THE BIOMEDICAL ENGINEERING HANDBOOK

FOURTH EDITION

Medical Devices and Human Engineering

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Preface

During the past eight years since the publication of the third edition—a three-volume set—of *The Biomedical Engineering Handbook*, the field of biomedical engineering has continued to evolve and expand. As a result, the fourth edition has been significantly modified to reflect state-of-the-field knowledge and applications in this important discipline and has been enlarged to a four-volume set:

- Volume I: *Biomedical Engineering Fundamentals*
- Volume II: *Medical Devices and Human Engineering*
- Volume III: *Biomedical Signals, Imaging, and Informatics*
- Volume IV: *Molecular, Cellular, and Tissue Engineering*

More specifically, this fourth edition has been considerably updated and contains completely new sections, including

- Stem Cell Engineering
- Drug Design, Delivery Systems, and Devices
- Personalized Medicine

as well as a number of substantially updated sections, including

- Tissue Engineering (which has been completely restructured)
- Transport Phenomena and Biomimetic Systems
- Artificial Organs
- Medical Imaging
- Infrared Imaging
- Medical Informatics

In addition, Volume IV contains a chapter on ethics because of its ever-increasing role in the biomedical engineering arts.

Nearly all the sections that have appeared in the first three editions have been significantly revised. Therefore, this fourth edition presents an excellent summary of the status of knowledge and activities of biomedical engineers in the first decades of the twenty-first century. As such, it can serve as an excellent reference for individuals interested not only in a review of fundamental physiology but also in quickly being brought up to speed in certain areas of biomedical engineering research. It can serve as an excellent textbook for students in areas where traditional textbooks have not yet been developed and as an excellent review of the major areas of activity in each biomedical engineering sub-discipline, such as biomechanics, biomaterials, bioinstrumentation, medical imaging, and so on. Finally, it can serve as the "bible" for practicing biomedical engineering professionals by covering such topics as historical perspective of medical technology, the role of professional societies, the ethical issues associated with medical technology, and the FDA process.

Biomedical engineering is now an important and vital interdisciplinary field. Biomedical engineers are involved in virtually all aspects of developing new medical technology. They are involved in the design, development, and utilization of materials, devices (such as pacemakers, lithotripsy, etc.), and techniques (such as signal processing, artificial intelligence, etc.) for clinical research and use, and they serve as members of the healthcare delivery team (clinical engineering, medical informatics, rehabilitation engineering, etc.) seeking new solutions for the difficult healthcare problems confronting our society. To meet the needs of this diverse body of biomedical engineers, this handbook provides a central core of knowledge in those fields encompassed by the discipline. However, before presenting this detailed information, it is important to provide a sense of the evolution of the modern healthcare system and identify the diverse activities biomedical engineers perform to assist in the diagnosis and treatment of patients.

Evolution of the Modern Healthcare System

Before 1900, medicine had little to offer average citizens, since its resources consisted mainly of physicians, their education, and their "little black bag." In general, physicians seemed to be in short supply, but the shortage had rather different causes than the current crisis in the availability of healthcare professionals. Although the costs of obtaining medical training were relatively low, the demand for doctors' services also was very small, since many of the services provided by physicians also could be obtained from experienced amateurs in the community. The home was typically the site for treatment and recuperation, and relatives and neighbors constituted an able and willing nursing staff. Babies were delivered by midwives, and those illnesses not cured by home remedies were left to run their natural, albeit frequently fatal, course. The contrast with contemporary healthcare practices in which specialized physicians and nurses located within hospitals provide critical diagnostic and treatment services is dramatic.

The changes that have occurred within medical science originated in the rapid developments that took place in the applied sciences (i.e., chemistry, physics, engineering, microbiology, physiology, pharmacology, etc.) at the turn of the twentieth century. This process of development was characterized by intense interdisciplinary cross-fertilization, which provided an environment in which medical research was able to take giant strides in developing techniques for the diagnosis and treatment of diseases. For example, in 1903, Willem Einthoven, a Dutch physiologist, devised the first electrocardiograph to measure the electrical activity of the heart. In applying discoveries in the physical sciences to the analysis of the biological process, he initiated a new age in both cardiovascular medicine and electrical measurement techniques.

New discoveries in medical sciences followed one another like intermediates in a chain reaction. However, the most significant innovation for clinical medicine was the development of x-rays. These "new kinds of rays," as W. K. Roentgen described them in 1895, opened the "inner man" to medical inspection. Initially, x-rays were used to diagnose bone fractures and dislocations, and in the process, x-ray machines became commonplace in most urban hospitals. Separate departments of radiology were established, and their influence spread to other departments throughout the hospital. By the 1930s, x-ray visualization of practically all organ systems of the body had been made possible through the use of barium salts and a wide variety of radiopaque materials.

X-ray technology gave physicians a powerful tool that, for the first time, permitted accurate diagnosis of a wide variety of diseases and injuries. Moreover, since x-ray machines were too cumbersome and expensive for local doctors and clinics, they had to be placed in healthcare centers or hospitals. Once there, x-ray technology essentially triggered the transformation of the hospital from a passive receptacle for the sick to an active curative institution for all members of society.

For economic reasons, the centralization of healthcare services became essential because of many other important technological innovations appearing on the medical scene. However, hospitals remained institutions to dread, and it was not until the introduction of sulfanilamide in the mid-1930s and penicillin in the early 1940s that the main danger of hospitalization, that is, cross-infection among

patients, was significantly reduced. With these new drugs in their arsenals, surgeons were able to perform their operations without prohibitive morbidity and mortality due to infection. Furthermore, even though the different blood groups and their incompatibility were discovered in 1900 and sodium citrate was used in 1913 to prevent clotting, full development of blood banks was not practical until the 1930s, when technology provided adequate refrigeration. Until that time, "fresh" donors were bled and the blood transfused while it was still warm.

Once these surgical suites were established, the employment of specifically designed pieces of medical technology assisted in further advancing the development of complex surgical procedures. For example, the Drinker respirator was introduced in 1927 and the first heart–lung bypass in 1939. By the 1940s, medical procedures heavily dependent on medical technology, such as cardiac catheterization and angiography (the use of a cannula threaded through an arm vein and into the heart with the injection of radiopaque dye) for the x-ray visualization of congenital and acquired heart disease (mainly valve disorders due to rheumatic fever) became possible, and a new era of cardiac and vascular surgery was established.

In the decades following World War II, technological advances were spurred on by efforts to develop superior weapon systems and to establish habitats in space and on the ocean floor. As a by-product of these efforts, the development of medical devices accelerated and the medical profession benefited greatly from this rapid surge of technological finds. Consider the following examples:

1. Advances in solid-state electronics made it possible to map the subtle behavior of the fundamental unit of the central nervous system—the neuron—as well as to monitor the various physiological parameters, such as the electrocardiogram, of patients in intensive care units.
2. New prosthetic devices became a goal of engineers involved in providing the disabled with tools to improve their quality of life.
3. Nuclear medicine—an outgrowth of the atomic age—emerged as a powerful and effective approach in detecting and treating specific physiological abnormalities.
4. Diagnostic ultrasound based on sonar technology became so widely accepted that ultrasonic studies are now part of the routine diagnostic workup in many medical specialties.
5. "Spare parts" surgery also became commonplace. Technologists were encouraged to provide cardiac assist devices, such as artificial heart valves and artificial blood vessels, and the artificial heart program was launched to develop a replacement for a defective or diseased human heart.
6. Advances in materials have made the development of disposable medical devices, such as needles and thermometers, a reality.
7. Advancements in molecular engineering have allowed for the discovery of countless pharmacological agents and to the design of their delivery, including implantable delivery systems.
8. Computers similar to those developed to control the flight plans of the Apollo capsule were used to store, process, and cross-check medical records, to monitor patient status in intensive care units, and to provide sophisticated statistical diagnoses of potential diseases correlated with specific sets of patient symptoms.
9. Development of the first computer-based medical instrument, the computerized axial tomography scanner, revolutionized clinical approaches to noninvasive diagnostic imaging procedures, which now include magnetic resonance imaging and positron emission tomography as well.
10. A wide variety of new cardiovascular technologies including implantable defibrillators and chemically treated stents were developed.
11. Neuronal pacing systems were used to detect and prevent epileptic seizures.
12. Artificial organs and tissue have been created.
13. The completion of the genome project has stimulated the search for new biological markers and personalized medicine.
14. The further understanding of cellular and biomolecular processes has led to the engineering of stem cells into therapeutically valuable lineages and to the regeneration of organs and tissue structures.

15. Developments in nanotechnology have yielded nanomaterials for use in tissue engineering and facilitated the creation and study of nanoparticles and molecular machine systems that will assist in the detection and treatment of disease and injury.

The impact of these discoveries and many others has been profound. The healthcare system of today consists of technologically sophisticated clinical staff operating primarily in modern hospitals designed to accommodate the new medical technology. This evolutionary process continues, with advances in the physical sciences such as materials and nanotechnology and in the life sciences such as molecular biology, genomics, stem cell biology, and artificial and regenerated tissue and organs. These advances have altered and will continue to alter the very nature of the healthcare delivery system itself.

Biomedical Engineering: A Definition

Bioengineering is usually defined as a basic research-oriented activity closely related to biotechnology and genetic engineering, that is, the modification of animal or plant cells or parts of cells to improve plants or animals or to develop new microorganisms for beneficial ends. In the food industry, for example, this has meant the improvement of strains of yeast for fermentation. In agriculture, bioengineers may be concerned with the improvement of crop yields by treatment of plants with organisms to reduce frost damage. It is clear that future bioengineers will have a tremendous impact on the quality of human life. The potential of this specialty is difficult to imagine. Consider the following activities of bioengineers:

- Development of improved species of plants and animals for food production
- Invention of new medical diagnostic tests for diseases
- Production of synthetic vaccines from clone cells
- Bioenvironmental engineering to protect human, animal, and plant life from toxicants and pollutants
- Study of protein–surface interactions
- Modeling of the growth kinetics of yeast and hybridoma cells
- Research in immobilized enzyme technology
- Development of therapeutic proteins and monoclonal antibodies

Biomedical engineers, on the other hand, apply electrical, mechanical, chemical, optical, and other engineering principles to understand, modify, or control biological (i.e., human and animal) systems as well as design and manufacture products that can monitor physiological functions and assist in the diagnosis and treatment of patients. When biomedical engineers work in a hospital or clinic, they are more aptly called clinical engineers.

Activities of Biomedical Engineers

The breadth of activity of biomedical engineers is now significant. The field has moved from being concerned primarily with the development of medical instruments in the 1950s and 1960s to include a more wide-ranging set of activities. As illustrated below, the field of biomedical engineering now includes many new career areas (see Figure P.1), each of which is presented in this handbook. These areas include

- Application of engineering system analysis (physiological modeling, simulation, and control) to biological problems
- Detection, measurement, and monitoring of physiological signals (i.e., biosensors and biomedical instrumentation)
- Diagnostic interpretation via signal-processing techniques of bioelectric data
- Therapeutic and rehabilitation procedures and devices (rehabilitation engineering)
- Devices for replacement or augmentation of bodily functions (artificial organs)

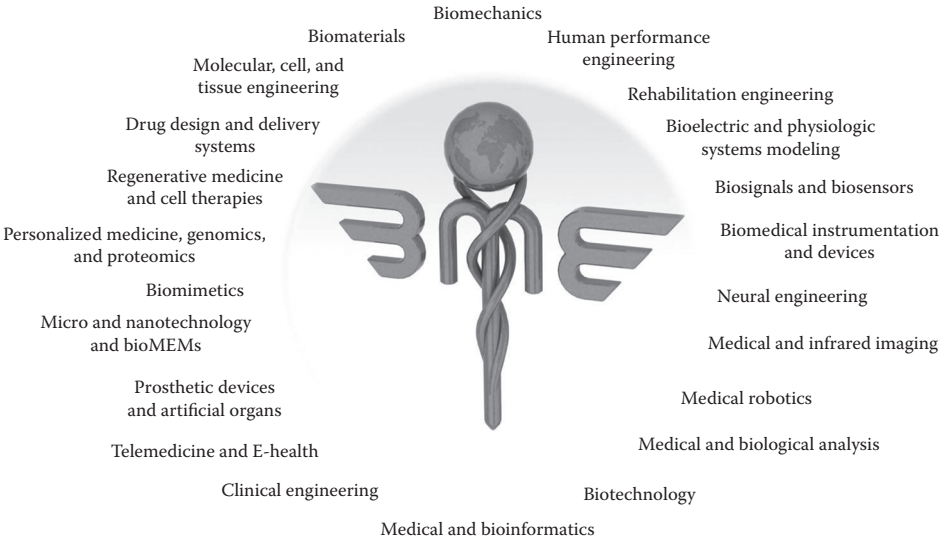

FIGURE P.1 The world of biomedical engineering.

- Computer analysis of patient-related data and clinical decision making (i.e., medical informatics and artificial intelligence)
- Medical imaging, that is, the graphic display of anatomic detail or physiological function
- The creation of new biological products (e.g., biotechnology and tissue engineering)
- The development of new materials to be used within the body (biomaterials)

Typical pursuits of biomedical engineers, therefore, include

- Research in new materials for implanted artificial organs
- Development of new diagnostic instruments for blood analysis
- Computer modeling of the function of the human heart
- Writing software for analysis of medical research data
- Analysis of medical device hazards for safety and efficacy
- Development of new diagnostic imaging systems
- Design of telemetry systems for patient monitoring
- Design of biomedical sensors for measurement of human physiological systems variables
- Development of expert systems for diagnosis of disease
- Design of closed-loop control systems for drug administration
- Modeling of the physiological systems of the human body
- Design of instrumentation for sports medicine
- Development of new dental materials
- Design of communication aids for the handicapped
- Study of pulmonary fluid dynamics
- Study of the biomechanics of the human body
- Development of material to be used as a replacement for human skin

Biomedical engineering, then, is an interdisciplinary branch of engineering that ranges from theoretical, nonexperimental undertakings to state-of-the-art applications. It can encompass research, development, implementation, and operation. Accordingly, like medical practice itself, it is unlikely that any single person can acquire expertise that encompasses the entire field. Yet, because of the

interdisciplinary nature of this activity, there is considerable interplay and overlapping of interest and effort between them. For example, biomedical engineers engaged in the development of biosensors may interact with those interested in prosthetic devices to develop a means to detect and use the same bioelectric signal to power a prosthetic device. Those engaged in automating clinical chemistry laboratories may collaborate with those developing expert systems to assist clinicians in making decisions based on specific laboratory data. The possibilities are endless.

Perhaps, a greater potential benefit occurring from the use of biomedical engineering is identification of the problems and needs of our present healthcare system that can be solved using existing engineering technology and systems methodology. Consequently, the field of biomedical engineering offers hope in the continuing battle to provide high-quality care at a reasonable cost. If properly directed toward solving problems related to preventive medical approaches, ambulatory care services, and the like, biomedical engineers can provide the tools and techniques to make our healthcare system more effective and efficient and, in the process, improve the quality of life for all.

Joseph D. Bronzino
Donald R. Peterson
Editors-in-Chief

Editors

Joseph D. Bronzino is currently the president of the Biomedical Engineering Alliance and Consortium (BEACON; www.beaconalliance.org), which is a nonprofit organization dedicated to the promotion of collaborative research, translation, and partnership among academic, medical, and industry people in the field of biomedical engineering to develop new medical technologies and devices. To accomplish this goal, Dr. Bronzino and BEACON facilitate collaborative research, industrial partnering, and the development of emerging companies. Dr. Bronzino earned a BSEE from Worcester Polytechnic Institute, Worcester, Massachusetts, in 1959, an MSEE from the Naval Postgraduate School, Monterey, California, in 1961, and a PhD in electrical engineering from Worcester Polytechnic Institute in 1968. He was recently the Vernon Roosa Professor of Applied Science and endowed chair at Trinity College, Hartford, Connecticut.

Dr. Bronzino is the author of over 200 journal articles and 15 books, including *Technology for Patient Care* (C.V. Mosby, 1977), *Computer Applications for Patient Care* (Addison-Wesley, 1982), *Biomedical Engineering: Basic Concepts and Instrumentation* (PWS Publishing Co., 1986), *Expert Systems: Basic Concepts* (Research Foundation of State University of New York, 1989), *Medical Technology and Society: An Interdisciplinary Perspective* (MIT Press and McGraw-Hill, 1990), *Management of Medical Technology* (Butterworth/Heinemann, 1992), *The Biomedical Engineering Handbook* (CRC Press, 1st Edition, 1995; 2nd Edition, 2000; 3rd Edition, 2006), *Introduction to Biomedical Engineering* (Academic Press, 1st Edition, 1999; 2nd Edition, 2005; 3rd Edition, 2011), *Biomechanics: Principles and Applications* (CRC Press, 2002), *Biomaterials: Principles and Applications* (CRC Press, 2002), *Tissue Engineering* (CRC Press, 2002), and *Biomedical Imaging* (CRC Press, 2002).

Dr. Bronzino is a fellow of IEEE and the American Institute of Medical and Biological Engineering (AIMBE), an honorary member of the Italian Society of Experimental Biology, past chairman of the Biomedical Engineering Division of the American Society for Engineering Education (ASEE), a charter member of the Connecticut Academy of Science and Engineering (CASE), a charter member of the American College of Clinical Engineering (ACCE), a member of the Association for the Advancement of Medical Instrumentation (AAMI), past president of the IEEE-Engineering in Medicine and Biology Society (EMBS), past chairman of the IEEE Health Care Engineering Policy Committee (HCEPC), and past chairman of the IEEE Technical Policy Council in Washington, DC. He is a member of Eta Kappa Nu, Sigma Xi, and Tau Beta Pi. He is also a recipient of the IEEE Millennium Medal for "his contributions to biomedical engineering research and education" and the Goddard Award from WPI for Outstanding Professional Achievement in 2005. He is presently editor-in-chief of the Academic Press/Elsevier BME Book Series.

Donald R. Peterson is a professor of engineering and the dean of the College of Science, Technology, Engineering, Mathematics, and Nursing at Texas A&M University in Texarkana, Texas, and holds a joint appointment in the Department of Biomedical Engineering (BME) at Texas A&M University in College Station, Texas. He was recently an associate professor of medicine and the director of the

Biodynamics Laboratory in the School of Medicine at the University of Connecticut (UConn) and served as chair of the BME Program in the School of Engineering at UConn as well as the director of the BME Graduate and Undergraduate Programs. Dr. Peterson earned a BS in aerospace engineering and a BS in biomechanical engineering from Worcester Polytechnic Institute, in Worcester, Massachusetts, in 1992, an MS in mechanical engineering from the UConn, in Storrs, Connecticut, in 1995, and a PhD in biomedical engineering from UConn in 1999. He has 17 years of experience in BME education and has offered graduate-level and undergraduate-level courses in the areas of biomechanics, biodynamics, biofluid mechanics, BME communication, BME senior design, and ergonomics, and has taught subjects such as gross anatomy, occupational biomechanics, and occupational exposure and response in the School of Medicine. Dr. Peterson was also recently the co-executive director of the Biomedical Engineering Alliance and Consortium (BEACON), which is a nonprofit organization dedicated to the promotion of collaborative research, translation, and partnership among academic, medical, and industry people in the field of biomedical engineering to develop new medical technologies and devices.

Dr. Peterson has over 21 years of experience in devices and systems and in engineering and medical research, and his work on human–device interaction has led to applications on the design and development of several medical devices and tools. Other recent translations of his research include the development of devices such as robotic assist devices and prosthetics, long-duration biosensor monitoring systems, surgical and dental instruments, patient care medical devices, spacesuits and space tools for NASA, powered and non-powered hand tools, musical instruments, sports equipment, computer input devices, and so on. Other overlapping research initiatives focus on the development of computational models and simulations of biofluid dynamics and biomechanical performance, cell mechanics and cellular responses to fluid shear stress, human exposure and response to vibration, and the acoustics of hearing protection and communication. He has also been involved clinically with the Occupational and Environmental Medicine group at the UConn Health Center, where his work has been directed toward the objective engineering analysis of the anatomic and physiological processes involved in the onset of musculoskeletal and neuromuscular diseases, including strategies of disease mitigation.

Dr. Peterson's scholarly activities include over 50 published journal articles, 2 textbook chapters, 2 textbook sections, and 12 textbooks, including his new appointment as co-editor-in-chief for *The Biomedical Engineering Handbook* by CRC Press.

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Biomedical Sensors

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23

Blood Glucose Monitoring

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The availability of blood glucose monitoring devices for home use has significantly impacted the treatment of diabetes with the American Diabetes Association currently recommending that Type 1 insulin-dependent diabetic individuals perform blood glucose testing four times per day. Grave health issues are associated with high and low blood glucose levels. Injection of too much insulin without enough food lowers blood sugar into the hypoglycemic range, glucose below 60 mg/dL, resulting in mild confusion or in more severe cases loss of consciousness, seizure, and coma. On the other hand, long-term high blood sugar levels lead to diabetic complications such as eye, kidney, heart, nerve, or blood vessel disease (Diabetes Control and Complications Trial Research Group 1993). Complications were tracked in a large clinical study showing that an additional 5 years of life, 8 years of sight, 6 years free from kidney disease, and 6 years free of amputations can be expected for a diabetic following tight glucose control versus the standard regimen (Diabetes Control and Complications Trial Research Group 1996).

Glucose monitoring and control in the perioperative setting also has a significant effect on patient outcomes since a large percentage of nondiabetic patients, as well as diabetic patients, become hyperglycemic during induction with anesthesia, throughout surgery, and several hours postsurgery. A study published in 2001 showed critically ill patients intensively controlled to between 80 and 110 mg/dL glucose had fewer complications and a 34% lower in-hospital mortality than conventionally managed patients where treatment was initiated when glucose was >215 mg/dL and maintained between 180 and 200 mg/dL (van den Berghe et al. 2001). Subsequently, in 2006, a standard of care for critically ill patients, recommending glucose be kept as close to 110 mg/dL as possible and generally <140 mg/dL, was widely adopted. Unfortunately, additional studies of intensive control in the ICU generally found an increased incidence of hypoglycemia and failed to confirm the initial found benefit in survival, so the guidelines were withdrawn in 2008 (NICE-SUGAR Study Investigators 2009). The accuracy required of the glucose measurements to allow tight glucose control and avoid hypoglycemia received relatively little attention during the studies discussed above, but the painful experience of resetting treatment guidelines has brought the subject of glucose measurement into sharp focus among clinical researchers (Rice et al. 2010).

TABLE 23.1 Landmarks in Glucose Monitoring

1941—Effervescent tablet test for glucose in urine
1956—Dip and read test strip for glucose in urine
1964—Dry reagent blood glucose test strip requiring timing, wash step, and visual comparison to a color chart
1970—Meter to read reflected light from a test strip, designed for use in the doctor's office
1978—Major medical literature publications on home blood glucose monitoring with portable meters
1981—Finger lancing device automatically lances and retracts tip
1987—Electrochemical test strip and small meter in the form of a pen
1997—Multiple test strip package for easy loading into meter
2001—Alternate-site blood sampling for virtually painless testing

The current Food and Drug Administration (FDA) and ISO guidelines on the accuracy of self-monitoring blood glucose systems have been in place since 1996 and state that 95% of the readings must be within 20% of a reference method value for glucose values ≥75 mg/dL and within 15 mg/dL of reference values for glucose values <75 mg/dL. In June 2009, an initiative was launched by ISO with strong support by the FDA to tighten the requirements so that 95% of the readings are within 15% of a reference method value for glucose values ≥75 mg/dL and within 10 mg/dL of reference values for glucose values <75 mg/dL, with implementation by 2012. While industry will certainly meet any government-mandated standard, the cost of the systems may rise and new features such as faster time to result and lower blood sample requirements may not advance as rapidly. The continued need for simple, accurate glucose measurements has led to continuous improvements in sample test strips, electronic meters, sample acquisition techniques, and more recently, continuous monitoring systems.

Self-monitoring blood glucose systems based on single-use test strips are available from a number of companies through pharmacy and mail order; however, the more recently introduced continuous monitoring systems require a prescription. Some of the landmarks in glucose testing are shown in Table 23.1. The remainder of the chapter comprises a history of technical developments with an explanation of the principles behind optical and electrochemical sensing, including examples of the biochemical reactions used in commercial products.

23.1 Historical Methods of Glucose Monitoring

Diabetes is an ancient disease that was once identified by the attraction of ants to the urine of an affected individual. Later, physicians would often rely on the sweet taste of the urine in diagnosing the disease. Once the chemical-reducing properties of glucose were discovered, solutions of a copper salt and dye, typically *o*-toluidine, were used for laboratory tests, and by the 1940s the reagents had been formulated into tablets for use in test tubes of urine. More specific tests were developed using glucose oxidase, which could be impregnated on a dry paper strip. The reaction of glucose with glucose oxidase produces hydrogen peroxide that can subsequently react with a colorless dye precursor in the presence of hydrogen peroxide to form a visible color (see Equation 23.3). The first enzyme-based test strips required addition of the sample to the strip for 1 min and subsequent washing of the strip. Visual comparison of the color on the test strip to the color on a chart was required to estimate the glucose concentration. However, the measurement of glucose in urine is not adequate since only after the blood glucose level is very high for several hours does glucose "spill-over" into the urine. Other physiological fluids such as sweat and tears are not suitable because the glucose level is much lower than in blood.

Whole blood contains hemoglobin inside the red blood cells that can interfere with the measurement of color on a test strip. To prevent staining of the test strip with red blood cells, an ethyl cellulose layer was applied over the enzyme and dye-impregnated paper on a plastic support (Mast 1967). In another early commercially available test strip, the enzymes and dye were incorporated into a homogeneous water-resistant film that prevented penetration of red blood cells into the test strips and enable their easy

removal upon washing (Rey et al. 1971). Through various generations of products, the formulations of the strips were improved to eliminate the washing/wiping steps and electronic meters were developed to measure the color.

23.2 Development of Colorimetric Test Strips and Optical Reflectance Meters

Optically based strips are generally constructed with various layers that provide a support function, a reflective function, an analytical function, and a sample-spreading function as illustrated in Figure 23.1. The support function serves as a foundation for the dry reagent and may also contain the reflective function. Otherwise, insoluble reflective or scattering materials such as TiO_2, $BaSO_4$, MgO, or ZnO are added to the dry reagent formulation. The analytical function contains the active enzyme. The reaction schemes used in several commercial products are described in greater detail later. The spreading function must rapidly disperse the sample laterally after application and quickly form a uniform sample concentration on the analytically active portion of the strip. Swellable films and semipermeable membranes, particularly glass fiber fleece has been used to spread and separate plasma from whole blood. Upon formation of the colored reaction product, the amount of diffuse light reflected from the analytical portion of the strip decreases according to the following equation:

$$\%R = (I_u/I_s)\, R_s \tag{23.1}$$

where I_u is the reflected light from the sample, I_s is the reflected light from a standard, and R_s is the percent reflectivity of the standard. The Kubelka–Munk equation gives the relationship in a more useful form:

$$C \propto K/S = (1 - R)^2/2R \tag{23.2}$$

where C is the concentration, K is the absorption coefficient, S is the scattering coefficient, and R is the percent reflectance divided by 100.

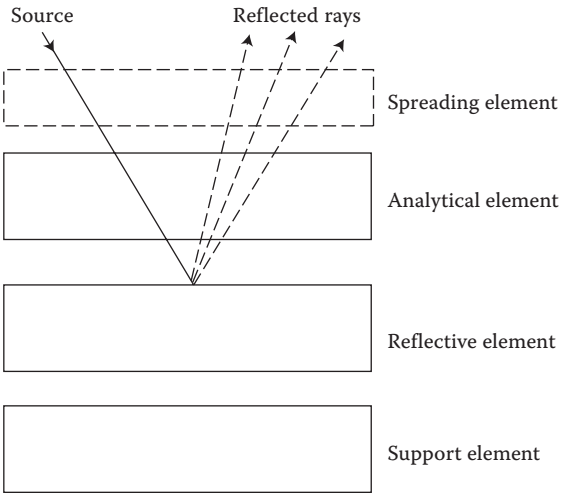

FIGURE 23.1 Basic functions of a reflectance-based test strip. (From Henning TP and Cunningham DD. Biosensors for personal diabetes management. In: *Commercial Biosensors*, pp. 3–46, 1998. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.)

The analytical function of the strip is based on an enzyme reaction with glucose and subsequent color-forming reactions. Although the most stable enzymes are chosen for product development, some loss in activity occurs during manufacturing due to factors such as pH, temperature, physical sheer stress, organic solvents, and various other denaturing actions or agents. Additional inactivation occurs during the storage of the product. In general, sufficient enzyme and other reagents are incorporated into the strip so that the assay reactions near completion in a conveniently short time. Reagent formulations often include thickening agents, builders, emulsifiers, dispersion agents, pigments, plasticizers, pore formers, wetting agents, and the like. These materials provide a uniform reaction layer required for good precision and accuracy. The cost of the materials in the strip must be low since it is used only once.

Many color-forming reactions have been developed into commercial products as indicated in the following examples. Manufacturers often use the same chemistry across multiple brands of strips and meters as indicated by the brief description of the active ingredients given in the test strip package insert. The glucose oxidase/peroxidase reaction scheme used in the Lifescan OneTouch™ (Phillips et al. 1990) and SureStep™ test strips is mentioned later. Glucose oxidase catalyzes the oxidation of glucose forming gluconic acid and hydrogen peroxide. The oxygen concentration in blood (ca. 0.3 mM) is much lower than the glucose concentration (3–35 mM), so oxygen from the atmosphere must diffuse into the test strip to bring the reaction to completion. Peroxidase catalyzes the reaction of the hydrogen peroxide with 3-methyl-2-benzothiazolinone hydrazone (MBTH) and 3-dimethylaminobenzoic acid (DMAB). A naphthalene sulfonic acid salt replaces DMAB in the SureStep strip.

$$\begin{aligned} \text{Glucose} + \text{oxygen} &\xrightarrow{\text{GOx}} \text{gluconic acid} + H_2O_2 \\ H_2O_2 + \text{MBTH} + \text{DMA} &\xrightarrow{\text{peroxidase}} \text{BMBTH-DMAB (blue)} \end{aligned} \tag{23.3}$$

The hexokinase reaction scheme used in the Bayer GLUCOMETER ENCORE™ test strip is shown later. Hexokinase, ATP, and magnesium react with glucose to produce glucose-6-phosphate. The glucose-6-phosphate reacts with glucose-6-phosphate dehydrogenase and NAD^+ to produce NADH. The NADH then reacts with diaphorase and reduces the tetrazolium indicator to produce a brown compound (formazan). The reaction sequence requires three enzymes but is insensitive to oxygen.

$$\begin{aligned} \text{Glucose} + \text{ATP} &\xrightarrow[Mg^{+2}]{\text{HK}} \text{G-6-P} + \text{ADP} \\ \text{G-6-P} + NAD^+ &\xrightarrow{\text{G-6-PDH}} \text{6-PG} + \text{NADH} + H^+ \\ \text{NADH} + \text{tetrazolium} &\xrightarrow{\text{diaphorase}} \text{formazan (brown)} + NAD^+ \end{aligned} \tag{23.4}$$

The reaction scheme originally used in the Roche Accu-Chek™ Instant™ test strip is shown later (Hoenes et al. 1995). Bis-(2-hydroxy-ethyl)-(4-hydroximinocyclohex-2,5-dienylidene) ammonium chloride (BHEHD) is reduced by glucose to the corresponding hydroxylamine derivative and further to the corresponding diamine under the catalytic action of glucose oxidase. Note that while oxygen is not required in the reaction, oxygen in the sample may compete with the intended reaction creating an oxygen dependency. The diamine reacts with a 2,18 phosphomolybdic acid salt to form molybdenum blue. More recent forms of the Accu-Chek Instant, Compact™, and Integra™ brand test strips were formulated with the oxygen-independent enzyme glucose dehydrogenase containing pyrroloquinoline quinine (GDH-PQQ) and the same reagents used to form molybdenum blue.

$$\begin{aligned} \text{Glucose} + \text{BHEHD} &\xrightarrow{\text{GOx}} \text{diamine} \\ P_2Mo_{18}O_{62}^{-6} + \text{diamine} &\longrightarrow MoO_{2.0}(OH) \text{ to } MoO_{2.5}(OH)_{0.5} \text{ (molybdenum blue)} \end{aligned} \tag{23.5}$$

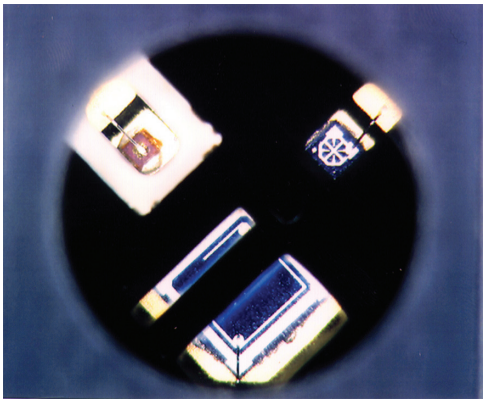

FIGURE 23.2 Photograph of light-emitting diodes and photodetector on the OneTouch meter. Photodetector at bottom, 635 nm light-emitting diode at top left, 700 nm light-emitting diode at top right. Optics viewed through the 4.5 mm hole in the strip after removal of the test strip reagent membrane. (Courtesy of John Grace.)

The reaction scheme used in the Roche Accu-Chek Easy™ test strip is shown later (Freitag 1990). Glucose oxidase reacts with ferricyanide and forms potassium ferric ferrocyanide (Prussian Blue). Again, oxygen is not required but may compete with the intended reaction.

$$\text{Glucose} + \text{GOx (ox)} \rightarrow \text{GOx (red)} \tag{23.6}$$

$$\text{GOx (red)} + [Fe(CN)_6]^{-3} \rightarrow \text{GOx (ox)} + [Fe(CN)_6]^{-4}$$

$$3[Fe(CN)_6]^{-4} + 4FeCl_3 \rightarrow Fe_4[Fe(CN)_6]_3 \text{ Prussian blue}$$

Current optical test strips and reflectance meters typically require 1.5–10 μL of blood and read out an answer in 10–30 s. A significant technical consideration in the development of a product is the measurement of samples spanning the range of red blood cell concentrations (percent hematocrit) typically found in whole blood. Common hematocrit and glucose ranges are 30–55% and 40–500 mg/dL (2.2–28 mM), respectively. The Lifescan OneTouch meter contains two light-emitting diodes (635 and 700 nm), which allows measurement of the color due to red blood cell and the color due to the dye. Reflectance measurements from both LEDs are measured with a single photodetector as shown in Figure 23.2. All glucose meters measure the detector signal at various timepoints and if the curve shape is not within reasonable limits an error message is generated. Some meters measure and correct for ambient temperature. Of course, optical systems are subject to interference from ambient light conditions and may not work in direct sunlight. Optical systems have gradually lost market share to electrochemical systems that were introduced commercially in 1987. Optical test strips generally require a larger blood sample and take longer to produce the result than electrochemical strips. Presently, optical reflectance meters are more costly to manufacture, require larger batteries, and are more difficult to calibrate than electrochemical meters.

23.3 Emergence of Electrochemical Strips

Electrochemical systems are based on the reaction of an electrochemically active mediator with an enzyme. The mediator is oxidized at a solid electrode with an applied positive potential. Electrons will flow between the mediator and electrode surface when a minimum energy is attained. The energy of the electrons in the mediator is fixed based on the chemical structure but the energy of the electrons in the solid electrode can be changed by applying a voltage between the working electrode and a second

electrode. The rate of the electron transfer reaction between the mediator and a working electrode surface is given by the Butler–Volmer equation (Bard and Faulkner 1980). When the potential is large enough all the mediator reaching the electrode reacts rapidly and the reaction becomes diffusion controlled. The current from a diffusion-limited reaction follows the Cottrell equation:

$$i = (nFAD^{1/2}C)/(\pi^{1/2}t^{1/2}) \tag{23.7}$$

where i is the current, n is the number of electrons, F is Faraday's constant, A is the electrode area, C is the concentration, D is the diffusion coefficient, and t is the time. The current from a diffusion-controlled electrochemical reaction will decay away as the reciprocal square root of time. This means that the maximum electrochemical signal occurs at short times as opposed to color-forming reactions where the color becomes more intense with time. The electrochemical method relies on measuring the current from the electron transfer between the electrode and the mediator. However, when a potential is first applied to the electrode, the dipole moments of solvent molecules will align with the electric field on the surface of the electrode causing a current to flow. Thus, at very short times, this charging current interferes with the analytical measurement. Electrochemical sensors generally apply a potential to the electrode surface and measure the current after the charging current has decayed sufficiently. With small volumes of sample, coulometric analysis can be used to measure the current required for complete consumption of glucose (Feldman et al. 2000).

The reaction scheme used in the first commercial electrochemical test strip from MediSense (now Abbott Diabetes Care) is shown later. Electron transfer rates between the reduced form of glucose oxidase and ferricinium ion derivatives are very rapid compared with the unwanted side reaction with oxygen (Cass et al. 1984; Forrow et al. 2002). The Abbott Diabetes Care Precision QID™ strip includes the 1,1′-dimethyl-3-(2-amino-1-hydroxyethyl) ferrocene mediator, which has the desirable characteristics of high solubility in water, fast electron-shuttling (bimolecular rate constant of $4.3 \times 10^5\ M^{-1}\ s^{-1}$), stability, and pH independence of the redox potential (Heller and Feldman 2008). Electrochemical oxidation of the ferrocene derivative is performed at 0.6 V. Oxidation of interferences, such as ascorbic acid and acetaminophen present in blood, are corrected for by measuring the current at a second electrode on the strip that does not contain glucose oxidase.

$$\begin{gathered}\text{Glucose} + \text{GOx (oxidized)} \rightarrow \text{gluconolactone} + \text{GOx (reduced)} \\ \text{GOx (reduced)} + \text{ferricinium}^+ \rightarrow \text{GOx (oxidized)} + \text{ferrocene} \\ \text{Ferrocene} \rightarrow \text{ferricinium}^+ + \text{electron (reaction at solid electrode surface)}\end{gathered} \tag{23.8}$$

Several electrochemical test strips use ferricyanide rather than ferrocene as the electrochemical mediator although the potential required for oxidation is higher than for ferrocene derivatives. The LifeScan OneTouch FastTake™ and Ultra™ brand test strips include glucose oxidase and either 11 or 22 μg ferricyanide per strip. The strip readout is reduced from 15 to 5 s with the larger amount of ferricyanide mediator. Many Roche Accu-Chek strips, including the Comfort Curve™, Compete™, Advantage™, Aviva™, and Active™, are formulated with the oxygen-independent enzyme GDH-PQQ and ferricyanide as the mediator. An organic mediator, nitrosoanaline is used with GDH-PQQ in the Roche Accu-Chek Performa™ test strip.

The reaction scheme used in the Abbott Diabetes Care Precision-Xtra™ and Sof-Tact™ test strips is shown later. The GDH enzyme does not react with oxygen and the phenanthroline quinine mediator can be oxidized at 0.2 V, which is below the oxidation potential of most interfering substances.

$$\begin{gathered}\text{Glucose} + \text{GDH/NAD}^+ \rightarrow \text{GDH/NADH} + \text{gluconolactone} \\ \text{GDH/NADH} + \text{PQ} \rightarrow \text{GDH/NAD}^+ + \text{PQH}_2 \\ \text{PQH}_2 \rightarrow \text{PQ} + \text{electrons (reaction at solid electrode surface)}\end{gathered} \tag{23.9}$$

The working electrode on most commercially available electrochemical strips is made by screen printing a conductive carbon ink on a plastic substrate; however, more expensive noble metal electrodes are also used. Historically, test strips have been manufactured, tested, and assigned a calibration code. The calibration code provided with each package of strips is sometimes manually entered into the meter by the user but other systems automatically read the calibration code from the strips. Meters designed for use in the hospital often have bar code readers to download calibration, quality control, and patient information. Test strips are supplied in bottles or individual foil wrappers to protect them from moisture over their shelf-life, typically about 1 year. The task of opening and inserting individual test strip into the meter has been minimized by packaging multiple test strips in the form of a disk-shaped cartridge or a drum that is placed into the meter. Disks or drums typically contain 10–17 test strips.

23.4 Enzyme Selectivity and Falsely Elevated Readings

Formulations containing GDH-PQQ became popular due to the lack of oxygen interference and the high catalytic activity of the enzyme relative to glucose oxidase (5000 U/mg vs 300 U/mg). However, GDH-PQQ oxidizes a wide range of sugars with reaction rates generally in the order: glucose (100%), maltose (58%), lactose (58%), galactose (10%), mannose (10%), and xylose (10%). Normally, the concentration of the other sugars is so much lower than the glucose concentration in blood that there is little interference. Until recently, it was not appreciated that patients receiving peritoneal dialysis using the osmotic agent icodextrin absorb and metabolize the icodextrin to shorter polysaccharides, mainly maltose, causing erroneously high glucose measurements. In addition, some injected drug products contain maltose as a part of the formulation, which also leads to high glucose readings. To address this issue, the FDA recently issued a public health notification recommending against the use of GDH-PQQ in glucose test strips (FDA Public Health Notification 2009). Research studies have shown that site-directed mutagenesis of GDH-PQQ can reduce the reactivity to maltose to about 10% that of glucose but cannot achieve the selectivity of either glucose oxidase or NADH-dependent glucose dehydrogenase (Igarashi et al. 2004). Besides adequate activity and selectivity, any new enzyme developed for use in test strips must have good thermal stability. Protein engineering approaches for improving enzyme stability include increasing the hydrophobic interaction in the interior core region of the protein, reducing the water-accessible hydrophobic surface area, and stabilizing the dipoles of the helical structure.

23.5 Improvements in User Interactions with the System and Alternate Site Testing

Both Type 1 and Type 2 diabetic individuals do not currently test as often as recommended by physicians, so systems developed in the last few years have aimed to improve compliance with physician recommendations while maintaining accuracy. Historically, the biggest source of errors in glucose testing involved interaction of the user with the system. Blood is typically collected by lancing the edge of the end of the finger to a depth of about 1.5 mm. Squeezing or milking is required to produce a hanging drop of blood. The target area on test strips is clearly identified by design. A common problem is smearing a drop of blood on top of a strip resulting in a thinner than normal layer of blood over part of the strip and a low reading. Many strips now require that the blood drop be applied to the end or side of the strip where capillary action is used to fill the strip. Partial filling can be detected electrochemically or by observation of the fill window on the strip. The small capillary space in the Abbott Diabetes Care Freestyle™ electrochemical strip requires only 300 nL of blood.

Progressively thinner diameter lancets have come to the market with current sizes typically in the 28–31 gauge range. Most lancets are manufactured with three grinding steps to give a tri-bevel point. After loading the lancet into the lancing device, a spring system automatically lances and retracts the point. The depth of lancing is commonly adjustable through the use of several settings on the device or use of a different end-piece cap. Unfortunately, the high density of nerve endings on the finger makes

the process painful and some diabetic individuals do not test as often as they should due to the pain and residual soreness caused by fingersticks. Recently, lancing devices have been designed to lance and apply pressure on the skin of body sites other than the finger, a process termed "alternate site testing." The use of alternate site sampling lead to the realization that capillary blood from alternate sites can have slightly different glucose and hematocrit values than blood from a fingerstick due to the more arterial nature of blood in the fingertips. The pain associated with lancing alternate body sites is typically rated as painless a majority of the time and less painful than a fingerstick over 90% of the time. A low-volume test strip, typically 1 μL or less, is required to measure the small blood samples obtained from alternate sites. Some care and technique is required to obtain an adequate amount of blood and transfer it into the strips when using small blood samples.

Significant insight into blood collection from the skin was uncovered during the development of an alternative site device, the Abbott Diabetes Care Sof-Tact meter, which automatically extracts and transfers blood to the test strip (see Figure 23.3). The device contains a vacuum pump, a lancing device, and a test strip that is automatically indexed over the lancet wound after lancing. The vacuum turns off after sufficient blood enters the strip to make an electrical connection. The key factors and practical limits of blood extraction using vacuum combined with skin stretching were investigated to assure that sufficient blood could be obtained for testing (Cunningham et al. 2002). The amount of blood extracted increases with the application of heat or vacuum prior to lancing, the level of vacuum, the depth of lancing, the time of collection, and the amount of skin stretching (see Figure 23.4). Particularly important is the diameter and height that skin is allowed to stretch into a nosepiece after the application of vacuum as shown in Figure 23.5. Vacuum combined with skin stretching increases blood extraction by increasing the lancet wound opening, increasing the blood available for extraction by vasodilatation, and reducing the venous return of blood through the capillaries. The electrochemical test strip used with the meter can be inserted into a secondary support and used with a fingerstick sample when the battery is low.

The size of a meter is often determined by the size of the display although electrochemical meters can be made smaller than reflectance meters. The size and shape of one electrochemical meter, with a

FIGURE 23.3 Sof-Tact meter with cover opened to load test strip and lancet. Test strip is inserted into an electrical connector. The hole in the opposite end of the test strip allows the lancet to pass through. The white cylindrical lancet is loaded into the lancet tip holder in the housing. To perform a test, the cover is closed, the gray area of the cover placed against the skin and the front button depressed.

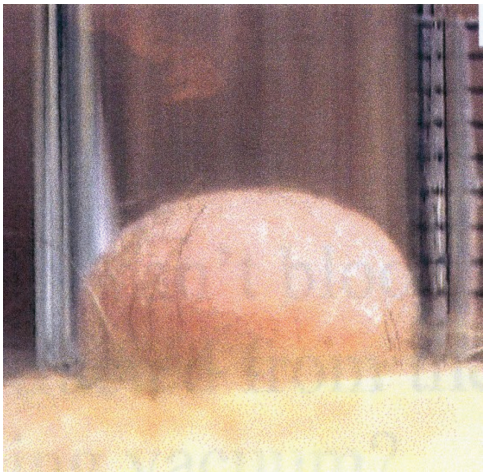

FIGURE 23.4 Photograph of skin on the forearm stretching up into a glass tube upon application of vacuum. Markings on tube at right in 1 mm increments. (Courtesy of Douglas Young.)

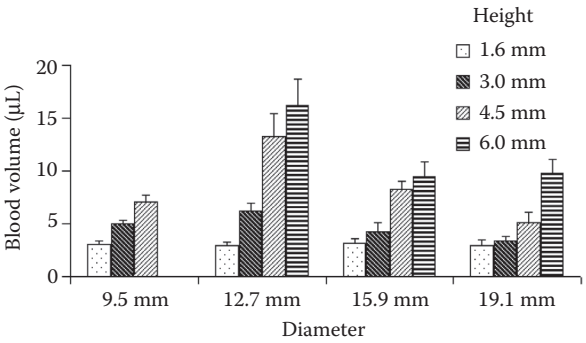

FIGURE 23.5 Effect of skin stretching by vacuum on blood volume extracted from lancet wounds on the forearm. Mean blood volume ± SE in 30 s with −7.5 psig vacuum for nosepieces of different inner diameter and inside step height. (From Cunningham et al., 2002. *J Appl Physiol* 92: 1089–1096. With permission.)

relatively small display, is indistinguishable from a standard ink pen. All meters store recent test results in memory and many allow downloading of the results to a computer. The variety of meters available in the market is mainly driven by the need to satisfy the desires of various customer segments that are driven by different factors, such as cost, ease of use, or incorporation of a specific design or functional feature. Advanced software functions are supplied with some meters to allow entry of exercise, food, and insulin doses, and a personal digital assistant–meter combination was brought to market.

23.6 Continuous Glucose Sensors

All the currently marketed continuous glucose-sensing systems in the United States have similar components. The sensor is contained within a sharp metal housing that is inserted through the skin, then the metal portion is retracted leaving the sensor in the skin. The sensor has a glucose oxidase working electrode portion located under the skin and electrical contacts that are connected to a battery-operated electrochemical potentiostat outside the skin. The electrical components often wirelessly transmit data to a remote display unit where the most recent glucose result and trend data are available. After insertion into the skin, the sensor is calibrated using blood glucose test strips, so a test strip meter is often

incorporated into the system for this purpose. Initial calibration and recalibration requirements of the systems has become progressively less demanding over the past several years, but insertion of the sensor into the body changes the sensitivity of present-day sensors enough that some calibration is required. Mechanistic studies of the body's reaction to sensor insertion and testing of more biocompatible coatings is a very active area of investigation both in academia and in industry. However, limited information is available on advances in the area of biocompatible coatings, due to the proprietary nature of the work. Sensors are currently approved for use for up to 7 days, with the risk of infection at the insertion site becoming a concern at longer times.

The sensors marketed by Medtronic and Dexcom are based on a first-generation scheme where the working electrode oxidizes hydrogen peroxide generated by the reaction of glucose and oxygen as catalyzed by glucose oxidase. The working electrode must be covered with a material that is more permeable to oxygen than to glucose since the typical 0.1–0.3 mM concentration of oxygen in the body is much lower than the 2–30 mM concentration of glucose. The Medtronic sensor is a three-electrode system with a working, counter, and reference electrode, so the reference electrode area can be fairly small since no current passes through the reference electrode. The electrodes are fabricated on a thin flexible piece of plastic apparently using thin-film deposition techniques with a membrane polymer coating composed of a diisocyanate, a diamino silane, and a diol, which forms a polyurethane polyurea polymer (VanAntwerp 1999; Henning 2010). The Dexcom sensor is a two-electrode system consisting of a thin platinum wire and a larger silver wire with a silver chloride coating on the outside. During the oxidation of the hydrogen peroxide at about 0.6 V, the silver chloride is reduced. The glucose-limiting membrane is apparently a hydrophilic block copolymer of polyethylene glycol and a polyurethane mixed with a hydrophobic polyurethane polymer (Tapsak et al. 2007). Both the Medtronic and Dexcom sensors are inserted about 12 mm into the skin at a 45° angle but the form of the inserter and the method of electrical contact are of different design (Henning 2010).

The Abbott Diabetes Care sensor is based on a second-generation scheme where an exogenous mediator, in this case an osmium redox polymer, rather than oxygen reacts with the glucose oxidase (Feldman et al. 2003). The mediator can be added at higher effective concentrations than oxygen, eliminating the problem of low oxygen concentration. The sensor is a three-electrode design screen printed on a plastic substrate as shown in Figure 23.6. The reduced mediator is oxidized at a low potential, 0.04 V, so common electrochemical interferences in blood such as acetaminophen and ascorbic acid will not react at the working electrode. The current density of second-generation sensors can be much higher than in the first-generation system since the diffusion of glucose does not have to be reduced to below that of oxygen. The Abbott Diabetes Care sensor is inserted about 5 mm into the skin at a 90° angle.

The GlucoDay™ system based on microdialysis sampling of interstitial fluid was developed in Europe and introduced commercially by Menarini Diagnostics (Poscia et al. 2003). A microdialysis fiber 5 mm

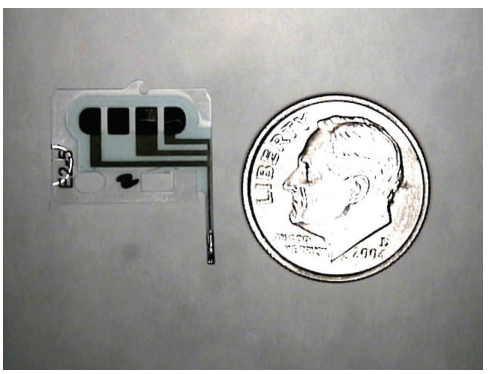

FIGURE 23.6 Abbott Diabetes Care sensor showing size relative to a U.S. dime. (Courtesy of Abbott Diabetes Care.)

long is inserted through the skin by a medical professional, perfused with a buffer solution at a flow rate of ~10 μL/min using a micropump, and the glucose content of the solution measured with a first-generation glucose sensor. The system is calibrated with a blood glucose test strip and the monitoring conducted for up to 48 h, after which the fiber is removed. At present, the high level of professional medical personnel involvement is a significant commercial limitation of the technology.

One 12-h device, the Cygnus GlucoWatch™ based on transdermal reverse iontophoresis (Kurnik et al. 1998) gained FDA approval but the acceptance of the device in the market was poor due to the need to calibrate the device with multiple fingersticks and poor precision and accuracy. The device is no longer commercially available.

23.7 Future Directions

Advances in self-monitoring glucose test strips and meters are difficult to predict given the already highly refined nature of the products in terms of cost of manufacture, size, reliability, ease of use, and time-to-result. Accuracy may be improved through the use of more advanced electrochemical measurements with improved signal-processing strategies or the use of redundant arrays of electrodes on a single strip. Emerging fabrication technologies such as nanoimprint lithography and electrochemical or electrode-less deposition of metals are capable of producing very fine detail without the use of expensive masks. The significant international investment in nanotechnology is producing a wide variety of advanced materials that prove useful in new products. Newly engineered enzymes and electron transfer chemistries may emerge to address selectivity, activity, stability, and other crucial factors. In this regard, several methods have already been reported to electrically connect the glucose oxidase catalytic center to an electrode, gold nanoparticle, or carbon nanotube (Cunningham and Stenken 2010).

The performance of continuous glucose monitoring systems has been rapidly improving and should soon reach the state where the signal is reliable enough to provide input into an insulin infusion pump to produce a "closed-loop" system. However, development of an appropriate algorithm to translate the glucose value into the correct insulin infusion pump setting is quite challenging. A strictly hardware-based system is ignorant of many important factors affecting future blood glucose levels, such as the size of the meal the patient will eat, the amount of exercise planned, or the level of daily stress encountered. So, systems allowing user input of information or "open-loop" control systems may prove more successful. Long-term sensing may involve surgical implantation of a battery-operated unit although many issues remain with the long-term stability of the sensor, miniaturization of the sensing electronics, and data transmitter and biocompatibility of the various materials of construction.

Many fluorescence-based sensing approaches have been investigated by academic and industrial groups. Perhaps the most interesting system involves the injection of glucose-sensitive fluorescent microspheres into the skin to create a "tattoo." The glucose measurement is then made by placing an appropriately designed intensity or time-based fluorometer over the skin area. Many reversible glucose-binding fluorescent systems have been reported with boronic acid derivatives, lectins, or glucose-binding proteins serving as the glucose-selective agent and fluorescent dyes, preferably with absorbance wavelengths above that of hemoglobin, serving as the reporter (McShane and Stein 2010). The *in vivo* stability of the glucose-selective agent and fluorescent dye will likely become more apparent as results from ongoing animal trials are published. Additional work may be needed to overcome the host response to the microspheres and to decrease the immunogenicity of the protein component, if used.

A number of noninvasive spectroscopic approaches have been investigated; however, the amount of clinical data reported to date is very limited. Near-infrared spectroscopy has received the most focused attention with careful analysis of instrumental capabilities and calculation of the net analytical signal indicating currently available hardware can generate glucose-specific information from physiological levels of glucose in body tissue. Additional work is needed to show how this information can be obtained in a reliable and practical manner. Raman spectroscopy and surface-enhanced Raman spectroscopic approaches have advanced through initial animal studies demonstrating partial proof-of-principle.

Likewise, the optical rotation of polarized light by glucose has been utilized to measure glucose particularly in the accessible portion of the aqueous humor of the eye.

Glucose changes also affect the osmotic strength of interstitial fluid, and sensors based on chemical swelling or shrinking of polymers, optical changes in the refractive index, and osmotic effects on electrochemical capacitance have been refined through *in vitro* studies. Prospective clinical trials are needed to more clearly identify the potential of these approaches.

Glucose monitoring of alternative body fluids such as sweat, saliva, gingival crevicular, or tear fluid has been investigated but these fluids generally have a lower glucose concentration than blood and the glucose content of these samples, obtained using traditional methods, does not change in a fixed proportion to the blood glucose concentration. Future studies may explore the possibility that acquisition of smaller physiological samples may show better correlation with blood glucose levels due to the lower anatomical and physiological stress required to obtain smaller volumes of fluid. Further miniaturization and refinement in the design of devices for the collection of small blood or interstitial fluid samples as well as insertion of sensing components into or through the skin is anticipated. Overall, the future of blood glucose monitoring looks very challenging and exciting.

Defining Terms

Alternate site testing: Lancing sites other than the finger to obtain blood in a less painful manner. The small volume of blood obtained from alternate sites requires use of a test strip requiring 1 μL or less of blood.

Type 1 Diabetes: The immune system destroys insulin-producing islet cells in the pancreas, usually in children and young adult, so regular injections of insulin are required (also referred to as juvenile diabetes).

Type 2 Diabetes: A complex disease based on gradual resistance to insulin and diminished production of insulin. Treatment often progresses from oral medications to insulin injections as disease progresses. Also referred to as adult onset diabetes and non-insulin-dependent diabetes mellitus (NIDDM).

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Further Information

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Reviews and descriptions of many marketed products are available online at: www.childrenwithdiabetes.com.

Interviews of several people involved with the initial development of blood glucose meters are available online at: www.mendosa.com/history.htm.