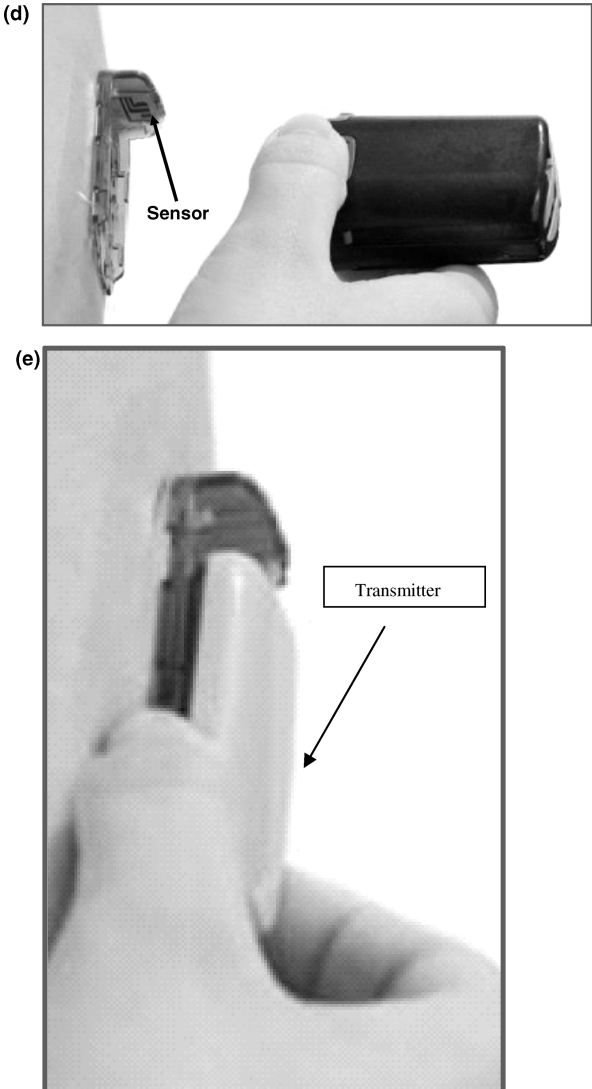


Figure 5.19 (continued).

adhesive bandage (Figure 5.19a and b). The user then removes a locking pin on the inserter and presses the insertion button (Figure 5.19c). The inserter is spring loaded and moves a needle with a sensor held with the needle into the skin. The needle is automatically withdrawn from the skin while the tip of the sensor remains in the skin.

A large portion of the sensor remains outside the skin and is used to provide the electrical contacts to the sensor. The inserter is removed from the patch and discarded (Figure 5.19d). A transmitter device is slid into the sensor support mount (Figure 5.19e). The transmitter contains electrical contacts that contact the conductive pads on the sensor. The transmitter contains a circuit that measures the electrochemical reaction occurring at the working electrode and transmits the signal information to a receiver. The transmitter measures the skin temperature, which is used in the calculations of interstitial glucose. All electrochemical sensor have some temperature dependence due to both the thermodynamics of the electrode processes and because diffusion rates are temperature dependent. The receiver displays the present glucose result and is updated every 1 min. The receiver stores a glucose value in its memory every 10 min.

The system does not display a glucose result for the first 10 h of operation to allow the equilibration of the sensor inside the body. The user is instructed to calibrate the sensor at hours 10, 12, 24, and 72, after insertion, by a blood glucose measurement. The blood glucose meter is built into the receiver, so the calibration is done automatically when a blood glucose measurement is made. After 5 days the user is instructed to remove and dispose of the sensor support mount. The transmitter is reusable and contains replaceable batteries. The transmitter and mount are water resistant and can be worn during showers. The receiver is not water resistant because the receiver contains the open port for insertion of a blood glucose test strip.

The tip of the sensor is inserted at an angle of approximately 90° to the skin to a depth of about 5 mm (Figure 5.20). The sensor contains electrodes that are patterned by screen printing. The electrode system functions as a three-electrode system with a working electrode, counter electrode, and a silver/silver chloride reference electrode. The working electrode contains glucose oxidase bound to a polymer that contains mediator molecules also bound to the polymer (Figure 5.2). Glucose oxidase reacts with the glucose and the reduced enzyme reacts with the mediator in the polymer. The reduced mediator reacts with other mediator sites in the polymer until eventually a reduced mediator near the metal surface of the electrode is oxidized by the metal surface poised at a low potential, 0.04 V, resulting in a current. The reaction uses an exogenous mediator, so the sensor is second generation. The use of a mediator lessens the requirement for oxygen, so the sensor can operate in low-oxygen environments better than first-generation sensor that depend on oxygen as a coreactant. Lessening the oxygen dependence also lessens the need to slow down the glucose diffusion because of the high concentration of glucose compared to oxygen. The current density of the Navigator sensor can be significantly higher than first-generation sensors because the diffusion of glucose does not need to be slowed down as much to accommodate oxygen. The low potential that is a function of the mediator potential means that common electrochemical interferences found in blood will not react at the working electrode. This eliminates the need for complex membranes to reduce or eliminate the diffusion of interferences to the metal surface that are required for first-generation sensor designs.

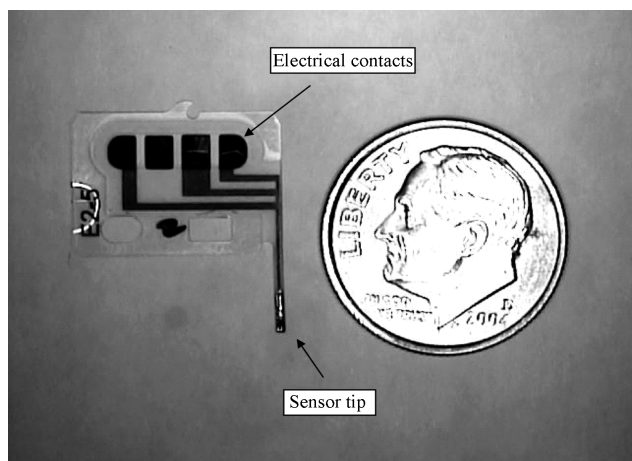


Figure 5.20 Abbott sensor showing size relative to U.S. dime. Copyright 2008 Abbott. Used with permission.

5.6 CLINICAL PERFORMANCE OF COMMERCIALLY AVAILABLE CGM PRODUCTS

5.6.1 Typical Performance

Blood glucose monitors have been commercially available for over 20 years. Specific international standards have been developed for the clinical performance of blood glucose monitors. The clinical testing required to get such a monitor through regulatory bodies and bring them to the market is fairly well understood. Continuous glucose monitors are much younger and international standards for clinical performance have not been established. The manufacturers of these new devices face a challenge in designing clinical trials to prove the efficacy of these new devices. CGM devices can generate hundreds to thousands of data points per day compared to the 2–4 blood glucose measurements that a typical person with diabetes generates daily. CGM devices also have the capability to set off alarms when abnormal glucose values are detected or even projected to happen. The accuracy of these alarms is another new area not found in blood glucose monitors and for which no standards exist. This implies that the field of clinical testing of CGM devices is evolving as the technology evolves. Making comparisons between the different manufacturers' clinical trials is challenging because the trials are run differently, but at present there is no better way of looking at relative performance. In the future we will probably see head-to-head comparisons of the different devices in a clinical trial, which will improve our understanding of the relative performance of the devices.

Two types of clinical trials are typically performed by CGM manufacturers for submission to regulatory bodies to obtain approval to sell their devices. The first type of trial is generally called the accuracy trial. Clinical trial subjects are placed in a clinic or hospital for a large portion of their day. The CGM device is calibrated

by taking capillary blood and measuring the blood on a glucose meter. The times at which the calibration occurs are specified by the manufacturer. Blood samples are taken from the subjects on a regular basis and analyzed on a laboratory analyzer that is considered to be very accurate. The glucose analyzers made by YSI are considered to be the “gold standard” for whole-blood glucose analysis and are frequently used as reference instruments. Because the blood sampling must be made frequently and the amount of blood required for the YSI analyzer is not as small (few hundred microliters) as required by a blood glucose meter, a catheter is normally placed in a vein for blood sampling. The blood is sampled at the same time as the CGM device reports a glucose result, so the two glucose results are paired together. The clinical trial attempts to generate glucose values over as wide a range as is safely possible. During the several day trials, the subject may be asked to eat and delay their insulin shot to create a temporary high glucose reading as well as inject a larger amount of insulin than normal to create a temporary low glucose reading. The subjects are in a clinic at the time of the glucose extremes, so they are closely monitored by the study staff to prevent any adverse events. The YSI glucose values can be plotted versus the CGM glucose values resulting in a scatter plot that can be used to access the accuracy of the new device using a number of different metrics.

The second main type of clinical trial is the home use trial. Subjects use the CGM devices at home as they would expect a normal customer to use the device. They wear a device for the intended length of time and then start a new device. The subject may do this for 21 days to 6 months. They record their glucose values from capillary glucose measurements made on glucose meters. The capillary glucose results are paired with continuous glucose results made at the same time. The paired glucose values are plotted in a scatter plot and standard metrics are used to access the accuracy of the device. Home glucose meters do not have the accuracy and precision of a laboratory analyzer such as the YSI glucose analyzer, so more error is introduced into the home use trial by the reference instrument than in the accuracy trial. The home use trial is also conducted under normal living conditions and not in a well-controlled clinic situation, so the control over the trial is less leading to an expected lower accuracy.

The different manufacturers publish their own results in their user manuals. Mean absolute relative difference and bias results from the three manufacturers are shown in Table 5.2. The MARD measures indicates the average difference while the direction of the difference and the bias indicates if the differences are uniform or skewed to positive or negative values. The Clarke error grid analysis for the three manufacturers (Table 5.3) shows a wide difference in A zone results between the

TABLE 5.2 Accuracy Determined by Relative Difference and Bias

CGM system	Number of subjects	Number of points	Mean absolute relative difference	Bias
Guardian RT	16	3941	19.7%	−15.0 mg/dL
Dexcom STS	91	676	26%	~11%
FreeStyle Navigator	56	20362	12.8%	0.8 mg/dL

TABLE 5.3 Clarke Error Grid Analysis

CGM system	A	B	C	D	E
Guardian RT	61.7	34.4	0.2	3.5	0.2
Dexcom STS	49	41	4	7	0
FreeStyle Navigator	81.6	16.7	0.1	3.0	0.01

TABLE 5.4 Guardian RT Clarke Error Grid by Glucose Range

Glucose range (mg/dL)	Number of data points	A	B	C	D	E
40–80	356	60.1	16.0	0.6	22.5	0.8
81–120	769	60.2	39.7	0.1	N/A	N/A
121–240	2362	62.5	37.	0.2	N/A	0.2
> 240	454	61.0	25.8	0.2	3.5	0.2

N/A: This zone is not in the Clarke error grid for that glucose range.

different manufacturers. Tables 5.2 and 5.3 summarize the most common way of looking at the data, but the following examples show that the same raw data can be looked at in many different ways. The Clarke error grid results for the Guardian RT are shown by glucose range in Table 5.4. The table shows the challenge in the low glucose range with data points falling in the D zone. As can be seen from the grid (see Figure 1.7), the A zone becomes narrow around 75 mg/dL and there is no B zone between the A and D zone on the upper side of the A zone. In the low glucose range, D zone values are easier to reach than other portions of the grid. The FreeStyle Navigator system grid results by day of wear are shown in Table 5.5. The day-to-day performance is very consistent, indicating that performance does not deteriorate over the 5 days of wear. The sensor lifetime as a function of hours of wear is shown in Table 5.6 for the Dexcom STS device. The table shows how long a sensor is expected to last for that time window. For example 8% of the sensors lasted for 4–18 h. The sensor lifetime from the manufacturers, 3–7 days, is an expression of how long a typical sensor will last, but there is no guarantee that each sensor will last the full time. As can be seen from Table 5.6, it cannot be predicted as to how long a sensor will continue to function inside the body.

TABLE 5.5 FreeStyle Navigator System Clarke Error Grid by Day of Wear

Day of wear	A	B	C	D	E
Day 1	82.5	16.4	0.2	0.9	0.0
Day 2	82.4	16.6	0.1	0.9	0.1
Day 3	79.4	18.3	0.0	2.2	0.0
Day 4	84.0	14.2	0.0	1.8	0.0
Day 5	80.9	16.9	0.0	2.1	0.0

TABLE 5.6 Dexcom STS Estimated Sensor Lifetime

Hours of use	Percentage of sensors
4–18 h	8%
20–35 h	6%
45–64 h	11%
65–72 h	75%

TABLE 5.7 Precision of CGM Systems

CGM system	Number of data points	Coefficient of variation
Guardian RT	11,475	17.2%
Dexcom STS	N.A. (not available)	21%
FreeStyle Navigator	312,953	10%

Precision is normally one of the easiest performance parameters to measure for an *in vitro* medical diagnostic test. Multiple tests are run using the same sample and the standard deviation is calculated. Precision is not so easily tested for *in vivo* medical diagnostic tests. If we want to perform the normal precision test on an *in vivo* device, we would need to insert multiple devices in the same person. This would introduce the question of the glucose being the same at every spot in the body. The best that the CGM manufacturers have been able to do is to place two CGM devices in the same person and compare the results from the two sensors for precision. Because both devices are in the same person, they should read the same glucose level. This *in vivo* precision measurement is not the same as the *in vitro* measurement. The *in vivo* measurement can produce thousands of paired points from one subject, but are the data points independent because they are coming from the same person? The precision data from the three manufacturers are shown in Table 5.7.

5.6.2 Performance When Glucose is Changing Rapidly

Glucose passes fairly freely between the blood capillary walls and the interstitial space. In nonhospitalized subjects, glucose enters the blood from the digestive tract or is released from the liver. Glucose is consumed by the cells of the body as long as the insulin is present. A complex dynamics of glucose entering the blood stream and being used up by the cells exists. Blood glucose meters measure the glucose in capillary blood, while CGM devices measure glucose in interstitial fluid. When the blood glucose is not changing, it is expected that the interstitial glucose will be approximately the same as the blood glucose. When blood glucose is changing rapidly, the interstitial space may not be able to equilibrate fast enough to match the blood glucose. There may then exist conditions under which the blood glucose values measured using a blood glucose meter will not agree with the interstitial glucose

TABLE 5.8 Accuracy of FreeStyle Navigator System by Rate of Glucose Change

Rate of change (mg/dL/min)	Percentage of data points	Clarke error grid zone				
		A (%)	B (%)	C (%)	D (%)	E (%)
Less than -2	3.1	54.6	42.3	1.3	1.8	0.0
-2 to -1	8.8	71.7	26.2	0.3	1.8	0.0
-1 to 1	74.7	84.9	13.5	0.0	1.5	0.0
1-2	10.0	79.8	18.9	0.0	1.3	0.0
>2	3.5	63.5	34.7	0.0	1.7	0.0

measurement made with the CGM device. The situations are typically temporary and the two will soon agree. The important consideration is that calibration of the CGM with blood glucose concentrations may lead to a poor calibration of the CGM device when blood glucose is changing rapidly. Since it is known that blood glucose will rise rapidly after a meal, this is not a recommended time for calibration. The overall accuracy of the blood glucose and interstitial glucose values is also influenced by changing blood glucose values. The accuracy at various rates of change has been calculated and as expected the accuracy is best when the blood glucose is not changing rapidly (Table 5.8). Two manufacturers also display arrows that indicate the rate of glucose change of the sensor. These arrows will provide a helpful indicator to the user of when to calibrate.

5.7 FUTURE OF CGM

5.7.1 Long-Term Implanted Sensors

The CGM sensors described in this chapter have a lifetime of 3–7 days inside the body. The sensors will, therefore, need to be changed by the user on a regular basis if they want to know their glucose concentrations at all times. A sensor that could be implanted for a long period of time would eliminate the need to frequently change the sensor. The development of a long-term sensor is however very challenging. Sensors based on the reaction of glucose with glucose oxidase leading to the passage of current will likely require large batteries to be implanted with the sensor if they are expected to last for a year. The larger the device, the more the damage will be caused by the implantation procedure. Larger devices may also require surgical implantation that is not very appealing for the users or payers for the technology. A larger device may also be more prone during movement to break blood capillaries and cause internal bleeding that is believed to be bad for sensor performance. In addition, most enzymes such as glucose oxidase are not very stable at elevated temperatures, such as inside the body, and for long periods of time. Because of the preceding reasons, more effort has been put into developing small optical sensors that can be implanted under the skin. The proximity of the sensor to the surface of the skin means the light excitation and light transduction devices can be outside the skin, which minimizes the size of the device that needs to be implanted under the skin. A device that includes the

measurement technology to also be implanted will present miniaturization challenges. Such a device would need telemetry capability to be able to transmit the signal outside the body to a receiver. The devices typically do not rely on an enzyme to transduce the glucose. The sensor technologies often involve a glucose binding event that changes an optical property of the sensor. Glucose binding sites, such as concanavalin A, are more stable than most enzymes. The optical change could be a fluorescent signal or an optical interference change, or possibly even a color change. All the systems, whether optical or electrochemical, will face long-term problems with the body capsule formed around the sensor. The body will initially try to destroy the implanted sensor but once the body gives up trying to destroy the sensor, it will start walling off the sensor with a thick fibrous layer. The thick fibrous layer will slow down the diffusion of glucose to the sensor and lead to long response times. Efforts have been made to promote the ingrowth of capillaries around an implant by using textured surfaces or by releasing substances that promote capillary growth around the implant.

5.7.2 Tight Glycemic Control in the Hospital

The body responds to serious illness or trauma by allowing the blood glucose level to rise significantly, hyperglycemia. This occurs in patients with diabetes and patients without diabetes. Hyperglycemia was thought to be a natural response of the body to try and heal itself and went untreated in the hospital unless it was severely high. Clinical studies were begun in the early 1990s in patients undergoing heart surgery where the glucose level was left high in some patients and other patients received treatment to lower their blood glucose.³⁹ Surprisingly, the group that received the glucose lowering treatment had a significant reduction in infection after the surgery. It was not known if the effect was specific to patients undergoing heart surgery or would benefit the general hospital population. Another study was done with hospitalized diabetic patients that involved glucose lowering treatment in the hospital and after their release from the hospital.⁴⁰ The mortality rate was nearly half for the treated group and again the number of infections in the treated group was reduced. In 2001, Dr. Greet van den Berghe published a controlled clinical trial studying the effect of reducing the glucose level in hospitalized ICU patients to near normal levels.⁴¹ A statistically significant lowering of the mortality rate was found in those studies. Although the results are controversial, Dr. van den Berghe suggests that the nearer to normal the glucose can be maintained, the better off the patient is. In most of the published studies from the hospital intensive care units, the lowering of glucose levels seems to benefit the nondiabetic patients more than the diabetic ones.

Since 2001 most hospitals have decided to aggressively reduce glucose levels in their ICU patients but this is not easy for the hospital to do so and does carry with it health risks to the patient. Reducing the glucose level requires frequent blood glucose determinations and insulin adjustments. A commonly quoted statistic is that each patient under strict glucose control requires an additional 2 h of nursing time per day. Lowering the blood glucose level brings with it the risk that the glucose level can be lowered too far and the patient will become hypoglycemic. Hypoglycemia increases the risk of significant complication and can cause death. Two recent European clinical

studies involving strict glycemic control have been suspended because of higher mortality rates in the strict glucose control arm of the studies. There is at present a significant need for a technology that can continuously monitor the patient and alarm the staff to any low or high glucose levels. Such a sensor would reduce staffing costs and lower the risk of hypoglycemia for strictly controlled patients.

Significant challenges exist for the implementation of current continuous glucose sensors in the ICU. Clinical studies are needed that demonstrate that the subcutaneous tissue where the current sensors reside in will accurately track blood glucose values in severely ill patients. Severely ill patients can experience edema that might affect subcutaneous glucose values by diluting the glucose. Microcirculation can be shut down in patients in shock as well as by various vasodilating drugs. The decrease in peripheral circulation could lead to less glucose transport to the subcutaneous space around the sensor and glucose values lower than the blood. One solution is to adapt the continuous sensors for use in blood. The sensor could be placed directly in an artery or blood could be sampled from an artery using a pump. Once such system was sold but was not commercially successful. Using the sensors directly in blood has its own problems associated with getting access to the blood and clotting. The need for a continuous glucose sensor in critical care is so great that companies will be driven to provide technical solutions in the near future.

5.7.3 Closed-Loop Control of Glucose

The ultimate use for continuous glucose monitoring would be to combine the glucose information with an insulin pump to provide a system that automatically maintains the user's glucose level within prescribed limits. The sensor and pump are combined in a "closed loop" to mimic the function of the pancreas and therefore form an "artificial pancreas." The performance of continuous glucose sensors has been steadily improving and should reach the state where they could be relied on to provide guidance for the pump. Current insulin pumps deliver insulin with the precision and accuracy necessary for the closed loop. A third vital element needed is the algorithm to translate the glucose values into the correct insulin infusion instructions for the pump.

Many factors contribute to the current glucose level in your body as well as what it will be in the future. How big a meal will you eat and how many carbohydrates will it contain? When do you plan on exercising and for how long and how strenuous? Are you under stress today at work? The glucose sensor has no way of knowing any of these things in advance, so it is always reacting to changes in your condition but cannot anticipate those changes. The glucose sensor and pump will always be chasing to control the glucose. One suggestion is that the user will need to input information, such as an upcoming meal, into the control algorithm so that the system can react, pump insulin, ahead of time. This is referred to as "open-loop" control. Another possibility is that a second drug will be added to the pump that raises glucose. The current systems using only insulin can only lower glucose. Infusion of a drug such as glucagon causes an increase in glucose by releasing glucose that is stored in the liver. The closed-loop system would then have the power to both raise and lower glucose that would make closed-loop control easier. There is, however, a limited supply of glucose, enough for 1–2 days, stored in the liver, so there is some concern that a system that requires

significant corrections using glucagon will end up depleting the glucose in the liver. If that happens, then the closed-loop system can only lower glucose levels because the glucagon will not be effective. The future looks very challenging and exciting for closed-loop control of glucose.

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In Vivo Glucose Sensing

Leading experts explain the many approaches to *in vivo* glucose sensing and point to new directions in research

Soon, people with diabetes will be able to depend on reliable, user-friendly *in vivo* glucose sensing systems to monitor their blood sugar levels. This volume brings readers fully up to date with recently commercialized *in vivo* sensing systems as well as current efforts to develop new and improved systems. The authors, leading pioneers and researchers in the field, include an MD and both academic and industrial researchers. Together, they review the many approaches to solving the "glucose sensing problem," helping readers apply the latest technology and advance their own research efforts.

Following an introductory chapter that sets forth the promise and challenges of glucose sensing, the book explores:

- Understanding and controlling the wound-healing response to facilitate implanted sensors
- State-of-the-technology implants, including electrochemical sensors and microdialysis devices
- New approaches to develop non-invasive, optical-based methods for measuring *in vivo* glucose

Chapters describe both analytical approaches and *in vivo* results, underscoring the need for a deep understanding of sensing technology as well as human anatomy and physiology. Throughout the book, detailed figures help readers better understand how and why various sensor systems work. In addition, color reproductions of tissue and histological slides draw attention to important features of the body tissue/sensor interface.

From established technologies to the most recent research advances, this book explains the current state of knowledge, sets forth the challenges, and points to new breakthroughs for *in vivo* glucose sensing.

DAVID D. CUNNINGHAM, PhD, is a Volwiler Associate Research Fellow at Abbott Diagnostics.

JULIE A. STENKEN, PhD, is Professor and 21st Century Chair of Proteomics at the University of Arkansas

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