Microsystem Technologies for Medical Applications

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Abstract

Medical technologies are evolving at a very rapid pace. Portable communication devices and other handheld electronics are influencing our expectations of future medical tools. The advanced medical technologies of our future will not necessarily be large expensive systems. They are just as likely to be small and disposable. This paper reviews how microsystems are already impacting health care as commercial products or in clinical development. Example systems for point-of-care testing (POCT), patient monitoring tools, systemic drug delivery, local drug delivery, and surgical tools are described. These technologies are moving care from hospitals to outpatient settings, physicians' offices, community health centers, nursing homes, and the patients' homes. Microsystems that are rapidly adopted fulfill significant medical needs and are compatible with existing clinical practice.

BACKGROUND

How and where people receive healthcare in the United States is changing. The period from 1980 through 2007, for example, saw total hospital admission stay relatively constant (see table 104 in Reference 1). The average length of stay, however, dropped from 10 to 6.3 days. The number of outpatient visits to hospitals of all kinds more than doubled. Annual growth rates for hospital inpatient surgical procedure volumes are approximately 1%, whereas outpatient surgical procedures are growing at 4%. Specialized freestanding facilities for specific procedures such as colonoscopy are experiencing annual growth rates of 6%. Surgical procedures in the physician's office are growing at 4%. During the period 1980–2007, community hospitals performed an increasing number of procedures; as a percentage, these rose from 16.3% to 62.7%. Some of the rise can be attributed to utilization of ambulatory diagnostic procedures such as MRI/CT/PET (Magnetic Resonance Imaging/ X-ray Computed Tomography/Positron Emission Tomography), which increased fourfold during the period 1996 to 2007 as these technologies came into widespread use (see figure 25 in Reference 1). There is, however, a clear trend indicating an emphasis on reducing hospital length of stay (LOS) and designing procedure-specific, high-efficiency practice settings.

These changes in LOS and settings of care can be attributed to several factors. First, cost containment measures instituted by Medicare and Medicaid programs, insurance companies, and employers are a major influence. Hospitals are sites of intense health care utilization and not surprisingly the most expensive care settings. Movement of health care services to other settings can dramatically reduce costs, however, only if equivalent outcomes can be obtained. Second, the introduction of expensive outpatient diagnostic procedures may complicate understanding of the shift from a cost/benefit perspective. Nonetheless, technology and evidence-based health management clearly have allowed a reduction in hospital stays and a shift in services from hospitals to ambulatory outpatient settings, community health centers, nursing homes, and the patients' homes. Signs indicate that the developed world has already made changes similar to those in the United States, and there is no reason to believe that developing countries will not follow.

The emerging technologies that will make such a shift in services safe and effective may look very different from the medical technologies of the past. Advanced medical technologies are often associated with capital-intensive equipment such as robotic surgery systems, particle accelerators, or MRI, CT, and PET imaging systems that require intense usage to be economically viable. The medical technologies of our future may be much less capital intensive and much more distributed among the various venues for health care services. This article reviews some of the new microsystem-based technologies that are changing medical practice and are perhaps just the first wave of products that can reduce the intensity of health care utilization while maintaining a high standard of care.

MICROSYSTEM TECHNOLOGIES

This article uses the term "microsystem technologies" to indicate a superset of devices referred to as microelectromechanical systems (MEMS). MEMS devices often integrate mechanical, electrical, and optical elements, such as actuators and transducers, to perform specific functions. MEMS devices primarily use semiconductor fabrication methods for their manufacture but may additionally rely on alternative fabrication methods such as embossing, printing, machining, and plating. Microsystems exploit the levels of integration and efficiency of manufacture obtained by MEMS but more often are fabricated from plastic rather than silicon.

The goal of this paper is to describe the breadth of microsystem technology applications in medicine today. Emphasis is placed on devices in use or undergoing clinical trials. This path has

been taken by others, and the reader is encouraged to read elsewhere (2). Further emphasis is placed on the functional aspects of the microsystem devices and less on the fabrication method, as companies often do not disclose the details of the fabrication methods of such devices. There are, however, many excellent reviews of MEMS technologies (3).

DIAGNOSTICS

Microsystems have made their largest clinical impact thus far in the area of chemical diagnostics and specifically in the area of point-of-care testing (POCT), that is, tests performed near or at the site of care. One of the most commonly cited examples of POCT is the home pregnancy test. The advantage of POCT is that results are often simple (such as positive or negative) and may be obtained in near-real time.

More recently, POCT testing has become more sophisticated by reporting quantitative results. One such example is the single-use glucose sensors used by diabetics. The chemistry and technology behind these sensors have been well described in the literature (4). Briefly, the strips contain a dry layer of enzymes and mediator molecules that convert the glucose contained in a small sample of blood into a detectable signal. Currently the signal can be detected in one of two ways, either electrochemically or photometrically. The blood volume required for the test has dropped by more than an order of magnitude since 1990, which has made the repeated glucose testing required by diabetics less painful and cumbersome. Blood volumes as small as 0.3 μL are now routinely used to measure glucose levels within 5 s with a precision of 2–3% and a deviation within 5% of a lab reference. Accu-Chek of Roche Diagnostics GmbH (Mannheim, Germany), Ascensia Microfil of Bayer HealthCare AG (Leverkusen, Germany), Chemstrip bG of Boehringer Ingelheim GmbH (Ingelheim, Germany), Freestyle and Precision Xtra of Abbot Diabetes Care, Inc. (Alameda, CA), and One Touch of LifeScan, Inc. (Milpitas, CA) incorporate different test strip chemistries and designs to improve measurement speed, specificity, accuracy and precision.

All chemistries in glucose strips use glucose-specific enzymes that catalyze the oxidation of glucose and transfer electrons from that reaction to a mediator. Most glucose test strips then electrochemically determine the redox state of the mediator; for example, a mediator such as hexacyanoferrate(III) is reduced to hexacyanoferrate(II). The reduction product is then determined amperometrically. Thus, the disposable strip must allow integration of a microelectrode.

Production of the strips incorporates many aspects of advanced printed circuit board (PCB) manufacturing, and this is particularly true of electrochemically based glucose determinations (**Figure 1**). The Accu-Chek Aviva electrochemical test strip, for example, uses gold micro- and macroelectrodes that interface with a handheld reader (5). The interdigitated microelectrode array, where amperometry is conducted, is in contact with reagents and blood sample during use. The typical microelectrode width is 100 μm with a 100-μm separation, which is too small for conventional screen printing methods, and PCB methods of resist fabrication and etching are too expensive. Instead, these microelectrodes are manufactured by feeding a roll of ribbon including an 80-nm gold laminate into a broad-field laser ablation apparatus. This apparatus includes a laser source, a chromium-plated quartz mask, and optics. Energy sufficient for ablation is absorbed at the gold-substrate interface. The broad-field optics obviates the need to raster the ablation laser, which dramatically increases throughput and improves precision. MEMS-based fabrication technology also has been used in the sample layer of the TheraSense Freestyle test strip, which sits on top of its microelectrodes and is approximately 50 μm thick (4).

The fluid elements of glucose strips are simple but were the precursors to subsequent POCT fluidic designs. Blood must be drawn into the sample chamber by capillarity and then dissolve and react with reagents previously dried upon the microelectrode array; as such, hydrophilic interior

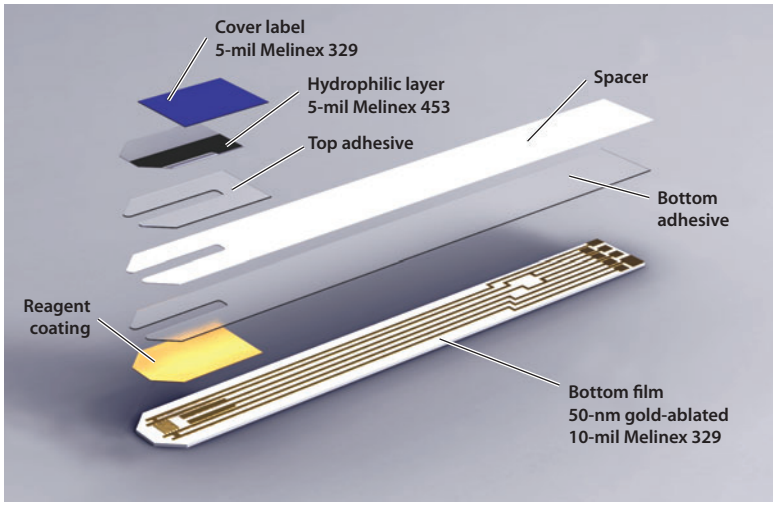

Figure 1

An exploded view of an electrochemical blood glucose test strip. Both electrical and fluidic elements are included. These include the conductive traces and electrodes on the bottom layer as well as a dried reagent layer. Materials are included to ensure that the small droplet of blood is drawn into the sensor by capillarity.

packaging surfaces are required. The reagents can be screen printed or direct printed in place. The reagent layer effectively acts as a filter preventing erythrocytes from entering the reaction zone. It is kept thin enough and measurement times fast so that the layer does not become clogged with erythrocytes. Thus, glucose test strips provided a proving ground for fluidic control, filtration, and dissolution of reagents in the context of microsystem technologies and handling of biological samples for diagnostics.

POCT devices now contain even more sophisticated chemistries and sensitive detection schemes. Enzyme-linked immunosorbent assays (ELISAs) have long been a mainstay of biomolecule quantification. The high specificity and affinity of antibody binding coupled with fluorescence detection has meant that nanomolar or lower concentrations can be detected and quantified. ELISA's main disadvantage as a method for POCT is the number of reaction and washing steps required to carry out the assay. Replicating such steps in a microsystem has proven difficult but not impossible (6–8). Biosite Diagnostics, Inc. (San Diego, CA) has, for example, developed what is essentially a chip-based POCT for several cardiac markers, the most important of which is B-type natriuretic peptide (BNP). BNP is produced by the heart ventricles in response to ventricular volume expansion. The circulating concentration of BNP is elevated in congestive heart failure (CHF) patients and, most importantly, is proportional to the severity of their disease (9). Thus, it has become a useful clinical tool for monitoring these patients. The Biosite system consists of disposable test strips and a portable reader, and it provides results within 15 min.

The Biosite strip is a multicompartment reaction and fluidic system that integrates reaction timing and washing with fluorescence detection (**Figure 2**) (10). This strip makes extensive use of microcapillary structures and hydrophilic or hydrophobic surfaces to drive fluid through the multiple compartments of the strip and to direct the load during lamination of the upper and lower portions of the strip. The compartments and elements that are important are the addition zone, sample reaction barrier, reaction zone, time gate, diagnostic element, and the used reagent

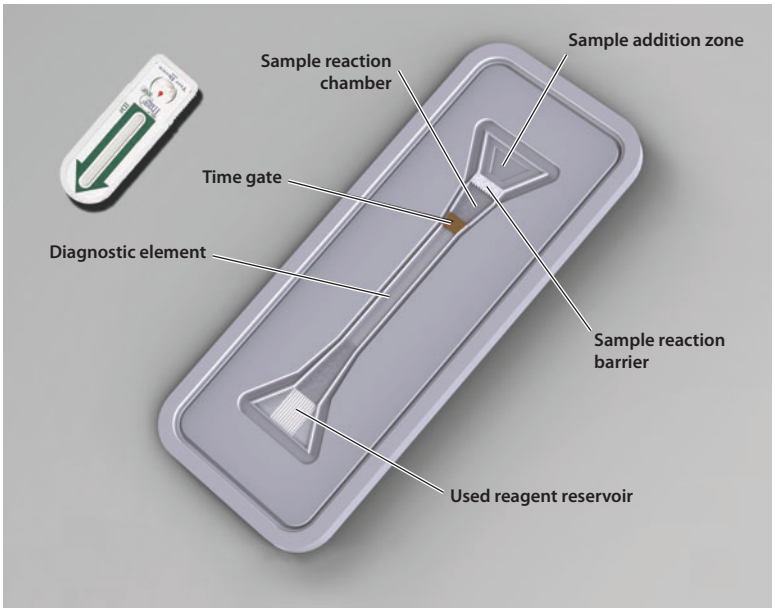

Figure 2

Elements of the Biosite point-of-care testing test strip for B-type natriuretic peptide. The strip is shown in the upper left and the author's rendering of the important fluidic and chemical elements is shown in the rest of the figure. Blood is placed in the sample addition zone and is drawn by capillarity through the reaction chamber and diagnostic elements.

reservoir. The disposable strip is a plastic assembly with deposited reagents on a bottom layer and a top layer that also contains an analysis window.

The sample addition zone receives a small sample of blood. The volume of blood contains enough analyte (BNP) to test and sufficient additional fluid to wash excess reagents from the downstream diagnostic element. Thus, a separate washing fluid is not required. The key is to prevent contamination of some of the fluid in the sample with the reagents used in the test. This fascinating approach is typical of what is required to make sophisticated analytical methods possible in strip-based POCT.

The reaction chamber that immediately follows the addition zone determines a well-defined reaction volume that obviates the need for precise pipetting of the blood sample. The reaction volume also contains dried reagents that are reconstituted when exposed to fluid. The reaction chamber and addition zone are separated by a reaction barrier composed of a capillary network that provides sufficient diffusional resistance to prevent transport of reagents into the addition zone over the course of the test. The excess fluid from the sample is, therefore, left uncontaminated.

The chemical derivatization of BNP for subsequent immunoassay occurs in the reaction volume and takes time. Thus, the reaction mixture must be prevented from immediate capillary flow into the diagnostic element. This is accomplished by the time gate, which makes use of a surface that is only transiently hydrophobic. The native surfaces of common plastics and elastomers are often hydrophobic and must be surface modified for aqueous solutions to wet them. Such a hydrophobic surface will effectively prevent the reaction mixture from entering the diagnostic element. Binding of surface-modifying agents within the contacting solution over time can change the contact angle and improve the wetting of fluid on the surface. The time gate exploits the time required for this

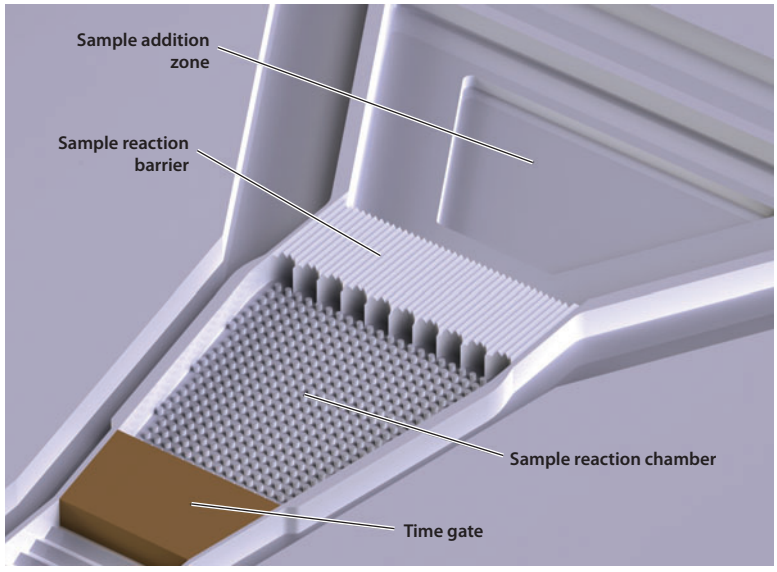

Figure 3

A render by the author indicating some of the microscopic features exploited for ensuring uniform deposition of reagents in the sample reaction chamber. The textured surface causes the reagent solution to spread uniformly during drying. The vertical dimensions in this render are exaggerated for clarity.

to happen. A simple example is to start with a surface covered with a dried polyelectrolyte such as polyacrylic acid. This surface is surprisingly hydrophobic. When exposed to a solution with a pK_a greater than that of the acid groups, however, the polymer becomes charged and thus hydrophilic. This transition takes time and provides the basic reaction period for the time gate. Adjustment of the time occurs by changing the dimensions of the time gate and the capillary features within it.

The diagnostic element contains the heart of the immunoassay. Antibodies to the target analyte are bonded to the bottom surface of the element. Fluorescent-tagged analyte is captured on this surface and measured after washing. Typically the antibody is directly bonded to carrier particles (such as latex) that are then applied to a surface, as in the Biosite device. This approach increases the amount of antibody per unit area and improves the detection limit of the fluorescence measurement. Depositing this reagent uniformly over the surface of the diagnostic element is critical for reproducible measurement. The diagnostic element in the Biosite device is a textured surface composed of microposts and grooves. These features hold the drying fluid through capillarity and facilitate uniform drying of reagents during manufacture of the strip. Without such texture, the drying fluid would form large menisci near the edge of the wetted area, and much of the reagent would be deposited near the edges. Similar surface textures are used to prepare uniform layers of reagent in the reaction chamber as shown in **Figure 3**.

The close proximity of the upper and lower surfaces in the diagnostic element (typically 100 μm) is important, as it decreases the volume of fluid in the diagnostic element and improves the capture efficiency of the antibody. The small distance also reduces the time required for diffusion of the protein analyte. The potential downside of this approach is, of course, that the total amount of analyte in the element will be small, which may limit the ultimate sensitivity of the any assay built on this technology.

The used reagent reservoir forms the last important element of this strip technology. This reservoir has sufficient volume and capillary suction to pull the entire original sample through each element of the strip. The plug flow of the fluid through the strip can then make use of that portion of the sample that has not been contaminated with reagent. This is important as the reagent would compromise the fluorescent determination of analyte if it were not washed from the diagnostic element. The capillary network required in the Biosite strip is formed by microgrooves fabricated in the base layer of the strip.

Other microsystems for analysis of protein targets include those for other myocardial injuries such as Abbott Laboratories' (Abbott Park, IL) i-STAT® and Amic AB's (Uppsala, Sweden) 4castchip® (11). The i-STAT is a handheld portable device that uses disposable immunoassays to quantitatively detect cardiac markers such as troponin, CK-MB (Creatine kinase with sub units M and B).

Microsystem diagnostic devices based on mechanical action are also used. Close monitoring of blood coagulation time is a requirement for maintenance of several therapeutics, most commonly for therapy with warfarin, an anticoagulant used for thrombosis prevention. Dosing warfarin is complicated, as it interacts with many drugs and diet. Thus, many patients can have blood coagulation times [measured as prothrombin time (PT)] that are dangerously long and can increase the risk of hemorrhage. Most commercial PT devices use optical analysis. In contrast, Microvisk Ltd.'s (Denbighshire, U.K.) device uses a mechanically based MEMS sensor in which a microcantilever is used to detect the change in viscosity as a small blood sample begins to coagulate.

Investigational studies have been performed at Debiotech SA (Lausanne, Switzerland) to look at the use of MEMS-based pumps to provide hydrostatic pressure for blood flow in capillaries (13). The time of flow for a fixed pressure head can be correlated to PT. The Debiotech SA device contains two primary components: a microcavity with a Ti/Pt microresistor for generating heat and a microchannel coated with reagents that activate the coagulation cascade. The microresistor heats, which causes thermal expansion of the air inside the microcavity. The resistor is switched off to allow the air to cool just as a blood sample is placed above the microfluidic channel. The cooling of the air inside the microcavity causes the blood sample to be drawn into the microchannel. The time elapsed before flow stops is a measure of PT.

The regulatory hurdles for the point-of-care systems described above are not insignificant. Medical diagnostic systems for chemical markers are typically large automated systems housed in a hospital or a commercial laboratory. Such laboratories are regulated by the Centers for Medicare & Medicaid Services (CMS) through the Clinical Laboratory Improvement Amendments (CLIA) (14). CLIA regulates approximately 200,000 laboratories throughout the United States that are highly integrated and perform many tests on a routine basis. The regulations provide a means for any given test to be waived from CLIA controls and inspections. Such waivers are granted for tests deemed to be simple and to have an insignificant risk of an erroneous result. The Food and Drug Administration (FDA) determines the criteria that any given test must meet to be considered simple and whether it has a low risk of error. The standards depend on the clinical consequence of an error. A false positive result, for example, may prompt a physician to prescribe a therapy with significant morbidity or side effects. The overall risk/benefit may not then be favorable. Although POCT tests may look simple from the user perspective, they must meet extremely high standards.

Expanding the repertoire of POCT targets beyond proteins is an important challenge for the future. For example, the miniaturization and automation of genetic phenotyping of pathogens is appearing on the clinical landscape. A recent study deployed benchtop automated polymerase chain reaction (PCR) machines in a multicenter trial in developing countries (15, 16). This study showed the effectiveness of an automated test for *Mycobacterium tuberculosis* (MTB) and resistance to rifampin (RIF). The system used was the Cepheid GeneXpert System (Sunnyvale, CA) (17),

which includes single-use cartridges for sample processing and integrated multicolor real-time PCR. The MTB/RIF test is performed directly on patient sputum in approximately two hours of hands-free operation. Although this system is certainly not a handheld device and test time is still long, it is a harbinger of things to come.

THE FUTURE OF POINT-OF-CARE TESTING

The next phase of POCT requires some significant shifts in the basic chemistry behind the devices. Sample preparation for existing approaches is too complex, and reaction/amplification times are too long. Detection methods, for example, depend on optical methods that require separation steps. These factors create more system complexity, particularly with respect to fluid handling.

A new paradigm may be the use of superparamagnetic particulate reagents with molecular targeting. Lowery (18) presents a comprehensive review of this approach, and Josephson (19) and Perez (20) provided early descriptions of what are now called magnetic relaxation switches (MRSw). Iron oxide nanoparticles are superparamagnetic and become magnetic under the application of an applied magnetic field. Water molecules in the neighborhood of each particle experience the local inhomogeneity of the magnetic field as they diffuse. These changes in field affect the rate at which proton spins on water relax after radio frequency pulses. Specifically, the transverse relaxation time (T_2) of a solution changes significantly in the presence of these particles. Interestingly, the state of agglomeration of the particles also affects the T_2. Thus, if particles in a solution are made to agglomerate, the T_2 of the suspension will change. A MRSw-based sensor is created by covalently bonding a molecular targeting ligand such as an antibody to the surface of such particles. The particles will then coagulate in the presence of multivalent analytes. Alternatively, mixtures of particles with different molecular targeting ligands will coagulate with an analyte that possesses epitopes for each of the ligands.

The MRSw process is illustrated in **Figure 4** and is not unlike classical agglutination assays. However, MRSw sensors are read magnetically rather than optically. This means that optically opaque samples can be used, which in principle simplifies sample preparation. In addition,

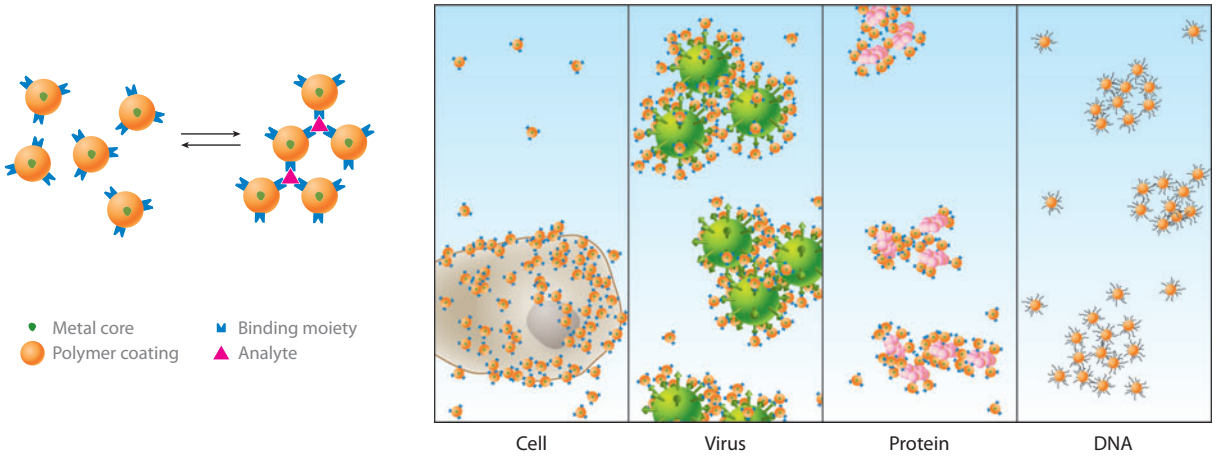

Figure 4

Microscopic behavior of magnetic relaxation switch particles in the presence of a target analyte [adapted from Lowery (18) and used with permission].

molecular targeting moieties are spread throughout the solution while bonded to these nanoparticles rather than attached to a surface, as for example in an ELISA. Thus, the diffusion distance for the analyte to react with the targeting ligand is of the order of the distance between particles in solution rather than the macroscopic dimension of the sample. That is, MRSw is a bulk reaction rather than a reaction at a surface and is in principle faster than the corresponding classical capture assay. This approach has been used to quantitate cellular, viral, protein, DNA, and even small molecule analytes with sensitivity in the femtomole range and is now being commercialized by T2 Biosystems, Inc. (Cambridge, MA) (21). The systems under construction are small benchtop devices with disposable cartridges that integrate an entire panel of tests for a given sample. The panel can consist of analytes from any of the classes shown in **Figure 4**, as the same basic detection scheme is used for each. This is unlike any other molecular diagnostic assay; the basic chemistry and detection method varies with the analyte class. Additionally, the basic hardware for MRSw detection has been demonstrated in miniature (22).

PATIENT MONITORING

Microsensors and transducers have long been used in medicine, for example during diagnostic and surgical procedures. Many of these measurements are minimally invasive and have low morbidity rates. This area is huge, so we will touch on just two cases as examples. One is intravascular ultrasound in coronary arteries for arteriosclerotic disease. This high frequency ultrasound technique is based on micropiezo transducers and produces microscanned images (23) from the tissue surrounding a catheter. Another example is static pressure measurements on the end of a catheter such as in intra-aortic balloon pumping (IABP) therapy. Real-time monitoring is required during IABP of the dicrotic notch on the arterial waveform, also known as the onset of ventricular diastole, when aortic pressure transiently increases and the aortic valve has closed. This graphic change in aortic pressure is indicative of the aortic valve's operation and needs to be detected with adequate resolution so that the aortic balloon will inflate at the proper time in the cardiac cycle (24). A fiber-optic pressure transducer such as that from FISO Technologies, Inc. (Quebec City, QC) has been used. This sensor has a resolution of 0.3 mm Hg and is small enough (outer diameter = 550 μm) to be attached to the distal end of an IAB catheter (25). The Fabry-Perot interferometer-based sensor is integral to the fiber-optic catheter. FISO Technologies has not disclosed the manufacturing method, but analogous sensors have been described elsewhere (26). These micro-optical mechanical system–based devices are unaffected by radiofrequencies and electromagnetic waves and do not interfere with other clinical instrumentation, which is a major consideration with all medical devices.

Ambulatory systems for continuous monitoring are becoming increasingly important in clinical settings and are the focus of this section. The longest history is probably in cardiology, where implanted devices for actuation and data logging have been in use for many years. Cardioverter defibrillators (CDs) and pacemakers for treating cardiovascular diseases, in particular tachyarrhythmia, sudden cardiac arrest, and bradyarrhythmia, are the most important examples. Microsystem technology has enabled these devices to become more accurate, effective, and long lasting (in terms of battery life). For example, Medtronic's Secura™ DR is an implantable CD that can both monitor and regulate a patient's heart rate by providing single- or dual-chamber rate-responsive pacing, defibrillation, or cardioversion for at least 7 years (27). Secura can communicate with several external devices to relay data and receive programming.

Until recently, cardiac monitors solely for diagnostics have been wearable devices such as Holter monitors. These multielectrode devices are somewhat cumbersome but offer continuous recording of electrocardiograms (ECGs), which can identify transient cardiac arrhythmias. Microsystem

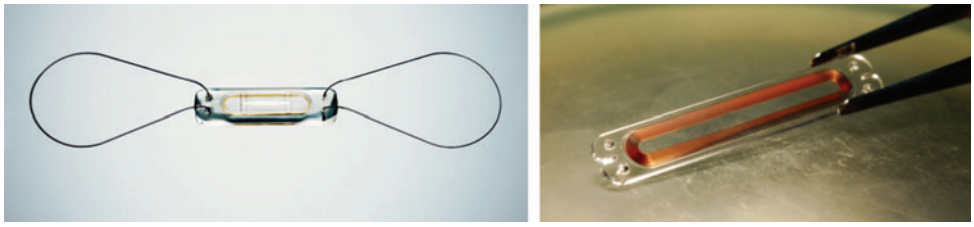

Figure 5

Images of the CardioMEMS EndoSure™ implantable pressure sensor. The sensor can be placed in position by a PTFE (polytetrafluoroethylene)-coated NITINOL (Nickel Titanium Naval Ordinance Laboratory) super elastic wire. From Reference 69.

engineering has reduced the size of these devices so that they now can be fully implanted for longer term monitoring. Leadless small ECG recording devices developed by Medtronic, Inc. (Minneapolis, MN) and St. Jude Medical (St. Paul, MN) are known as Reveal® and Confirm®, respectively. Each device is approximately 60 mm (length) × 19 mm (width) × 8 mm (thickness), which allows it to be implanted subcutaneously. The devices do not require leads, which further reduces the invasiveness of the procedure compared with other implantable cardiac devices as well as decreases patient recovery time. The cardiac monitors are also programmable with the aid of an external, handheld communication device and can store data up to 240 s prior to and 60 s after the onset of a cardiac-related episode (27, 28). Evidence of the clinical benefit of such devices is a matter of current study (29, 30).

Autonomous cardiac pressure sensors are emerging for clinical applications. MEMS pressure sensors of various types have long been studied (31). In addition to the interferometer technology mentioned above, capacitive devices have been developed that have particular advantages in cases in which the sensor is implanted and connected wirelessly. CardioMEMS Inc. (Atlanta, GA) has developed such a device. The EndoSure™ wireless pressure measurement system (**Figure 5**) was originally indicated for measuring intrasac pressure during endovascular abdominal aortic aneurysm (AAA) and endovascular thoracic aortic aneurysm (TAA) repair (32). The paper clip–sized device is 15 mm × 30 mm and is interrogated by an external radiofrequency reader. Inductive coupling provides sensor power. A key feature of this sensor is that its small size permits it to be inserted during AAA or TAA repair and left indefinitely in the aneurysm sac for continuous monitoring. The features that no additional procedures are required and that the device fits seamlessly into an existing procedure will probably characterize all rapidly adopted microsystem technologies in medicine.

The engineering of such capacitive sensors is relatively simple. The simplified electrical circuit description for these sensors is that of an LC (inductor-capacitor) circuit. The capacitive element is a sealed microcavity within fused silica with two metal films for electrodes. The cavity is small, and therefore the electrodes are in close proximity. Small deflections of the electrodes due to ambient stress change the resonant frequency of the LC circuit. Coupling an external antenna to the coil inductor of the device permits interrogation of the sensor. The resonant frequency of the device changes the frequency spectrum of the transmitted signal, from which the resonant frequency and bandwidth of the sensor can be determined. Medical-grade silicone encapsulates the entire device.

The CardioMEMS device also has been explored for use in the ventricles of the brain to monitor intracranial pressure (ICP) and cerebrospinal fluid (CSF) flow in patients with hydrocephalus. Current ICP monitoring uses intraventricular catheter-based systems, which restrict the patient

to hospital settings and are accompanied by risks, patient discomfort, and expense (33). Theon Sensors (Athens, Greece) has developed a wireless, implantable MEMS device for measuring ICP in patients with brain disorders and trauma. Operating at an industrial-scientific-medical (ISM) frequency (2.4 GHz), the novel device is intended to be a less invasive means of continuously and accurately monitoring ICP. The device is a battery-powered, MEMS capacitive element coupled to an antenna in a 10-mm diameter metallic cylinder. It is implanted in the subarachnoid space, just below the dura mater, so that the capacitive pressure sensor can measure changes in ICP (33). Continuous monitoring of ICP could lead to closed loop control of microvalves integrated with shunts for hydrocephalus (34).

Integrated Sensing Systems (ISSYS), Inc. (Ypsilanti, MI) has also developed a batteryless, radio frequency (RF) device that uses a capacitive pressure sensor implanted via a minimally invasive outpatient procedure (35). It provides a resolution of less than 1 mm Hg and has a communication/powering distance of 3–4 cm, but it has not yet been approved for use in humans. Campus Micro Technologies GmbH (Bremen, Germany) has developed an implantable device, similar to CardioMEMS's EndoSure, that is targeted at monitoring aneurysm repair (35). Like the ISSYS device, it can achieve a resolution of less than 1 mm Hg, using an array of 16 capacitive pressure sensors (75 μm × 75 μm) and a reference array, but has a transmission distance of a mere 5 mm. A final example is Remon Medical Technology's (Natick, MA) ImPressure®, which has dimensions 9 mm × 3 mm × 1.5 mm and is similar in purpose to EndoSure and Campus Micro Technologies' device. Its technology differs, however, as it utilizes acoustic waves to transmit power and data, which is purported to be very efficient through surrounding tissue. It does not require an antenna, which makes it more compact, and it performs just as well as catheter-based sensors. Despite its clinical success, technical specifications pertaining to the device are scarce (35).

A major milestone for these technologies may have been achieved in the spring of 2010 when the first clinical reports for monitoring CHF patients were announced (36). The prevalence of CHF in the United States was recently estimated to be 5.7 million with more than 670,000 new cases annually, more than a million hospital discharges, an annual health burden more than $37.2 billion, and a mortality of 300,000 per year (37). The increased pulmonary arterial pressure that occurs as the heart fails is a primary source of morbidity in these patients. Despite the common use of diuretics to control the pulmonary edema as well as antihypertensives, the disease remains difficult to manage. Appropriate dosing varies with diet, exercise, and advancement of the disease. Thus, CHF patients are frequently hospitalized during periods of crisis. The CHAMPION multicenter trial enrolled 550 NYHA (New York Heart Association) Class III heart failure patients, who received a permanent CardioMEMS sensor implanted in a pulmonary artery. The control group received the standard of care for CHF, whereas the treatment group received care based on measurements by the implanted sensor. The reduction in the risk of a heart failure–related hospitalization at 6 months was 30%. The impact on hospitalizations continued to increase over time, reaching 38% at one year, which was the full duration of the trial. No device failures or morbidity associated with the device were reported. The results of a single trial must always be treated with caution, but if borne out, this is a wonderful example of the impact of medical monitoring in chronic disease management.

Finally, a noncardiac application of MEMS pressure sensors is measurement of intraocular pressure (IOP). The Triggerfish® by Sensimed AG (Lausanne, Switzerland) (**Figure 6**) is undergoing tests for use in measuring IOP during the diagnosis and treatment of glaucoma (38, 39). Current measurements of IOP provide only a snapshot obtained during a visit with a physician. IOP can, however, fluctuate throughout the day in glaucoma patients. The Triggerfish offers continuous, noninvasive IOP monitoring (40). The disposable contact lens-like device is made of

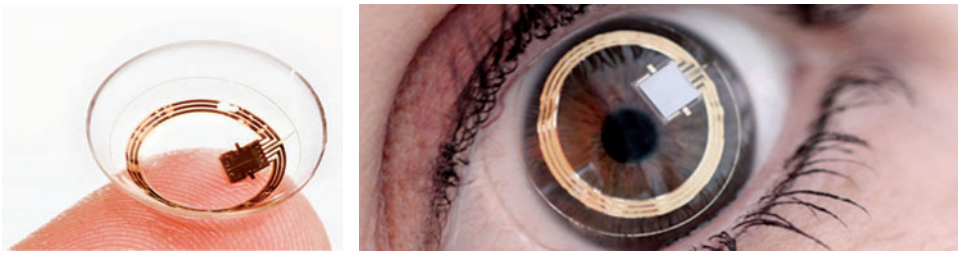

Figure 6

Microelectromechanical system–based pressure sensor for measurement of intraocular pressure. Photos from Reference 39.

hydrophilic silicone and incorporates MEMS strain gauge sensors (platinum-titanium film), a gold film loop antenna, and an ASIC (application-specific integrated circuit) chip thinned to 50 μm. The system exploits the familiar inductive power concept (39, 40). The strain gauge is used to measure changes in corneal curvature caused by changes in IOP (40). Added radial strain gauges are used to compensate for changes in temperature.

SYSTEMIC DRUG DELIVERY

Drug delivery systems that make use of MEMS technology were recently reviewed elsewhere (41, 42). The discussion below focuses on the microsystems aspects of technologies for systemic and local drug delivery that are experiencing an increased clinical impact. This is particularly true for parenteral drug delivery applications in which the drug half-life is short or the dosing regimen requires frequent administration. Ambulatory delivery systems based on small belt-worn pumps have been available for quite some time; the most extensive use has been for delivery of insulin. All of these use some form of miniature syringe pump driven by an electrical actuator. Example pumps include Minimed's Reveal™ (Northridge, CA), Animas's One Touch® Ping™ (West Chester, PA), and Smiths Medical's Cosmo® (St. Paul, MN). These precision instruments deliver drug through a disposable needle-cannula and tubing set, which is worn for several days at a time. Some units now provide a wireless interface between a handheld glucose meter and a microprocessor on board the pump that can provide recommendations to the user about dosing. The main deficiencies of these systems are size, cost, complexity, and the tubing between the pump and the insertion site. Manufacturers have been improving the size by employing microelectronic integration and miniaturization. Complexity has been reduced by employing sophisticated software and electronic alarms to help guide patient decisions about dosing. The typical thickness of the pump unit today is 20 mm, and the footprint is 80 mm × 50 mm, yielding a total volume and weight of approximately 90 ml and 100 g, respectively. The pumps are durable medical goods and are expected to last five years or more, but the up-front set-up cost is approximately $5,000. Kinking of the tubing from the pump to the needle-cannula set is the source of many problems for the user. This occurs because of relative motion between the pump and the insertion site and may not be obvious, as it can occur just below the skin surface.

"Patch pump" systems have appeared on the market in an attempt to leapfrog belt-worn pumps. These systems integrate the pump with the needle-cannula and remove the need for a separate tube. Designers of these systems intend them to be small enough that they are perceived as a transdermal device. They adhere to the skin with pressure-sensitive adhesive in much the same way as a transdermal drug delivery patch. Significant portions of the system are intended to be

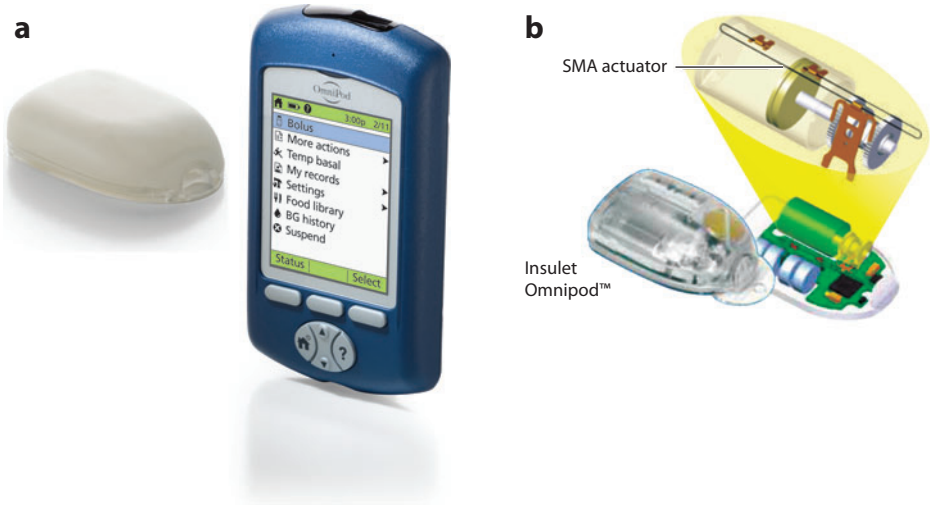

Figure 7

(*a*) OmniPod™ by Insulet, Inc. (Bedford, MA) (43). (*b*) Shape-memory activation (SMA) actuator mechanism of the OmniPod™ from the Autosplice, Inc. (San Diego, CA) product catalog (44).

disposable. Insulin is a potentially toxic drug, so although disposable systems must be low-cost, they must also meet high requirements for reliability and precision. Two approved patch pump systems are commercially available: the Medingo (Yoqneam Illit, Israel) Solo™ and Insulet's (Bedford, MA) OmniPod™ (43). Both systems communicate wirelessly with a handheld controller that has a user interface appropriate for diabetic patients. The Solo™ takes a click-together approach with an insulin unit that is frequently replaced and a pump portion intended to last several months. The OmniPod's™ pump (see **Figure 7**) is fully integrated (with the exception of a handheld controller) and is intended to be disposed of after approximately 200 units (approximately 1.5 ml) of insulin are consumed. This may be three days for a typical type-1 diabetic patient. These pumps are significantly smaller than their belt-worn predecessors. The OmniPod™ has a footprint of 41 mm × 61 mm and thickness of 18 mm. Its volume and mass are 30 ml and 34 g, respectively. The Solo™ is still smaller, with dimensions 35 mm × 54 mm × 8 mm, volume 12 ml, and mass 24 g.

The details of the OmniPod™ are illustrative of the level of technology employed by these devices. The user fills the reservoir with insulin and places the pump on the skin. A command is sent via the handheld controller to the pump to actuate the needle-cannula. A steel needle is inserted automatically into the subcutaneous space (approximately 6 mm depth) over 5 ms and immediately retracts. The needle inserts a soft polymer cannula into the skin. The cannula is left behind to deliver insulin over the subsequent days. Four coin cell batteries are used to power communication, logic circuits, and pump. The pump is essentially a disposable version of the syringe pumps found on its belt-worn predecessors.

The OmniPod™ pump is a lead screw–driven syringe, but the actuator that drives it demonstrates some interesting technology (44). In particular, a shape-memory actuator (SMA) powers the drive. Some NITINOL alloys can exhibit the shape memory effect owing to a martensitic phase transformation. A wire of this alloy will undergo an approximately 4% decrease in length as it is heated as well as a phase transformation to the high-temperature austenite phase. The two-way shape memory effect is attributed to small amounts of martensite persisting at higher

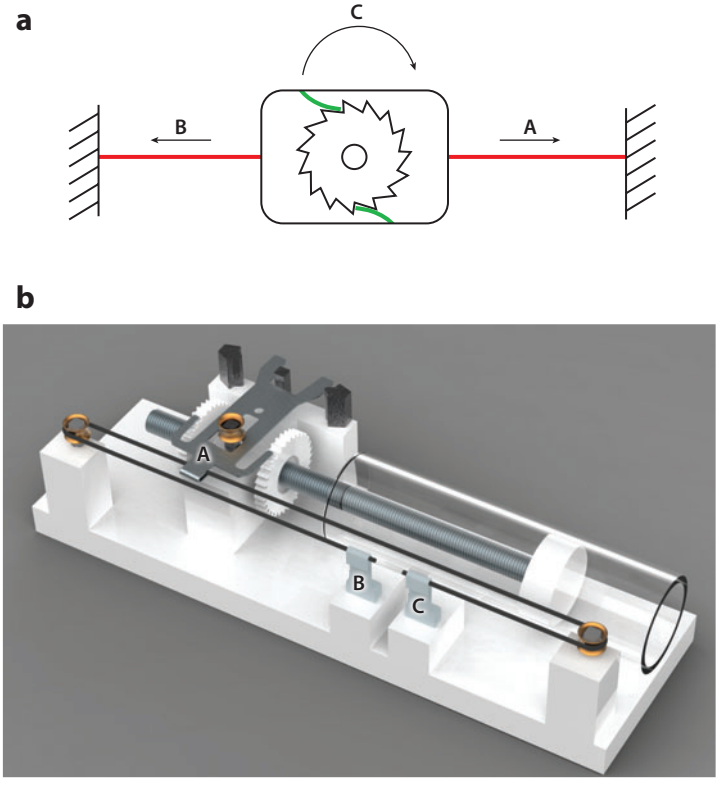

Figure 8

(*a*) Schematic of the shape-memory actuator (SMA) used to drive the lead screw in the OmniPod™ (47). Two SMAs are shown in red. Each is attached to a cage surrounding a small gear at the end of the lead screw. The gear is engaged by two pawls (*green*). A current pulse on the right contracts the right SMA and moves the cage to the right. This is immediately followed by a pulse on the left SMA, which pulls the cage back. The action of the pawls leads to a ratcheting action with the gear. The result is rotational motion C. The linear motion of the SMAs is thus converted to the rotational motion required to drive the lead screw. (*b*) The author's rendering of the actuator mechanism within the OmniPod™. Alternating current pulses are applied between points A and B and between points A and C. The metal piece at A will toggle back and forth, alternately engaging and locking the two gears shown in the figure.

temperatures owing to stress inhomogeneities within the material. Thus, as the wire cools, this small amount of martensite nucleates the low-temperature phase and causes the wire to lengthen. The alloy composition determines the transformation temperature, which is typically between 70°C and 90°C. These materials have been used for other thin film–based micropumps (45, 46). Loads carried by SMA wires will vary with diameter, but a 150-μm wire has a maximum load of 330 g and requires approximately 400 mA current to heat it through the transition temperature and several seconds to cool back down. The maximum load increases quadratically with diameter, as does the required current, which fixes a limit for autonomously powered devices.

Some details of the approach taken in the OmniPod™ actuator are described in U.S. Patent 6,656,158 (47). A simplified schematic of the device's working principle is shown in **Figure 8**. The sequenced actuation of two SMAs is converted to stepped rotational motion required to turn a lead screw. The syringe piston can, therefore, be incremented precisely by the application of current pulses to the SMAs.

Another bioMEMS device that is intended to deliver insulin is Debiotech S.A.'s (Lausanne, Switzerland) Insulin Nanopump™. Its 65 mm (length) × 38 mm (width) × 11 mm (thickness) shell encapsulates a piezoelectric actuated micropump (46) that can achieve flow rates of 2 ml h^{-1} and a stroke volume of 160 nL with ±5% accuracy (48, 49).

Many parenteral drug therapies (therapies where drugs are administered in a way other than oral) could benefit from the use of such patch pumps, and they will undoubtedly be used for drugs other than insulin. Drugs with short half-lives or with side effects caused by bolus delivery are likely first candidates. Drug stability, total delivery volume, and subcutaneous delivery ability are obvious limitations that a given therapy will place on a wearable patch pump approach. Nonetheless, the opportunity to move parenteral drug delivery from a clinical setting to the home may enable new therapies and better outcomes. The perceived importance of patch pumps to future drug therapies is exemplified by the fact that more than 15 companies currently have active development programs. The pump mechanisms range from miniaturized syringe pumps to peristaltic pumps to more novel approaches including gas generation, piezoelectrics, electroosmosis, and shape-changing electrochemical systems.

SYSTEMIC DRUG DELIVERY USING FULLY INTEGRATED MICROSYSTEMS

The most sophisticated level of microsystem integration with drug delivery devices was perhaps reached with IONSYS™, as shown in **Figure 9**. This product delivers the narcotic fentanyl on demand via iontophoresis. Drug delivery by iontophoresis exploits the characteristic ionic charge of some drugs at physiologic pH. Such charged molecules do not partition significantly into the lipophilic stratum corneum but can be driven across by the passage of current. Delivery of drug through the skin can thus be modulated simply by controlling the current. Fentanyl is also quite potent, requiring only tens of micrograms for a physiologic effect.

Pain management in a postsurgical setting is most frequently performed by bolus injection of narcotic. Patients expected to experience prolonged pain are offered patient-controlled analgesia (PCA), a patient-actuated infusion pump connected to an intravenous line. The pump has software in which the actuation is locked out from patient control for set periods of time. This way, total opioid dose can be limited to a range thought to be effective without risking complications such as respiratory depression. There is evidence that PCA provides improved pain management, lower

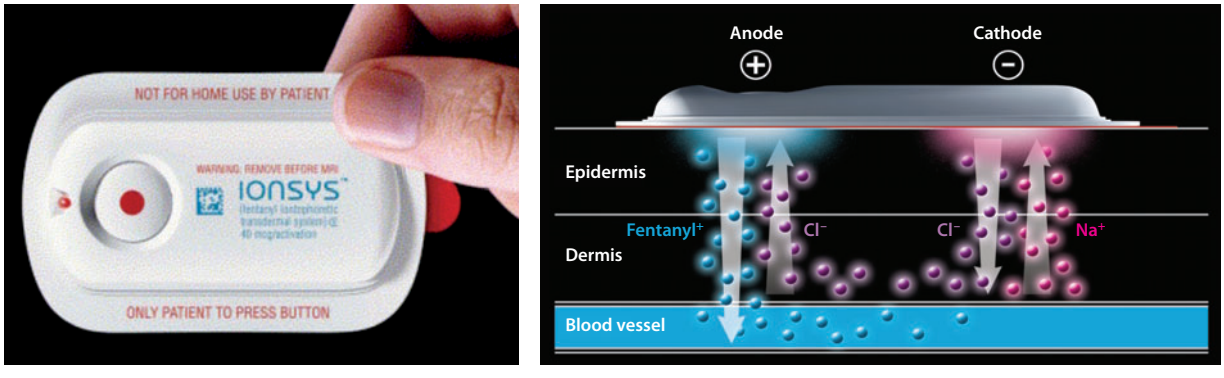

Figure 9

IONSYS™ iontophoretic system for delivery of fentanyl.

total opioid use, and less sedation over bolus injection (50). Administration of PCA is, however, associated with a comparatively high medical error rate, and given that morphine is a toxic drug, the consequences of such errors are not trivial (51). Most errors involved either the wrong dosage or the wrong drug caused by human factors or equipment, and 6.5% of these errors resulted in patient harm. In comparison, 1.5% of general medical errors result in patient harm.

The IONSYS™ system was developed to simplify the administration of PCA and reduce the occurrence of medical errors. It weighs only 15 g, and the exterior surface is composed of a soft polymer package with dimensions of 84 mm × 51 mm × 8 mm. Two hydrogel electrodes provide electrical contact with skin. The device is held in place with pressure-sensitive adhesive. Only the anode contains drug, and passage of current dispenses a 40-μg dose over 10 min. Software provided by an embedded ASIC actuates the dose only when the patient presses the surface button twice within 3 s. An audible tone and a red light-emitting diode indicate application of current. The logic permits a maximum of only six 40-μg doses per hour. Each IONSYS™ system operates for 24 hours or until 80 doses have been administered, whichever occurs first. Power is provided by a coin cell battery packaged with the device, and all electronics are integrated upon a PCB. The device is separated when finished into a bottom drug-contaminated portion and a top electronic portion, each of which is disposed of according to local regulations. IONSYS™ is probably the best example of a drug dosage device with a level of integration that rivals dedicated medical instruments such as PCA devices.

IONSYS™ was approved in Europe and launched in 2008. It was voluntarily withdrawn shortly thereafter when a small number of devices were found to experience corrosion in selected areas of the PCB. Apparently, the copackaging of electronics components with the aqueous hydrogel led to the possibility of chemical attack. Incline Therapeutics (Redwood City, CA) is now developing a redesigned system to prevent this failure mode.

MICRONEEDLES

Quite a large body of literature concerns microfabricated needles to enhance skin permeation. These can be individual fine needles such as BD's (Franklin Lakes, NJ) Soluvia™ microinjection system, which operates in the same way as a hypodermic syringe, except it uses a 1.5-mm length needle and dispenses a 0.1-ml volume (see for example, Intanza® or IDflu® vaccines). Penetration of the microinjection system is said by BD to be barely perceived by patients and the first reliable intradermal injection system (52). Intradermal tissue has a relatively high concentration of immune cells. Introduction of antigens into this tissue yields a high antibody titer for vaccines.

Microneedles can also be prepared in an array format; these are typically pressed against the skin to perforate the stratum corneum but not so deep that they elicit a sensation of pain (42, 53, 54). The enhancement of drug delivery rates when using microneedle arrays can be dramatic. The difficulties of formulating drugs to either adhere to the surface of the needles or to incorporate a liquid formulation to work with the microneedle array are among the many challenges that face this technology for any given application. The leader in this field is Zosano Pharma™, Inc. (Fremont, CA) (55), which is in Phase II trials with a parathyroid hormone (PTH)–coated microneedle array patch. The microgram dosage of PTH required for treatment of osteoporosis makes it an ideal candidate for this technology. An important requirement, however, is that the pharmacokinetics of PTH closely match that of the daily subcutaneous injection to achieve effectiveness.

The systems-level complexity of such microneedle devices has not been described in the literature, most of which covers how to reproducibly apply such devices to the skin. Microneedles and microneedle arrays are essentially mechanical devices with small penetration depths that the patient must engage with the skin in a reproducible way. Thus, they typically require auxiliary

Figure 10

Zosano patch applicator system (55).

devices. Zosano, for example, provides an applicator, as shown in **Figure 10**. The patch is applied to the skin with the applicator, which controls the applied force.

An alternative technology to microneedles is thermal ablation, which involves the controlled removal or creation of micropores in the stratum corneum by localized heating on a millisecond timescale. Similar to microneedles, it is painless, enhances transdermal drug delivery, and offers the same previously discussed benefits. One industry example is the PassPort™ developed by Altea Therapeutics Corporation (Atlanta, GA). The patch-like device consists of an array of 80-μm diameter tungsten wires (72–75 wires cm^{-2}), which are quickly heated with a brief surge of electric current (42). The PassPort can deliver both lipid-soluble and water-soluble drugs as well as drugs with a molecular weight greater than 500, an improvement over passive transdermal drug delivery devices (56). Another device that incorporates thermal ablation is ViaDerm™, developed by TransPharma Medical Ltd. (Lod, Israel). It consists of an electronic, handheld control unit, a disposable array of microelectrodes, and a drug patch. The 1 cm^2 microelectrode array (200 microelectrodes cm^{-2}) consists of microchannels 100-μm deep. This array is first attached to the control unit, which is then applied with light pressure to the desired application site to activate the thermal ablation process. Once the microchannels have been created, the drug patch is applied over the ablated area, where drug can more easily diffuse through the skin (42, 57). The size and number of channels influence the drug delivery rate.

SINGLE COMPARTMENT DRUG DELIVERY

Drug delivery to a single physiologic compartment or tissue rather than systemic delivery has emerged as a new opportunity for microsystems and devices made by microfabrication techniques.

Figure 11

CYPHER® drug-eluting stent by Cordis Corp. (Bridgewater, NJ). Drug coating reduces the rate of restenosis.

These devices make use of existing medical procedures to deploy them in a region of the body where delivery of a drug can affect the course of disease.

The most obvious example is that of drug-eluting stents (DESs). Restenosis of cardiac arteries following stent placement occurred at a high rate prior to the introduction of DES. Restenosis is the proliferation of smooth muscle cells in response to injury, which can begin to occlude the artery at the location of the stent. Reintervention procedures were required in as many as 10–20% of cases at nine months depending on the bare metal stent (58). Coating the stent with a thin drug-containing polymer film reduced the restenosis rate to low single digits. Drugs such as sirolimus or pactitaxel arrest the cell division cycle of the cells in the vicinity of the stent. One DES is CYPHER® by Cordis Corp. (Bridgewater, NJ) (**Figure 11**). The underlying metal stent is laser machined from a tube of 316L stainless steel. Most of the tube is machined away to leave the web-like structure of struts of 140 μm cross-section dimension. A film of elastomeric polymer matrix and drug is coated on the stent prior to assembly on the deploying balloon (59). Adoption of DES was rapid primarily for two reasons. First, there was a significant medical need because of the morbidity associated with bare metal stents. Second, virtually no change in the medical procedure used in stent placement was needed.

An additional example of local drug delivery is the drug-eluting punctal plug, a small medical device that can be inserted into the punctum of the eye to prevent drainage of tear fluid as a treatment for dry eye. These devices are tiny, typically are made from an elastomer such as silicone, and include very small features that retain the plug in the punctum. Patients tolerate the presence of these devices well. Several trials are under way to use the punctal plug as a delivery device for drug therapies of the eye. QLT, Inc., for example, loads a solid form of latanoprost into the inner reservoir of the plug (**Figure 12**). Slow elution of the drug into the tear fluid can potentially treat glaucoma. A second company has completed a trial for the same indication using the drug bimatoprost (60). These products again make use of a simple existing procedure to deploy the therapy.

A final example is drug therapies for the bladder. Several pathologies associated with the bladder, such as overactive bladder (OAB), interstitial cystitis/painful bladder syndrome (IC/PBS), and bladder cancer, have a significant impact on society. IC/PBS is a chronic urological condition

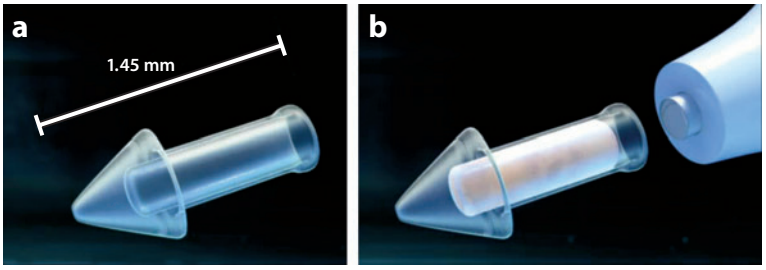

Figure 12

(*a*) Punctal plug and (*b*) device with drug-containing reservoir and applicator from QLT, Inc. (Vancouver, BC; **http://www.qltinc.com/index.htm**) delivers drug into tear fluid.

characterized by pain, urinary frequency, and urgency with or without urinary incontinence; a recent study indicates that the prevalence of IC/PBS symptoms exceeds one million people in the United States (61). The American Cancer Society estimated that 70,530 men and women will be diagnosed with and 14,680 will die of cancer of the urinary bladder in 2010, but the prevalence exceeds half a million, as it has an extremely high recurrence rate (62). The majority of these bladder cancer cases is early stage and treated by surgical removal of the lesion followed by drug therapy. The standard of care for early stage bladder cancer is intravesical drug therapy in which the drug is deployed by catheter directly to the bladder. Exposure to the drug is limited to the time before voiding. A similar approach is taken with IC/PBS patients in which lidocaine solutions are instilled into the bladder. Lidocaine has only a 90 min half-life, so the duration of action is quite limited. Thus, many catheterizations are required, and some patients are trained to instill solutions at home.

Among the most common urological procedures are catheterization and cystoscopy. Heejin Lee (63) while at MIT was and now Taris Biomedical Inc. (Lexington, MA) (64) is developing a drug delivery system for the bladder that exploits these simple procedures (**Figure 13**). The device is a dual-lumen silicon tube with one lumen that contains drug and another that contains a NITINOL superelastic wire that has been heat treated to form a retentive shape that will keep the device in the bladder. Drug release is controlled by the water permeability of the medical grade silicone and the presence of a laser-machined orifice. This nonresorbable device is unfolded into a

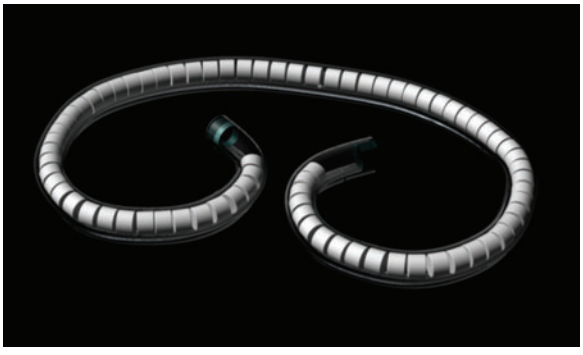

Figure 13

Device for drug delivery to the bladder from Taris Biomedical, Inc. (64).

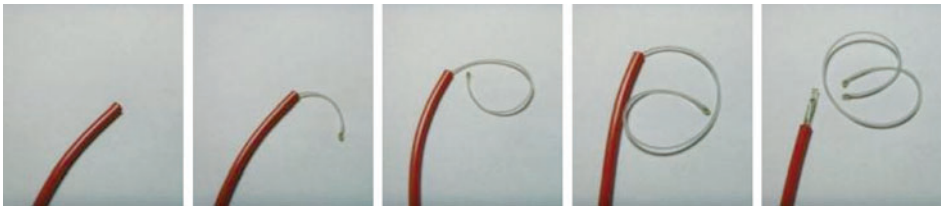

Figure 14

Deployment of bladder drug delivery device via catheter (63).

catheter for deployment (**Figure 14**) and releases drugs for several weeks. Removal is accomplished by cystoscopy. One clinical trial to assess device tolerability has been completed, and a Phase I study has begun (65, 66).

SURGICAL TOOLS

The advancement of technologies such as robotic surgery into the clinic is propelling a new wave of microsystem developments. Robotic surgery as practiced today is more correctly described as telemanipulator or master-slave actuation systems. These systems scale, filter, and translate the motion of a surgeon's hands to the surgical site by robotic manipulators that control endoscopic tools. The da Vinci Surgical System by Intuitive Surgical (Sunnyvale, CA), for example, consists of four robotic arms: one to manipulate a high-resolution endoscope and three to control precision endoscopic instruments that fully articulate. The surgeon operates the instruments remotely while viewing a magnified 3D enhanced image of the surgical field. There are as yet no haptics (sensory feedback), but one can imagine such addition as a future development. The penetration of this technology into the clinical setting has been remarkable; more than 800 hospitals in the United States and Europe now have these instruments. Retrospective studies have shown improved outcomes for specific procedures employing such tools using metrics such as adverse events, blood loss, and many others.

The power of robot-assisted endoscopic instruments has created an opportunity for endoscopic end effectors of greater capability. This requires, however, greater precision and complexity of fabrication. Microfabrica, Inc. (Van Nuys, CA) produces surgical microtools and other microdevices through a micromanufacturing process called MICA FREEFORM™ (67). This process is an additive, solid-free form fabrication technology based on metal plating. The final device is designed on computer-aided design software. That information drives an automated system that plates regions of final metal and resist over a surface in a layer-by-layer manner. The resist material is removed in a final processing step. Complete articulating structures (**Figure 15**) can be built directly with no assembly required with feature sizes as small as 4 μm and tolerances of 2 μm. Indeed, designs are possible for assembled structures that cannot be built any other way because of the topology of the components. Many assemblies can be made, as the manufacturing process permits the layering of many parts to be built at the same time. A recent example is a tissue removal instrument or microdebrider called the MicroShredder, which is intended to remove unwanted tissue caused by a congenital heart condition called tetralogy of Fallot. The 4.5 mm (length) × 2.5 mm (width) × 0.8 mm (thickness), Ni-Co alloy device is attached to a steerable needle, on which a proximal drive shaft connects to a pair of gear trains that drive two sets of cutting blades at its distal end. A channel between the two blades permits the flow of tissue debris as the cutting blades counterrotate (68).

Figure 15

Microsurgical tools produced by the MICA FREEFORM™ process: (*a*) scissors/graspers (1.2-mm wide), (*b*) 2-French forceps, and (*c*) hydraulically operated forceps. All of these devices are produced directly without assembly. Images are from Microfabrica, Inc. (Van Nuys, CA).

CONCLUSION

This review has focused on clinical or commercial stage microsystems applied to medicine. The impact of these systems is widespread and includes diagnostics, therapeutics, and surgical tools. Microsystems are also changing the image of medical technology, which for the general public is the expensive MRI or CT scanner. These technologies for medicine of the future will just as often be disposable as they are durable hardware. They will be in general practitioners' offices, in our homes, or embedded in our cell phones. Microsystems will make many sophisticated tests, diagnostic procedures, and interventional procedures possible in much less costly settings.

Microsystems will have a positive impact on the health care burden in the United States. The examples mentioned here concern conditions such as diabetes, cardiovascular disease, urological disorders, and cancer. The overall health care burden from these diseases is staggering. Better ways to manage these often chronic conditions must be a priority for a future in which we all can afford good health. Interestingly, the move to microsystem-enabled health care may not only make the cost of good health less in the United States, but it might also permit the distribution of advanced health concepts to the developing world. The same handheld molecular diagnostic instrument used in a community health center in Maine can be used in a clinic in Nairobi, Kenya.

Study of microsystems that are rapidly adopted reveals that they have several important attributes. First, they are focused on important medical needs. There is no reason to test a new technology if current practice already does almost as well. Second, any procedure associated with the product needs to exist already and be practiced often. Ideally, the physician will look at the microsystem product and know exactly what to do with it. Thus, the microsystem concept will have an advantage if deployment can use an existing procedure but the microsystem can improve outcomes, reduce morbidity, or be applied to a completely new indication.

DISCLOSURE STATEMENT

The author is a founder of Taris Biomedical, Inc., and T2 Biosystems, Inc.

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