A Small

Miniature diagnostic labs, PCR-on-a-chip, reports from the world of microscopic

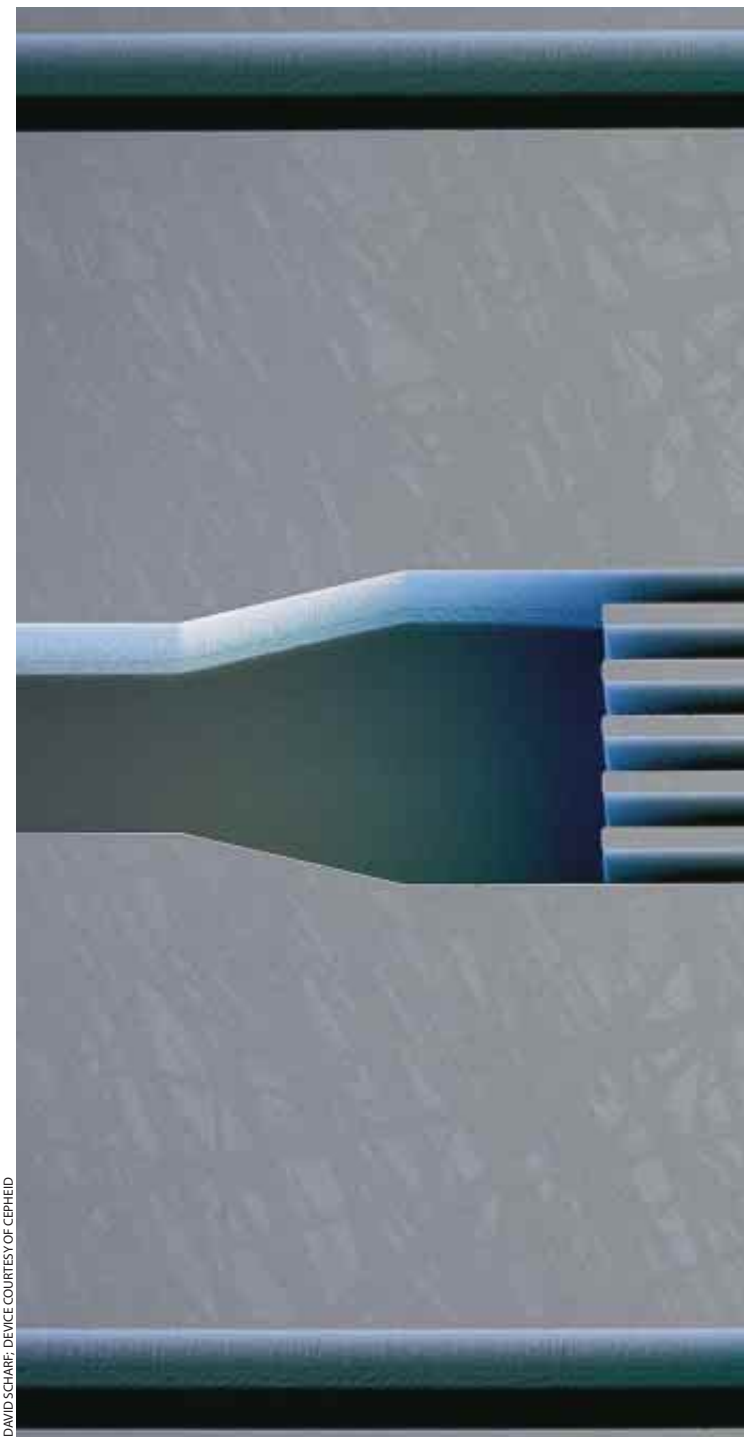
by David Voss

Back in the 1966 movie *Fantastic Voyage,* a band of intrepid travelers were scrunched down to the size of blood cells so they could swim through the veins of a big-shot diplomat and destroy a life-threatening blood clot. Today real-life explorers are attempting projects along the same lines: they are trying to shrink whole biomolecular laboratories and diagnostic instruments to such a size that they can be implanted in the body or easily carried around for on-the-spot analysis and treatment. These researchers are using the tools of bioMEMS—*mi*cro*e*lectro-*me*chanical *s*ystems with *bio*logical applications—in which everyday objects such as pipes, valves and pumps are re-created at dimensions of one micron (one millionth of a meter), or about the size of a bacterium.

Techniques for manufacturing miniature tools, such as photolithography and micromachining, hold the promise of producing biocompatible gadgets so small you could put 1,000 of them on a pencil eraser and so inexpensive you could use them and then brush them away like dust. High-tech but cheap gadgets are extremely desirable in biology and medicine: for instance, doctors would love to analyze test results using sophisticated chips that are as sterile and disposable as hypodermic needles or tongue depressors.

With such goals in mind, researchers have been asking if the complex technology of DNA sequencing and gene analysis could be reduced to the size of a credit card. Then perhaps you could carry around a credit-card-size biolab, breathe into it and find out if you were about to get the flu, based on which microbes were present in your system. Medical tests that currently require days in a large diagnostic lab might take minutes and cost much less. Now scientists are going beyond asking the questions to producing working models.

Chemistry labs around the globe spend many years and huge sums of money sifting through and testing collections of millions of compounds in search of those few that might have medical uses. With miniaturization, however, the lengthy slog through the chemicals in a pharmaceutical library might be slashed dramatically, resulting in many more successful drugs at lower cost. (Other time-consuming tasks such as gene sequencing make attractive



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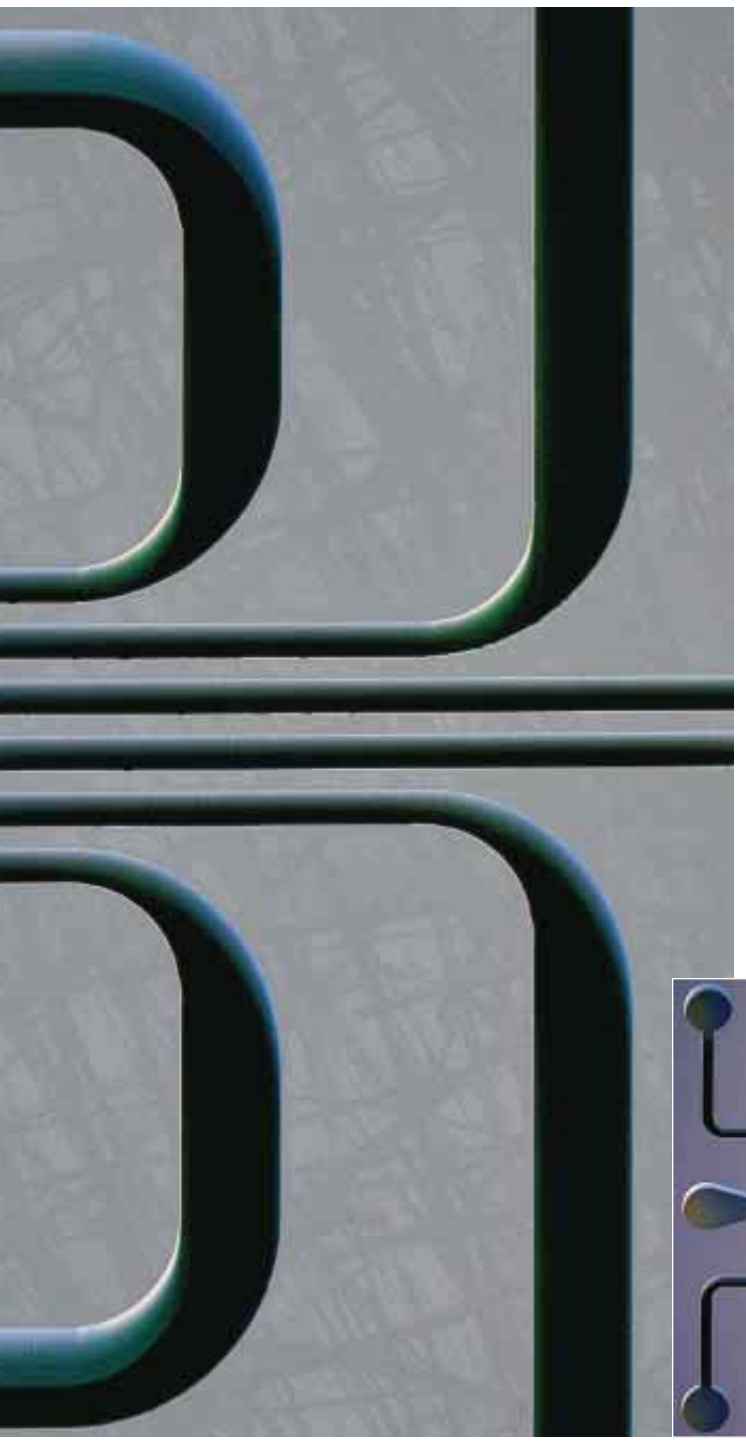
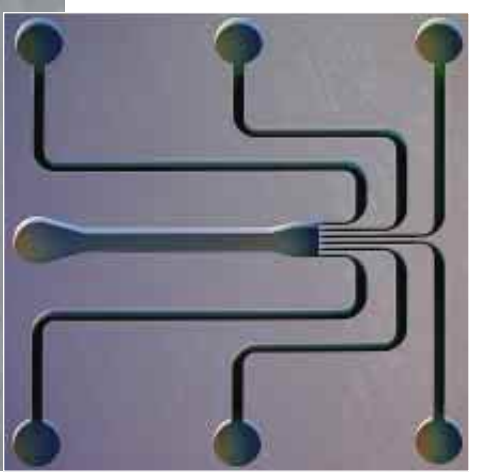
handheld biotoxin sensors and other biological and medical devices



targets for this technique as well; large batches of micromachines could be used for this job, each one grabbing a small chunk of DNA for sequencing.) Indeed, companies such as Caliper Technologies in Mountain View, Calif., are trying to shrink both the equipment and the testing time for finding new drug candidates.

Caliper's "liquid integrated circuits" move samples around a chip with electrical fields. Dose response curves, a benchmark for whether a new compound might have a biological effect, are being measured with the new technology by combining fluids in a microchannel and then testing how strongly the substance binds to cells. According to Michael R. Knapp, the company's vice president of science and technology, Caliper's goal is to create a single desktop system that could screen hundreds of thousands of substances in one day—a significant improvement over the 100,000 tests an entire company can run in 24 hours with current state-of-the-art techniques. An added benefit would be that microlabs require significantly less sample to perform tests.

In a related approach, Orchid Biocomputer in Princeton, N.J., has expanded the microlaboratory into a massively parallel chemical synthesis factory of three-dimensional microfluidic chips. Not only are the fluid channels embedded inside the chips in a horizontal plane, but different levels are hooked up to make 3-D microfluidic arrays. With these chemical factory chips, Orchid is developing a machine that creates 12,000 different chemical compounds in a couple of hours, the same amount of time it takes one chemist in a conventional synthesis lab to run one reaction. These chemicals are then tested for use as possible drugs.



MICROCHANNELS: The miniature mixing chamber (*inset*), sculpted in silicon, allows chemical reagents to mix during DNA analysis. The channels (*left*) sweeping away from the main chamber are 20 microns wide. (Magnification, *left:* 560×; *inset:* 69×)

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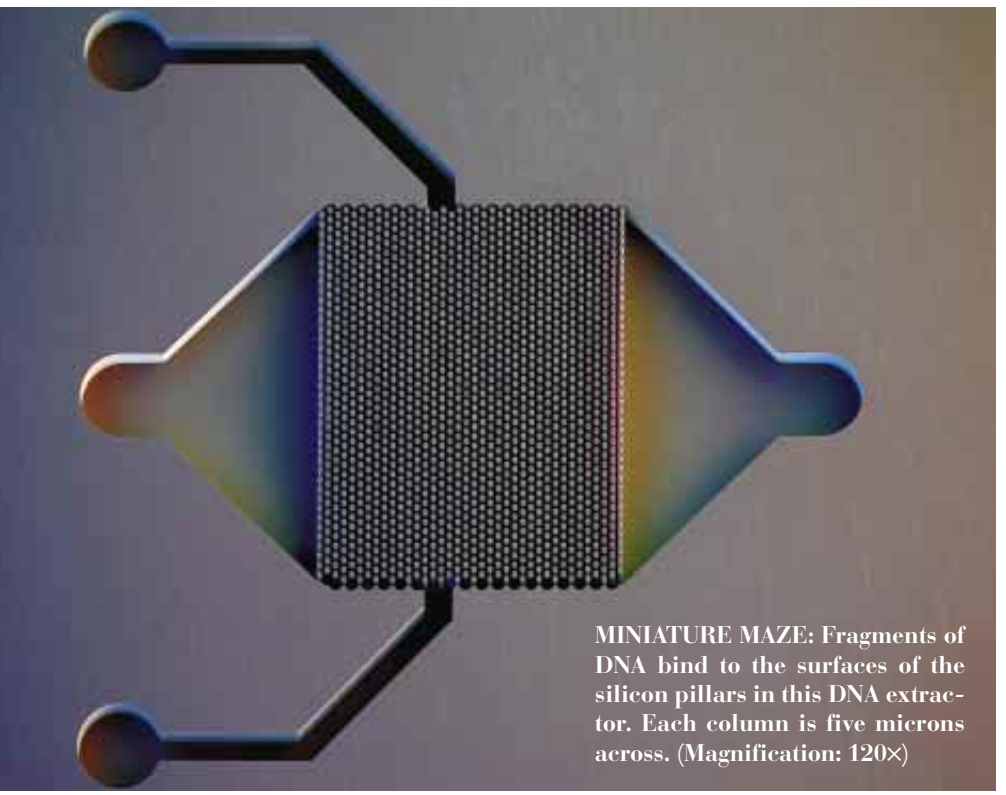
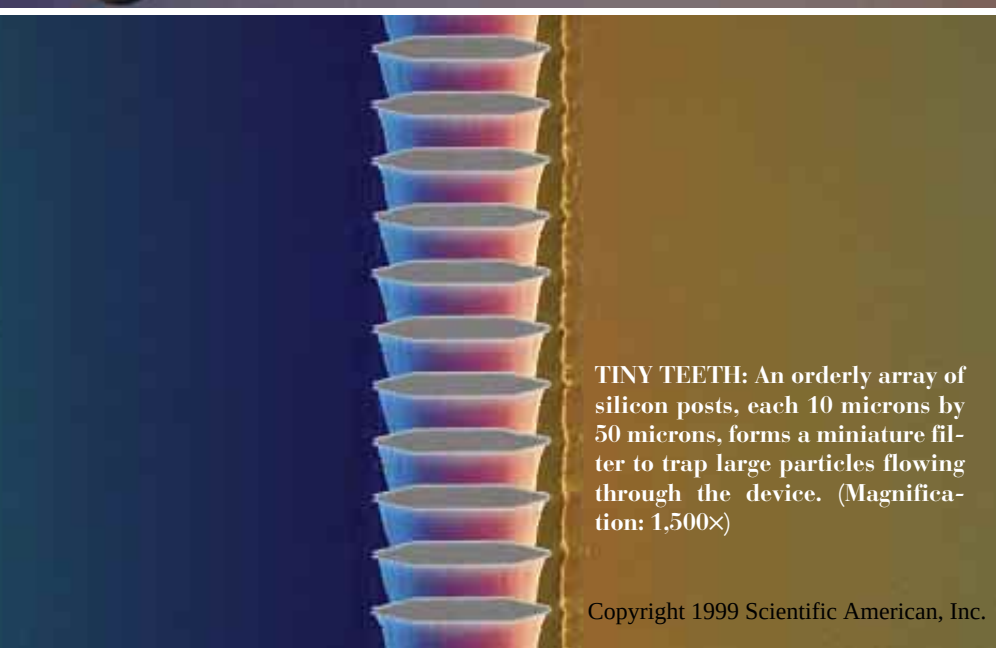
CELLULAR SCAFFOLDING: Microstructures resembling chain mail provide support and space for artificial tissue growth. (Magnification: 900×)



MINIATURE MAZE: Fragments of DNA bind to the surfaces of the silicon pillars in this DNA extractor. Each column is five microns across. (Magnification: 120×)



TINY TEETH: An orderly array of silicon posts, each 10 microns by 50 microns, forms a miniature filter to trap large particles flowing through the device. (Magnification: 1,500×)

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One particular reaction-on-a-chip has garnered special attention: chemistry professor Andrew de Mello and his co-workers at Imperial College of the University of London made headlines in 1998 with their device for running PCR on a chip. PCR, the polymerase chain reaction, is the workhorse of gene research. It's a chemical copying machine that takes small pieces of DNA in low concentration and generates exact replicas until there is enough sample to study. De Mello is now refining his prototype system. "The goal is to have a system where you can take the instrument to the sample, not the sample to the instrument," he says. This arrangement would shorten the length of time it takes to get results as well as lower the costs of analysis.

By carrying out the reaction in a tiny microchannel on a chip, rather than on laptop-computer-size plastic trays, scientists can take advantage of some unusual characteristics of reduced size. Matter behaves differently at micron dimensions; for instance, the physics of fluid flow are completely different. It is almost impossible to create turbulence in such small systems, so fluids can stream along side by side and never mix until they are forced to do so in a reaction chamber, thus eliminating some of the plumbing typically required for moving fluids around. Furthermore, heat transfer is rapid through such a small system, so temperatures can be raised and lowered quickly. As a result, de Mello says, his group can carry out the heating and mixing required for PCR in about 90 seconds instead of hours.

De Mello's team is now working to shrink down the other system components, such as the detection module. This device processes the results of PCR and adds fluorescent tags that light up if specific gene sequences are present. Right now his system uses a large gas laser that covers an entire tabletop; de Mello hopes to replace this setup with a solid-state laser about the size of a match head.

The ability to create these minilabs brings scientists closer to producing what some are calling "personal diagnostic systems," devices about the size of a Palm Pilot that take a blood or tissue sample, do a complex series of biochemical tests

DAVID SCHARF; DEVICE COURTESY OF KAIGHAM J. GABRIEL *Carnegie Mellon University (top)*; DEVICE COURTESY OF CEPHEID *(middle and bottom)*

and then display the results. It would be a big step forward for rapid screening for HIV, checking for toxins in food and testing for environmental contaminants.

Researchers at companies such as Cepheid in Sunnyvale, Calif., are developing handheld systems based on microfluidics and microelectronics. "We are now demo'ing our GeneExpert," says company president Kurt Petersen. "It takes five milliliters of urine and detects infectious diseases [including chlamydia and gonorrhea] in about 30 minutes." Results from such procedures usually take about two days to come back from a conventional diagnostic lab, he notes.

But microsystems are not limited to merely analyzing fluids taken out of the body. Researchers also are designing systems to put material directly into the body. One such application being considered is implant technology for diabetics. Not only are the daily lancings to check blood glucose levels and the insulin injections a painful burden, but the variations in blood chemistry caused by the discrete dosing are anything but optimal. A better treatment might be a continual trickle of insulin in response to constant monitoring of glucose concentration.

Marc Madou, director of the bioMEMS group at Ohio State University, has been working on his own version of this concept. His group has developed a material with an array of tiny holes and little artificial muscle elements that expand and contract in response to chemical changes. The idea would be to make an insulin reservoir out of this array and have the pores open and close in response to glucose levels, creating a direct chemical feedback loop. Madou says this is not feasible now but may be in several years, once researchers resolve the issues of how to prevent proteins in the body from clogging pores, how well the valves will close and what the leakage rate will be.

Another possible future use of bioMEMS is what Kaigham J. Gabriel, professor of electrical and computer engineering and robotics at Carnegie Mellon University, calls the "smart" hip joint. It's a striking example of how bioMEMS could integrate sensing and telecommunications. Hip replacement, now a fairly common medical procedure, involves replacing the worn-out joint with an artificial one made of titanium, ceramic and polyethylene. Unfortunately, after several years the artificial joint often loosens from the stresses of normal use, requiring surgical repair. Gabriel speculates that it might be possible to incorporate micropressure sensors into the area around the joint that would send data about the forces acting on the contact surfaces back to an external receiver. Other bioMEMS devices incorporated into the joint could realign the contact points, making it possible to adjust the configuration of the artificial joint constantly and thereby prolong its life.

Although smart hip joints may appear to be decades away, much progress is already being made. A group led by Farid Amirouche, a professor of mechanical engineering at the University of Illinois at Chicago, has tested pressure-sensitive films positioned inside joints. The data from these sensors will allow surgeons to position hip implants more accurately. Amirouche expects to start human clinical trials soon.

And if we can monitor the inside of our bodies, what about the surface? David J. Beebe of the University of Illinois at Urbana-Champaign has been working on a material that he calls "smart" skin, a flexible polymer film studded with tiny sensors. Smart skin isn't intended to replace natural skin but rather to serve as a way of obtaining data about how the body functions. It can be applied to fingers like bandages, and it reports back on stresses experienced during some hand activity.

Smart skin could, for example, be used to determine what forces acting on the joints of the hand might cause carpal tunnel syndrome; the data acquired from fingers moving on a keyboard could be correlated with mechanical models of the internal forces acting on the bones, muscles and nerves as a way to understand, prevent and treat the syndrome. Beebe says the sensors can also be used to study the bedsores that plague bedridden hospital patients and the wheelchair-bound.

Other explorations of bioMEMS are in the service of protecting soldiers from biological and chemical weapons. Such agents act in countless ways, but the one thing they all have in common is that they make cells sick. So why try to design a synthetic sensor when you can let the cells do the sensing, reasons Gregory T. A. Kovacs, a physician and professor of electrical engineering at Stanford University.

Kovacs has found a way to use cells as miniature sensors in a handheld detection system—a miniature canary-in-a-coal-mine. A thousand or so cells harvested from chickens or rodents are grown in a cheap disposable cartridge and maintained with life support to regulate temperature and to supply nutrients. When something comes along to disturb the cells—such as toxic chemicals or bacteria-laden air—the monitoring equipment detects changes in the cells' electrical activity. An onboard microprocessor registers the disturbance and sounds the alarm.

After years of the hype and sound bites that have typically characterized the field of MEMS research, Kovacs is pleased to report that real systems are now starting to be demonstrated in rigorous ways. "The upside of this field is huge," he says. But Kovacs is quick to point out that despite very real progress, obstacles remain. In particular, researchers must address the issue of getting bioMEMS to interact in living environments where proteins are sticky, blood often clots, and bodies tend to surround implants with protective tissue. And scientists need a greater understanding of the biocompatibility of the materials in MEMS before any of our blood vessels or organs are retrofitted with microhardware. Yet with each advance, the scenario in *Fantastic Voyage* moves closer to science than fiction. SA

About the Author

DAVID VOSS is a freelance writer based in Silver Spring, Md. He dreams of having intelligent agents to research his articles and a flock of nanorobots to do the writing, leaving him more time to spend on the beach.

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