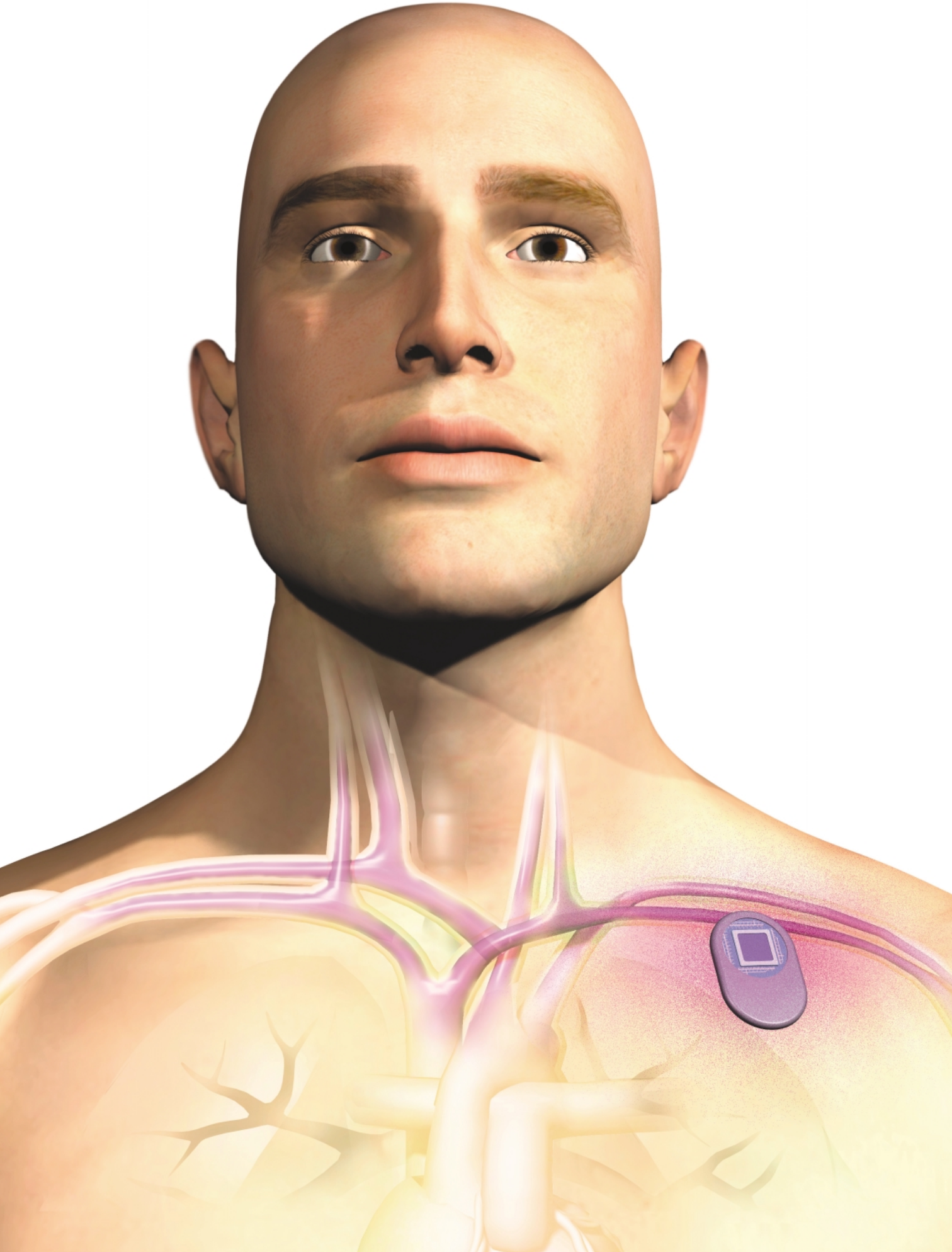


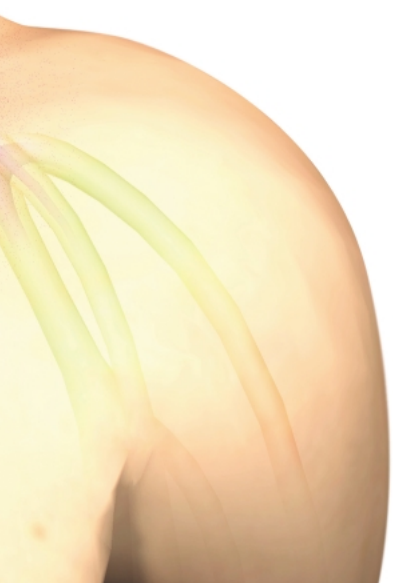
Aging + TECHNOLOGY

Second in a series of reports on biomedical engineering innovations

Chip Shots

By Carol Ezzell Webb

IMPLANTED SEMICONDUCTORS will allow drugs to be delivered exactly when and where they are needed

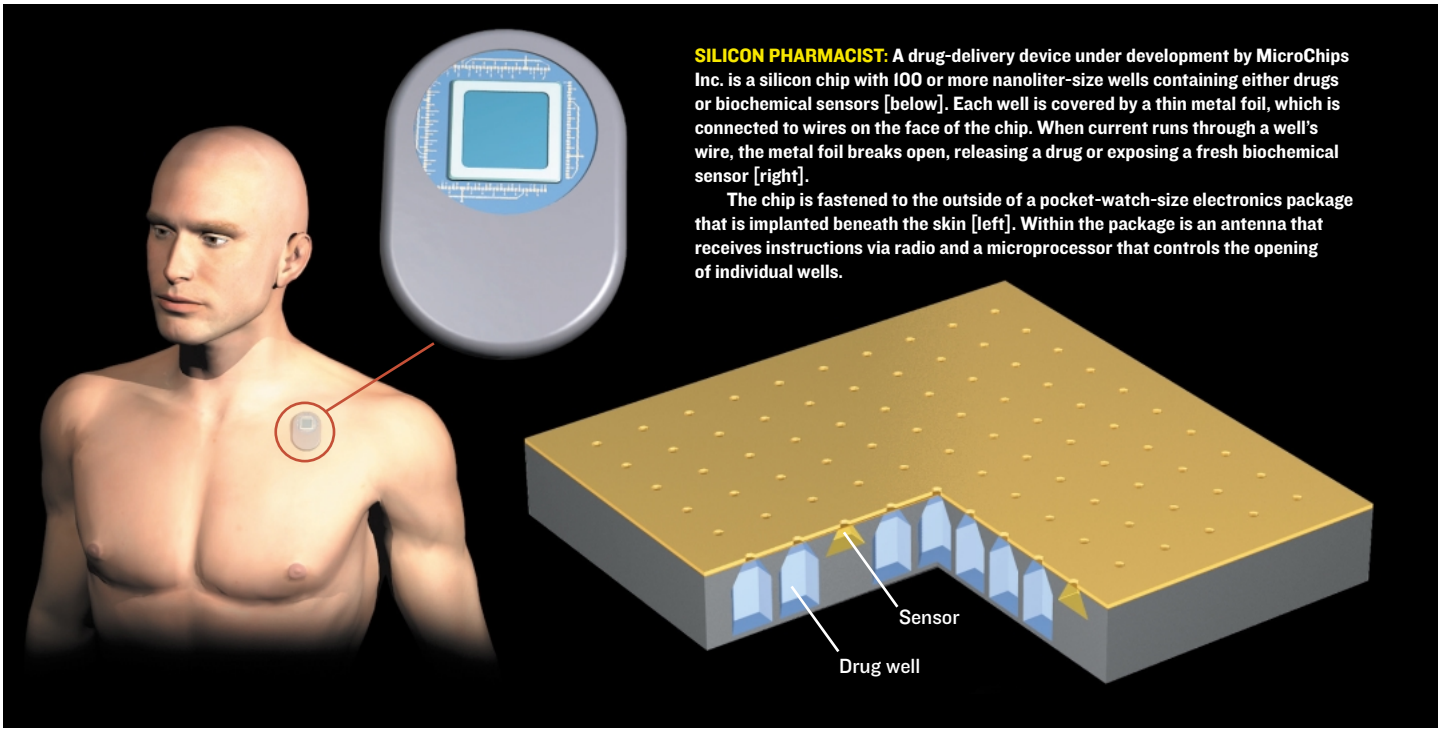


LOOK IN ANY MEDICINE CABINET and you're bound to find a veritable pharmacopeia: tablets, capsules, suppositories, syrups, inhalers, transdermal patches, and maybe even a syringe or two. In 2002 doctors wrote an average of 10.6 prescriptions for each person in the United States. As the population of the industrialized world ages, pharmaceutical companies are struggling to find compounds that ward off—or even reverse—the maladies that historically have plagued aging adults.

But for many of these scourges, the existing means of getting drugs into the body are only moderately effective and may be disruptive or downright painful. For instance, people with adult-onset diabetes—an increasingly common affliction of the middle to later years—suffer more complications if their blood sugar fluctuates widely. Popping pills and injecting insulin a few times a day can lead to peaks and troughs in blood sugar that can wreck small blood vessels, resulting, in the worst instances, in blindness or amputation of the feet or lower legs.

Some of the newer drug candidates for treating other illnesses are based on proteins discovered using information gleaned from the human genome. But they can't be taken orally or by injection because stomach acids chew them up or the liver filters them out of the bloodstream too quickly for them to be effective. And many of those wasted molecules are just the ones that aging bodies need to keep them hale and hearty.

To address these problems, electrical engineers are teaming up with gene jockeys and drug developers to invent new drug-delivery systems that marry electronics and semiconductors to biotechnology. Experts agree that new drugs need a degree of intelligence to get where they must go and to arrive on time, and that's where semiconductors come in.



SILICON PHARMACIST: A drug-delivery device under development by MicroChips Inc. is a silicon chip with 100 or more nanoliter-size wells containing either drugs or biochemical sensors [below]. Each well is covered by a thin metal foil, which is connected to wires on the face of the chip. When current runs through a well's wire, the metal foil breaks open, releasing a drug or exposing a fresh biochemical sensor [right].

The chip is fastened to the outside of a pocket-watch-size electronics package that is implanted beneath the skin [left]. Within the package is an antenna that receives instructions via radio and a microprocessor that controls the opening of individual wells.

Two approaches are just now being tested for feasibility. One features implantable microchips dotted with tiny drug reservoirs that pop open at the touch of a wireless telemetry button. The other relies on injections of nanometer-scale beads of semiconductors, termed quantum dots, that exploit the energy of electrons to kill cancer cells selectively.

The first disorders to be treated with these "smart" drug-delivery systems will probably be chronic diseases for which patients must take one or more drugs for months or years. Like adult-onset diabetes, many of these maladies—including congestive heart failure—predominantly affect older adults. Research into microchip-based devices, called biological microelectromechanical systems, or bioMEMS, is currently much further along than studies of quantum dots, just now being tested in academic labs as a means for delivering drugs.

In the microchip approach, bioMEMS would be implanted in the body and, ideally, would serve as "closed-loop" systems, holding not only the means to administer a drug but also sensors that could tell when a patient needs another dose. So far, though, only a handful of studies describing bioMEMS-based drug-delivery systems have appeared in peer-reviewed scientific literature, and few companies have such systems in development.

ONE SUCH COMPANY is MicroChips Inc., in Bedford, Mass. At the core of its device is a 15-millimeter silicon microchip that is made using essentially the same techniques for producing integrated circuits. Instead of transistors, however, the device is dotted with 100 tiny reservoirs that are filled with a drug [see illustration, "Silicon Pharmacist," and photo, "Drug Dispenser"]. Each reservoir is capped with a thin layer of platinum and titanium, all of which are fabricated into a network of circuitry that includes patterned gold conductors. It takes just a 4-volt zap to remove an individually addressable well covering, allowing the drug to diffuse out.

Best of all, the whole operation can be triggered by remote control. The bioMEMS unit is stuck to the outside of a sealed titanium case, roughly the size of a pocket watch, that contains a battery, a wireless telemetry chip, and a microprocessor.

MicroChips has been conducting experiments that track the performance of the chips in animals for three months or longer. The drug-dispensing chip and its associated electronics have been implanted under the skin of an animal's shoulder, where the device can be triggered wirelessly. "To administer a dose of drug, we just walk up to the animal and activate the device with a remote control," says John T. Santini Jr., president of MicroChips.

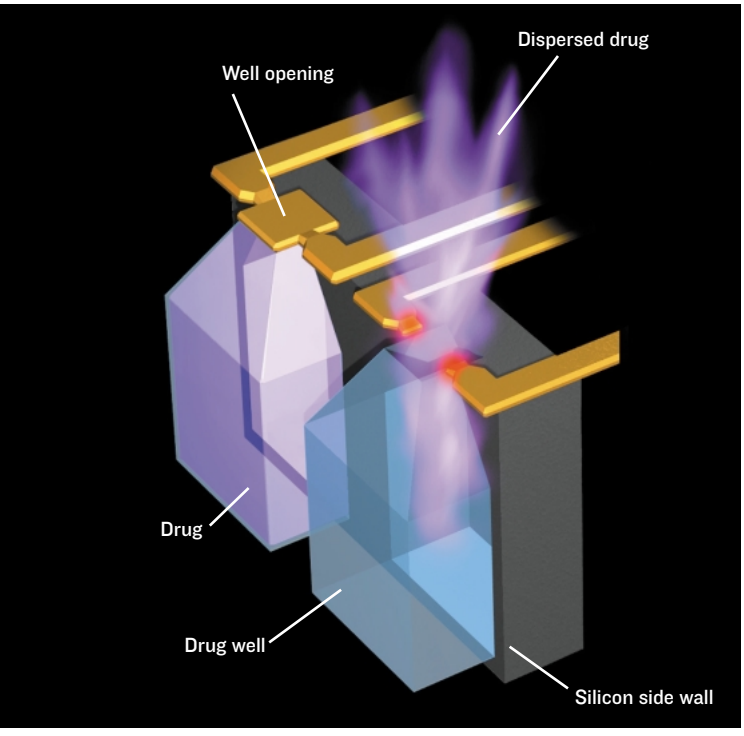
Another company, ChipRx Inc., in Lexington, Ky., has also pursued bioMEMS-based drug delivery, but development of its first product, an implantable matchstick-size drug-delivery vehicle that uses electrically activated artificial muscles to open and close drug reservoirs, is on hold for now. [For an overview of artificial muscles, see "Electric Flex," *IEEE Spectrum*, June 2004.] Marc Madou, cofounder of ChipRx and an engineering professor at the University of California at Irvine, says that for the immediate future ChipRx intends to concentrate on making genetically engineered proteins that might be dispensed as part of a closed-loop device.

WITH OR WITHOUT SENSORS, developers still don't know how long and how reliably bioMEMS will function once implanted into living systems, a factor that will determine whether doctors and their patients accept the devices. The objective is to design implants that can meter out precise doses of drugs for months or years before they must be removed or replaced. MicroChips' Santini says that his company has unpublished data from ongoing experiments in animals demonstrating that its chip has continued to release a drug for more than three months.

As with any medical implant, fouling might limit the useful lifetime of a bioMEMS device. In fouling, cells and molecules of

ABOUT THE AUTHOR CAROL EZZELL WEBB is a freelance journalist in Austin, Texas, specializing in biotechnology and biomedicine. She has been an editor at ***Scientific American*** and worked at ***The Journal of NIH Research*** and the science journal ***Nature***.

ALL ILLUSTRATIONS: JOHN MACNEILL



the body's immune response stick to the surface of an implant, preventing it from functioning properly. Many implants may also become surrounded by a thick capsule of scarlike tissue that essentially blocks them from communicating with the rest of the body. Coating the implants with anti-inflammatory drugs might prevent them from being attacked by the immune system.

"Fouling is a real biggie" among the issues confronting bioMEMS, says Burton Sage, cofounder and chief scientific officer of Therafuse Inc., in Carlsbad, Calif. His firm is developing wearable (but not implantable) pumps that exploit MEMS technology by using a tiny needle to administer precise doses of drugs, such as insulin, through the skin.

Sage adds that it is impossible to predict now whether fouling will foil the prospects of bioMEMS. The degree of fouling appears to depend on the chip's location in the body, the type of drug the device contains, and the kinetics of that particular drug's release and diffusion.

In the case of implantable sensors—a blood glucose meter, for example—bioMEMS might even be used to compensate for fouling, asserts Santini. Such sensors are now effective only for a few days or weeks, after which they become irreversibly clogged. Encasing multiple sensors in a bioMEMS device could yield an implant in which wells could be opened, one at a time, to reveal a fresh sensor when the old one has become clogged beyond use.

Therafuse's Sage wonders about another lifetime issue: how to refill the implants. "How do you put enough drug in there for the long term?" he asks. Retrieving and refilling a bioMEMS device would require outpatient surgery. To circumvent this, some scientists are designing implants with drug chambers that can be refilled from syringes without removing the devices from the body.

Among those who might be willing to undergo repeated implant placement, Sage says, are patients who have had a heart attack and are at high risk for another. In such instances, a bioMEMS could be loaded with a clot-dissolving drug or the heart stimulant epinephrine (also known as adrenaline). The patient could activate the implant at the first symptoms of a heart attack.

The ultimate goal, however, is to take the patient out of the loop by relying on microprocessors to do the regulation automatically. "The whole reason for wanting intelligent drug-delivery technologies is so you can do closed-loop sensing and drug administration," says Santini, whose company is working on precisely that challenge. Putting sensors and drug reservoirs on board the same chip could yield a device that would automatically monitor the presence of a given molecule in the blood and then administer the drug precisely when it is needed.

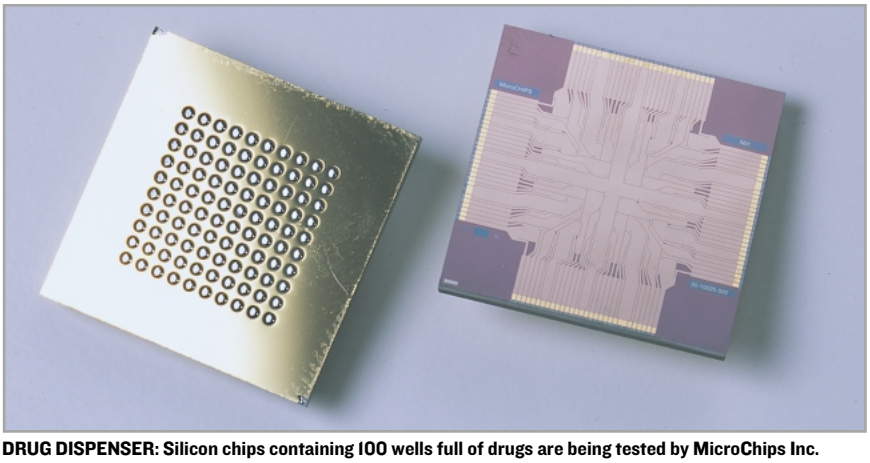
Such an approach would be a huge boon to people with congestive heart failure, says Nader Najafi, founder and president of Integrated Sensing Systems Inc., in Ypsilanti, Mich. In that disease, imbalances in water regulation by the body lead to fluid buildup around the heart, impeding its ability to pump blood. An automatic sensing and delivery system might detect increases in pericardial fluid and reduce the buildup by releasing a diuretic, a drug that causes the body to eliminate water. Congestive heart failure, which afflicts an estimated 15 million people worldwide, is the most frequent cause of hospitalization among those 65 and older in the United States and a major cause of death if not treated in a timely manner.

For now, Integrated Sensing Systems is conducting early research into the sensor side of things by attempting to develop a wireless, batteryless, implantable pressure sensor for use in congestive heart failure, according to Najafi. The company is still working out the details of exactly how the device would function; researchers at the company eventually intend to couple it to a mechanism for dispensing drugs to treat the disorder.

Under the company's current plans, physicians would implant a pressure-sensing bioMEMS into a patient's left heart ventricle during outpatient surgery by threading a cardiac catheter through the blood vessels and into the heart chamber. A signal from the sensor would then activate a diuretic drug-delivery system.

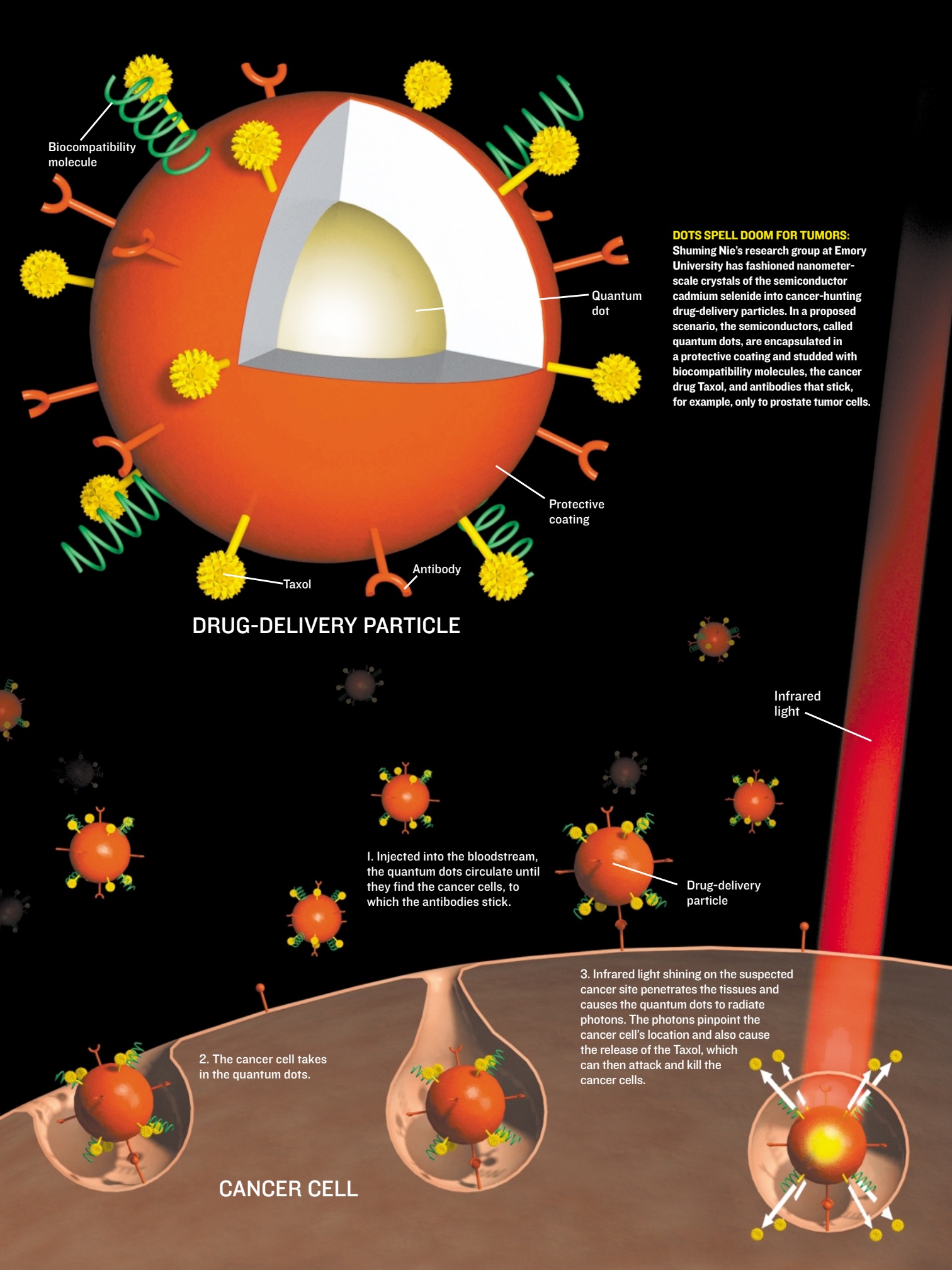
Right now, most researchers are working on either sensors or drug-delivery systems, but not both. "Everybody who is in this field is working toward closed-loop technology, but it's at least 10 years away," says Therafuse's Sage.

A VERY DIFFERENT KIND of semiconductor drug-delivery system, the quantum dot approach, might be just as far away. Quantum dots are crystals—often of the II-VI semiconductor cadmium selenide—which, because they are mere nanometers across, retain the



NICHOLAS EVELEIGH

DRUG DISPENSER: Silicon chips containing 100 wells full of drugs are being tested by MicroChips Inc. Each well [left, bottom of chip] can be opened independently by current flowing down a set of electrodes [right, top face of chip] and melting away a thin foil covering. [See illustration, "Silicon Pharmacist."]

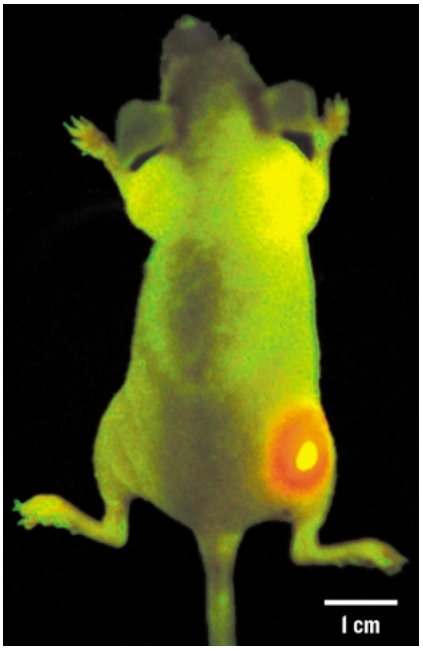

Biocompatibility molecule
Quantum dot
Protective coating
Antibody
Taxol
DRUG-DELIVERY PARTICLE
DOTS SPELL DOOM FOR TUMORS: Shuming Nie's research group at Emory University has fashioned nanometer-scale crystals of the semiconductor cadmium selenide into cancer-hunting drug-delivery particles. In a proposed scenario, the semiconductors, called quantum dots, are encapsulated in a protective coating and studded with biocompatibility molecules, the cancer drug Taxol, and antibodies that stick, for example, only to prostate tumor cells.
Infrared light
1. Injected into the bloodstream, the quantum dots circulate until they find the cancer cells, to which the antibodies stick.
Drug-delivery particle
2. The cancer cell takes in the quantum dots.
3. Infrared light shining on the suspected cancer site penetrates the tissues and causes the quantum dots to radiate photons. The photons pinpoint the cancer cell's location and also cause the release of the Taxol, which can then attack and kill the cancer cells.
CANCER CELL

quantum properties of single atoms. Critical for biomedical applications, these properties include the ability to absorb and emit photons of a very specific wavelength.

In single atoms, the wavelength depends on the type of atom involved, but with quantum dots the stimulation wavelength is related to their size. Smaller dots absorb and give off a shorter wavelength—that is, the light they absorb and emit is closer to the violet end of the spectrum—whereas larger dots produce longer wavelengths closer to the red end.

Most of the current commercial investment in quantum dots is related to their use in computing applications and lasers. The market for quantum dot–based chemicals for biomedical research—now roughly US $720 million—has also been growing, says Stefanie Lattner, portfolio executive at the publicly funded venture capital firm Innovation Works, in Pittsburgh. But at the moment, no venture capital money is chasing drug-delivery applications, she says.

That may be because studies of the therapeutic uses of quantum dots are still mainly at the academic level. Shuming Nie, adjunct professor of biomedical engineering at Emory University in Atlanta, is one of the first researchers to investigate quantum dots as drug-delivery systems. Specifically, Nie has chemically bound the breast and prostate cancer drug Taxol to quantum dots in an effort to deliver it specifically to tumor cells, leaving the rest of the body unaffected [see illustration, "Dots Spell Doom for Tumors"].



DIAGNOSIS BY DOT: Injected into a mouse, quantum dots stick to a tumor in the mouse's thigh. Glowing red under infrared light, the dots help to locate the tumor.

The scheme could increase the drug's efficacy and reduce its side effects. The American Cancer Society, in Atlanta, estimates that in 2004, 15 percent of cancer deaths among U.S. women will be from breast cancer; similarly, 10 percent of cancer deaths among U.S. men will be from prostate cancer.

Nie's group started its research by studding the Taxol-bound quantum dots with a molecule that binds to folic acid receptors, which are present on tumor cells at concentrations roughly 1000 times those found on normal cells. The receptor-targeting molecule allows the nanoparticles to home in preferentially on cancer cells. In work published in August, the Emory scientists got even better results using antibodies against prostate cancer cells rather than folic acid binders.

Nie and his co-workers injected the Taxol-coated nanoparticles into mice that had been surgically implanted with human prostate tumors. After the injections, they illuminated the mice with infrared light, which penetrates into their tissues and excites the quantum dots [see photo, "Diagnosis by Dot"]. As the energy states of the dots fall back, they emit energy sufficient to cleave the bonds between the Taxol and the particles, releasing the drug to attack tumor cells. "We have evidence that our quantum dot conjugates can get into cancer cells and kill them," says Nie.

He acknowledges that the approach will be more difficult for human patients, whose bodies are thicker than that of the average mouse. Infrared light will penetrate only a few centimeters into living tissues. "I don't think there's any hope for this in treating cancers of the internal organs," says Nie, "but it might work for [the skin cancer] melanoma or for breast cancer."

Sangeeta Bhatia, associate professor of bioengineering at the University of California at San Diego, is taking the idea of drug targeting to an even finer level. She's investigating the use of quantum dots for steering compounds to particular compartments or organelles within a cell—such as the nucleus, where the genes are, or the energy-producing mitochondria.

Addressing cancer drugs to specific organelles could reduce side effects. But the toxicity of the quantum dot materials—especially cadmium—has made Bhatia cautious. Indeed, environmentalists have made much of the possible health effects of nanoscale particles.

Earlier this year, Bhatia and her graduate student, Austin M. Derfus, reported that quantum dots containing cadmium do indeed kill cells. But they are no more noxious than ordinary elemental cadmium, which can accumulate in the body and has been linked to kidney damage, heart disease, hypertension, cancer, and bone and joint pain.

"The bottom line is that our initial findings suggest that quantum dots are not especially toxic just because they are nanomaterials," she says. Though that is not a great endorsement for a potential drug-delivery scheme, Bhatia and Derfus also showed that the nanoparticles can be made much less poisonous by encasing them in various types of protective coatings.

The U.S. government also wants to determine the overall safety of nanoparticles containing quantum dots. Peter E. Barker, project leader for the National Institute of Standards and Technology–National Cancer Institute Biomarkers Validation Laboratory, in Gaithersburg, Md., says that although he is optimistic about the future of the technology, many more experiments are needed. Barker is putting together an analysis of the safety of quantum dots, among other nanotechnologies, for the U.S. Environmental Protection Agency. "How long do quantum dots last in the body, and which organs clear them?" he asks. "How they are going to affect the viability of normal cells is still pretty much up in the air."

If quantum dots prove safe, Barker suggests they might be used to tag cancer cells in the blood, which could then literally be plucked from circulation using a cell sorter, such as those now employed in clinical laboratories to count various types of white blood cells. The approach could be used not only for leukemias and lymphomas but also to remove metastatic cells from solid tumors that are spreading by circulating in the blood.

Such a scenario is still far in the future. But scientists such as Santini and Nie dream of a day when semiconductors will help us triumph, at last, over heart disease and cancer, two of the worst remaining scourges of old age. ■

TO PROBE FURTHER

For a review of current bioMEMS technology, see Amy C. Richards Grayson et al., "A BioMEMS Review: MEMS Technology for Physiologically Integrated Devices," ***Proceedings of the IEEE***, Vol. 92, no. 1, January 2004, pp. 6–21.

Good background information on the physics of quantum dots is at Quantum Dot Corp.'s Web site, http://www.qdots.com. (The company says it has no plans to develop drug-delivery dots.)

Shuming Nie's recent research appears in the August 2004 issue of ***Nature Biotechnology***, Vol. 22, pp. 969–76.

View a video clip of the MicroChips bioMEMS dispensing a drug on the company's Web site, http://www.mchips.com.

SHUMING NIE