MICROELECTROMECHANICAL SYSTEMS IN UROLOGY

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Since the mid-1980s, minimally invasive surgery has evolved with the creation of such devices as 3-mm instruments and miniature probes for percutaneous therapies. However, one must ask, "When does it end? How small is too small?" This fundamental question is the foundation of microelectromechanical systems or MEMS technology. Although images of the 1966 film *Fantastic Voyage,* in which a group of humans are miniaturized and travel within the vascular system of a human, may come to mind, MEMS technology is in no way science fiction. Rather, it is the integration of decades of knowledge from many fields that allows us to interact with the physical world at a level once thought to be impossible.

MEMS technology is based on techniques used in the semiconductor fabrication industry and has generated significant enthusiasm among physicians and surgeons in recent years. At their most basic levels, MEMS are devices with dimensions of micrometers to a few millimeters that combine electrical and mechanical components to acquire data or do work. An exhaustive review of the biomedical applications of MEMS is beyond the scope of this review. Rather, its purpose is to introduce the urologist to this exciting technology and present the existing and future ways in which this technology will aid the clinician.

HISTORICAL BACKGROUND

MEMS originated in the microelectronics industry of the 1950s. MEMS began with the introduction of silicon into the fabrication of microelectronics.[1] Silicon's piezoresistivity, a measurement of the change in electrical resistance when exposed to mechanical strain or stress, was found to be high. Because of this unique characteristic, accurate microsensors and strain gauges could be constructed using silicon.[2] However, it was discovered that the epoxy bonds, which connected the metal diaphragms to the silicon sensor housings, degraded with time, leading to measurement error.[3]

By the early 1970s, researchers used silicon diaphragms to fabricate sensitive and resilient piezoresistive pressure sensors.[4] The development of chemical etching techniques made the fabrication of these small devices possible.[4,5] Chemical etching is a process of selectively subtracting layers of a substrate by dissolving them with chemical compounds such as potassium hydroxide. This subtraction of substrate allows the construction of holes, pits, and beams that can interact to create three-dimensional structures (Fig. 1). In 1973, batch-fabrication techniques, the production of thousands of devices from a single silicon wafer, were applied to the manufacturing of piezoresistive pressure sensors.[1] The integration of these techniques reduced the price of individual devices to below that of their macroscopic counterparts. For example, batch fabrication allows the advanced computer processors of today to be more powerful and less expensive than those available 20 years ago.

In 1987, a pivotal advance in the history of MEMS occurred with the development of movable joints that could interact in three dimensions.[6,7] This breakthrough permitted the integration of multiple components to make micromotors and microactuators (devices that convert energy, usually electrical or chemical, into mechanical action).[1] The commercialization of these devices led to the MEMS revolution of the 1990s.

With the advances in computer software technology in the 1990s, construction of formerly theoretical MEMS devices became reality. The 1990s were characterized by an increase in device complexity and the widespread application of MEMS devices in many commercial fields. Microactuators allowed MEMS devices to manipulate their microenvironments as opposed to only gathering data. The first electrostatic micromotor was produced in 1989 and had a diameter of 60 to 120 μm.[8,9] Similarly, microaccelerometers, devices that detect

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Submitted: December 19, 2002, accepted: January 13, 2003

UROLOGY 61: 883–887, 2003 • 0090-4295/03/$30.00
doi:10.1016/S0090-4295(03)00032-3

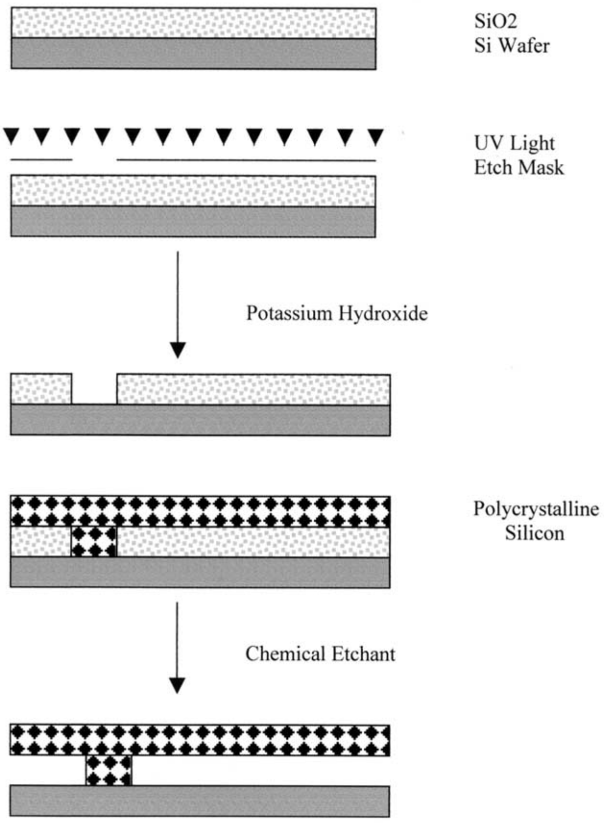

FIGURE 1. *Surface micromachining of free-standing beam. A layer of silicon dioxide (SiO_2) is grown on the silicon wafer and covered by a thin film (etch mask). A pattern in the etch mask allows areas of the SiO_2 to be exposed to ultraviolet light, making only those areas soluble. The soluble areas of SiO_2 are dissolved (etched) by a solvent (potassium hydroxide), and a pit is formed. Insoluble polycrystalline silicon is placed over the SiO_2 and fills the pit. The remaining SiO_2 is dissolved with a strong solvent, and a three-dimensional free-standing beam is fabricated.*

changes in the acceleration of an inertial mass and convert this mechanical energy into an electronic signal, were developed. These products revolutionized the automobile industry by replacing the 6-in. devices used to deploy airbags with more sensitive chips less than 1 mm in length. A final example of the diversification of MEMS devices in the 1990s is the micropump. Micropumps 100 to 400 μm in diameter and 1.5 μm thick have been developed that can deliver microliter amounts of substances.[10] These, or slightly larger, pumps have been widely used in the ink jet printing industry and are being applied to novel drug delivery systems.[9,11]

MEMS APPLICATIONS IN UROLOGY

MEMS have been used in the medical industry since the early 1980s. A variety of devices, such as pressure and chemical sensors, accelerometers, micromotors, and micropumps, have been used in patient care disciplines. Potential applications of MEMS in medicine include rapid screening for infectious and genetic diseases, telemetric recording of monitored patient data, precise implantable drug delivery systems, and precision surgery with micromotor control.[9] Successful application of these small, reliable, and inexpensive devices will decrease the pain and trauma of invasive procedures, decrease the length of hospital stay, and provide more frequent and accurate monitoring of patients at a low cost.[10] The applications of MEMS in medicine and urology can be broadly divided into diagnostic and therapeutic interventions.

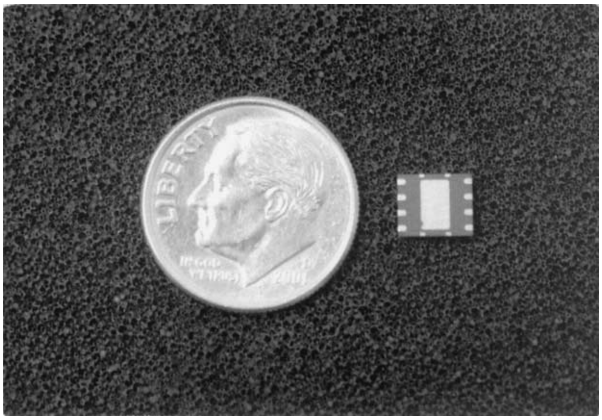

FIGURE 2. *MEMS-based recording chip. This chip records analogue data and stores it digitally for analysis with a personal computer at a later date.*

DIAGNOSTICS

The most successful application of MEMS technology in medicine to date is the use of piezoresistive pressure sensors to measure arterial blood pressure in the intensive care unit and operating room. Traditional quartz-capacitive sensors can cost up to $600 and must be sterilized and recalibrated before each use.[12] MEMS provide an accurate and inexpensive means of continuous blood pressure monitoring with microsensors that are housed in disposable plastic or ceramic packages and require no recalibration.[11]

Using a similar design, a team of urologists and bioengineers at the University of California, Los Angeles have designed a pressure microsensor that is 500 μm in length and can be placed percutaneously or cystoscopically to record pressure within different parts of the urinary tract. Although traditional pressure sensors could only measure pressure during a single anesthetic event, this sensor records data on a small circuit chip that is smaller than a dime (Fig. 2). This technology will allow patients to be at home while the data are collected. The sensor can then be removed manually or cystoscopically in the clinic for data analysis. Potential applications for this sensor include evaluation of ureteropelvic junction obstruction and vesicoureteral reflux, as well as home urodynamic studies.

An area of MEMS research that has generated a large amount of interest is the development of chemical and biosensors, the "lab on a chip." Much of the work in this area began with the development of miniature mass spectrometers.[12] Mass spectrometry is currently used in many diagnostic applications such as arterial blood gas monitoring and serum chemistry determination. However, because of large machines that must be cleaned and calibrated, as well as the human workforce needed to handle the specimens and interpret data, traditional mass spectrometers are associated with high expense. The Westinghouse Science and Technology Center is developing a mass spectrometer that is the size of a calculator to replace existing units that weigh more than 50 lb.[13] Similarly, Diaz *et al.*[14] constructed a miniature mass spectrometer that is 2 cm in diameter after packaging and provides greater resolution than traditional devices. Similar devices that measure serum chemistries, as well as perform blood-gas analysis, are now commercially available.

Another active area of MEMS diagnostic research is DNA bioanalysis and polymerase chain reaction (PCR). As genetic markers have become important in the pathologic classification and detection of disease, PCR has become an important tool in the clinical laboratory. One can study small amounts of DNA from single cells using the amplification technique of PCR. In 1998, de Mello *et al.* successfully performed PCR on a microchip.[15] Since then, MEMS hybridization chambers have been developed that hold 50 μL of a sample, as well as an oligonucleotide probe. These chambers are arranged into a series of arrays on a chip that is 11 mm by 11 mm. A polysilicon heater, in coordination with thermal microsensors, takes the sample through the cycles of PCR. This can be done in just longer than 60 seconds with a single drop of blood or tumor supernatant.[15] This technology will bring the laboratory to the patient. In urology, screening for syndromes or chromosomal anomalies, as well as the detection of tumor markers, could be done in the clinic.

Another area of urology that will benefit from MEMS technology is the diagnosis of urinary tract infection. A nucleic acid-based (genotypic) approach is more rapid and sensitive than the current methods of pathogen identification using cell culture. The traditional drawbacks of molecular diagnostic methods, including the need for experienced personnel to perform complex steps using large instruments, are addressed by using MEMS-based components for sample processing and analysis.

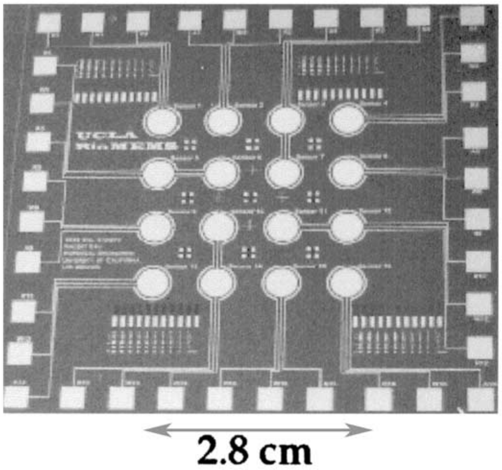

FIGURE 3. *An array of MEMS-based sensors for detection of uropathogens. This chip contains 16 wells in which urine may be analyzed for the presence of bacteria.*

A cooperative group at the University of California, Los Angeles has developed a system for the rapid detection of uropathogens. A molecular approach to detect uropathogenic bacteria will lead to earlier diagnosis and improve management of urinary tract infections. First, chemically modified single-stranded DNA oligonucleotide probes specific for *Escherichia coli* and *Proteus mirabilis* were designed. Then, bacteria obtained from clinical urine samples were grown in laboratory media, hybridized with the sequence specific DNA probes, and placed into miniaturized electrochemical DNA biosensors along with a signaling enzyme (Fig. 3). Compared with a standard hybridization sensor, the MEMS-based DNA biosensor was three orders of magnitude more sensitive in detecting uropathogens. Additionally, the total detection time from sample processing to detection was 45 minutes compared with the 2 to 3 days required for standard urine cultures.[16] Work has been started to detect bacterial gene products that would provide information regarding the antibiotic sensitivity of the uropathogens using the same MEMS-based biosensors.

THERAPEUTICS

Implantable and transdermal drug delivery microsystems allow patients both accurate and continuous dosing of medication and allow delivery of drugs directly to their intended sites of action. A group from the University of Minnesota has developed an implantable micropump that is 100 μm in diameter and 1.5 μm thick.[10] Many pumps can be connected in parallel or a series and coated with silicone to create an implantable drug delivery microsystem. Although intravenous administration of medications with this system is difficult at present, the potential for intrarenal, intraprostatic,

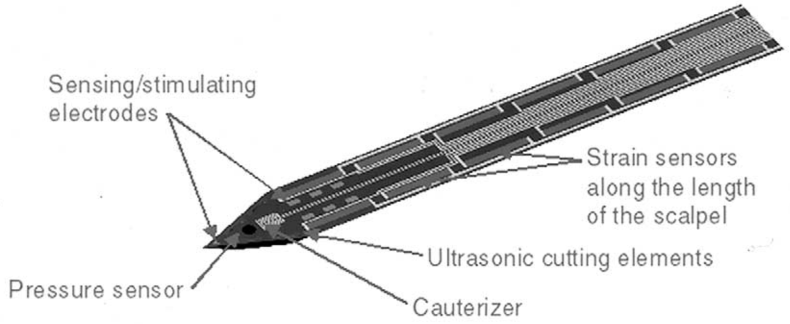

FIGURE 4. *Data Knife. Reprinted, with permission, from Verimetra, Inc., Pittsburgh, Pennsylvania.*

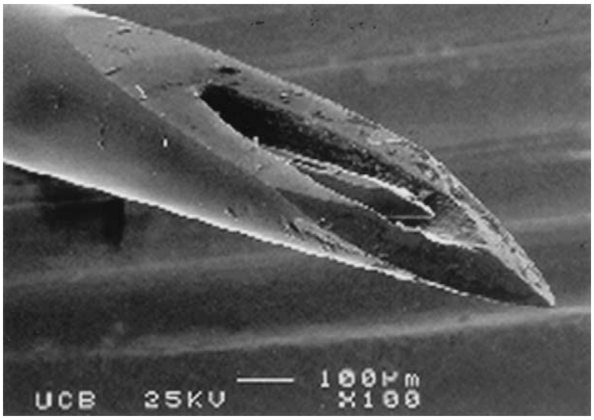

FIGURE 5. *Scanning electron micrograph of a MEMS-based hypodermic needle within the lumen of a standard 25-gauge needle. Reprinted, with permission, from Verimetra, Inc., Pittsburgh, Pennsylvania.*

and intravesical therapy in urology is great. Rather than rely on patient compliance for urine alkalinization when treating uric acid nephrolithiasis, micropumps could be placed directly into the renal pelvis either percutaneously or attached to the end of a fine stent. This system would allow continuous delivery of any medication to the renal collecting system or bladder. Intravesical mitomycin or dimethyl sulfoxide therapy could be performed as a clinic-based procedure with only one visit required for each complete course of treatment. Additionally, sensors could be integrated into the pumps that could analyze the chemical and infectious properties of urine during treatment. Finally, as the role for immunotherapy grows and medications become protein and DNA-based, implantable drug-delivery microsystems will provide an efficient and accurate method of administration. Tumor vaccines or immunomodulators could be delivered directly to the organ of concern and delivered in a constant manner, potentially decreasing systemic toxicity while achieving a high local concentration.

As urology embraces laparoscopy, the need for MEMS in surgical instrumentation grows. One advance has been the piezoelectric inchworm motor. These micromotors (some as small as 200 μm in length) have been used for accurate placement of replacement lenses after cataract removal in ophthalmology.[17] Additionally, a system for removing debris during retinal surgery using several pressure microsensors exists. Sensors in parallel control the vacuum that keeps the ocular surgical field clean. If a fault is detected by any of these sensors, the entire system shuts down.[11]

Because of the size of MEMS, a single MEMS-based instrument may perform many functions. Pittsburgh-based Verimetra, Inc. has designed the Data Knife, which incorporates pressure and strain sensors, as well as cautery and ultrasonic edges, into a "smart instrument" (Fig. 4). The goal of the Data Knife is to provide the minimally invasive surgeon with information about the environment in which the surgeon is working. On the basis of previously recorded tissue data, the Data Knife can inform the surgeon about the type of tissue the surgeon is dissecting, as well as the pressure used to manipulate it.[12] Devices such as this will be extremely useful in the world of laparoscopy, which is devoid of the tactile cues on which open surgeons rely.

MEMS fabrication technology can also provide improvements in existing surgical instruments. The standard grinding processes used to make scalpel blades and needles are inexpensive; however, the durability of the metal is poor, and replacement blades are frequently needed, even during a single case. Conversely, blades that are laser etched from diamond or ceramic are both accurate and durable, but the high cost limits their common use in clinical practice. However, MEMS technology provides surgeons with blades and needles that are atomically sharp and cheaper than metal (Fig. 5). [1] These instruments may improve the precision of reconstructive procedures, eliminating the need to change blades during a case.

Finally, the existence of pressure microsensors, expandable microactuators, and telemetric microchips may improve the treatment of common urologic problems. MEMS may improve the treatment of urinary incontinence with artificial urinary sphincters by reducing the size of scrotal components, as well as by replacing manual inflation and deflation with telemetrically driven signals for sphincter activation. Also, thermal microsensors may improve the accuracy of cryotherapy for the prostate and kidney. The ability to place sensors in the tissue of concern, whether the rectal wall or renal collecting system, without damaging that tissue may decrease the complications associated with this new technology. Finally, tools such as urethral stents, currently associated with numerous complications, may find application in practice with the addition of MEMS technology. A stent that expands and contracts at regular intervals may provide a better quality of life for the patient while avoiding the erosion and ingrowth of tissue that currently hinders its widespread use. Similar applications of micromotors may be used in novel ureteral stents to reduce encrustation, as well as intravesical irritation from excessive curl length.

CURRENT OBSTACLES

The previously described devices show that the potential benefits of MEMS in urology are numerous. We will know more about our patients and be able to interact with them in a minimally invasive manner. However, the success and impact of MEMS in medicine still has obstacles to overcome.

First, before surgeons and the population will accept these devices, we must resolve issues regarding biocompatibility. Because many of these devices will interact with biologically active materials for long periods, clinical research must continue where basic science research has concluded. This is an opportunity for urologists and the medical community in general to participate in the study design and application by collaborating with MEMS researchers both on academic campuses and in industry. Second, although an advantage of MEMS is its low expense, the initial research and development costs can reach millions of dollars. Efficient use of funding sources and the promotion of devices with clinical applications are essential if MEMS is to reach its full potential in surgery. A final issue that will require significant research is telemetry. As numerous "smart" devices are being developed, the need for remote transmission of data becomes important. Currently, MEMS telemetry units rely on subcutaneous coiled leads and batteries to transmit and store data.[1] However, if we are to truly manipulate the human body on a micron scale, we will need to provide devices with the freedom to interact with tissue without cumbersome wires.

CONCLUSIONS

MEMS is now at a critical point in its evolution. Its advantages have been recognized in the laboratory for years; however, industry and medicine are now attempting to determine the role that MEMS will take in society during the next decade. That role should be determined not only by MEMS engineers and members of industry, but by the physicians who will apply this exciting technology. With this review, we have attempted to provide an introduction of MEMS for practicing urologists to encourage this active participation. We hope that the description of the history of MEMS allowed readers to appreciate the diagnostic and therapeutic advances that have been made. Although many obstacles still exist in the advancement of MEMS devices in urology, the benefits will surely be worth the effort.

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