market. Not only would they have to wind their way through clinical trials and regulatory approval, they would have to come down in cost, too. Affymetrix chips can run anywhere between $45 and $850, not to mention the scanners and fluidics stations that go with them, which can cost more than $100,000. "To be viable [for diagnostics], the cost needs to come down to about $5," says Stanley Abromowitz of the National Institute of Standards and Technology. CMS's Kayyem says that his company's electronic detection scheme has a shot at making low-cost readers. But for now, the company has only a prototype device.

That's why Klyne and others argue that the initial breakthrough market will consist of genomics and pharmaceutical companies, which will use DNA arrays as a research tool to sift through the complex patterns of gene expression in cells and pinpoint particular genes that are turned on in disease. That's the approach being taken by MPM and its rival, diaDexus of Santa Clara, a joint venture between the big drug firm SmithKline Beecham and Incyte. DiaDexus, for example, has already used its arrays to show that prostate cancer cells crank out a protein called PLA2, while the same gene remains dormant in healthy cells. MPM researchers, meanwhile, have shown that melanoma cancer cells turn up production of a protein called melastatin. Both companies hope to turn these insights into new and improved diagnostic screens that would rely not on arrays themselves but on conventional and cheap techniques such as enzyme assays.

Other basic research with arrays is also beginning to pay off. In 1996, Collins and colleagues at NHGRI used Affymetrix chips to detect mutations in the familial breast cancer gene *BRCA1* in subjects at risk for the disease. Upstairs from Collins's lab, Jeffrey Trent and his colleagues are gauging, with their own array system, how radiation treatment affects gene expression in cancer cells.

What's certain is that these studies are just a taste of what is to come. Already, researchers with access to DNA arrays find themselves with an enviable problem: too much information. "We are drowning in cool data here," says Stanford array pioneer Pat Brown, whose team has made more than 7 million measurements of the expression of individual genes under different conditions. "More than 99% of the data we have is unpublished. It's so easy to think of an interesting experiment to do using this approach [that] we haven't been able to find the time to publish it all." –ROBERT F. SERVICE

FUTURE CHIPS
▶LABS ON A CHIP

Coming Soon: The Pocket DNA Sequencer

Microfluidics, chips that process tiny volumes of fluids rather than electronic signals, aim to put a whole lab in the palm of your hand

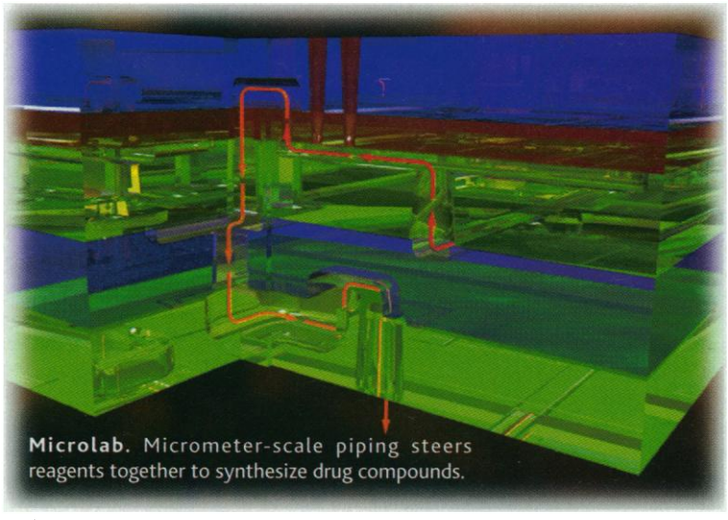
In May, a new private venture declared its aim to sequence nearly the entire human genome in 3 years for as little as $300 million. The plan beat the U.S. government's timetable by 4 years, at a tenth of the cost, and encouraged the government to move up its own genome deadlines. Leaders of the new venture, headed by genomics pioneer Craig Venter and funded by instrument maker Perkin-Elmer, hailed miniaturization—small, automated DNA sequencers—as the key. But the miniaturization behind this project is only a first step in the downsizing of the analytical laboratory.

The Venter project will replace conventional manually controlled DNA sequencers with machines that perform the same task nonstop, inside hair-thin capillaries the length of a knitting needle. But researchers at a handful of universities and companies hope to shrink sequencing equipment much further—all the way down to postage stamp–sized microchips etched with a maze of tiny channels and reaction chambers. Because these chips can be mass-produced with a technology similar to that used for silicon-based computer chips, they stand to push down drastically the price of DNA sequencing and, if used in quantity, speed up such sequencing too. And DNA sequencers are just one of the labs on a chip now in gestation.

A new breed of chipmaking companies is working to shrink to pocket size all types of chemistry equipment, including high-pressure liquid chromatography assays, high-throughput drug-screening systems, portable environmental screening equipment, biological weapons detectors, and even chemical production plants (see sidebar on next page). Harking back to the microelectronics revolution, researchers refer to these chips as "microfluidics" and expect them to have some of the same impact as the earlier development. "What will happen to laboratory equipment in the future is the same thing that happened to mainframe computers," says Wally Parce, research director for Caliper Technologies, a microfluidics company in Palo Alto, California.

Just as electronics miniaturization has led to computer-controlled home appliances and children's toys, Parce and others believe that the miniaturization of chemical equipment will lead to a host of as-yet-undreamed-of applications. "I even have folks at [NASA's Jet Propulsion Laboratory] who want to send [our microsystems] to Mars," says Rolfe Anderson of the biochip start-up Affymetrix in Santa Clara, California.

At present, however, these labs on a chip owe most of their appeal to their potential for doing the same job as existing equipment at a much lower cost. Current DNA sequencing, for example, requires a half-dozen tabletop machines to separate DNA from a tissue sample, select the desired fragment for analysis, amplify it, and sequence its component nucleotides—all at a high cost in technicians' salaries and in reagents. With microfluidics, both of those costs come down considerably. "The entire budget just falls



Microlab. Micrometer-scale piping steers reagents together to synthesize drug compounds.

CREDIT: ORCHID BIOCOMPUTER

off the scale," says geneticist David Burke of the University of Michigan, Ann Arbor. On page 484 of this issue, he and his colleagues describe a DNA analysis chip that uses just nanoliter volumes of reagents (about 100-fold less than what current sequencers use) and integrates the functions of all the different tabletop machines in a single device. These chip-based devices can't yet do the actual base-by-base sequencing of the larger machines. But then again, notes Burke, the field is just getting started.

In any case, the potential for microfluidics to work quickly and save money is beginning to draw a crowd. "It's a field that's moving very fast right now," says Barry Karger, a microfluidics expert at Northeastern University in Boston. Spurred by market forecasts ranging from $1 billion to $19 billion for the new devices, a bevy of start-up companies—including Caliper, Aclara BioSciences, Orchid Biocomputer, and Affymetrix—has jumped into the ring. Even established chip- and instrument-makers are getting involved, including Perkin-Elmer, 3M, Motorola, Packard Instruments, and Hewlett-Packard. "It's going to be a tremendous market out there in 4 or 5 years," says Ron Nelson, who heads research at Motorola in Phoenix, Arizona.

Small is beautiful

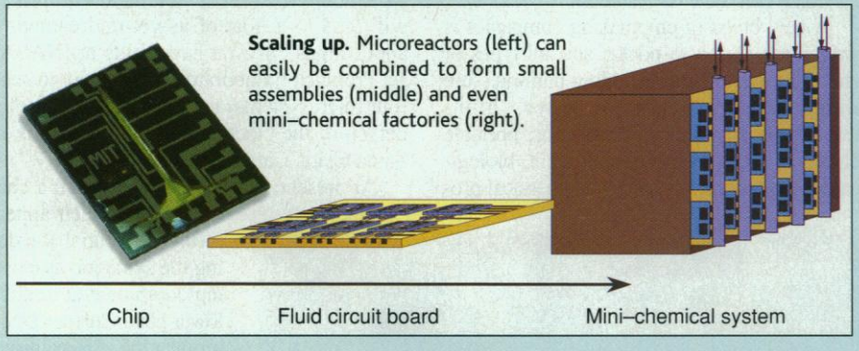
Microfluidics don't look much different from the integrated circuits at the heart of computers. In fact, most are made in a similar fashion, starting with sheets of very thin glass, silicon, or plastic. Photolithography machines carve out a series of complex, narrow channels that carry fluid to larger openings where individual reactions take place. The product of one reaction is then pumped further down the chip, mixed with more reagents, and allowed to react again.

Miniaturization Puts Chemical Plants Where You Want Them

Just before midnight on 2 December 1984, the Indian city of Bhopal became the site of the biggest industrial accident in world history. A cloud of toxic methylisocyanate (MIC) gas escaped from a pressurized tank at a Union Carbide chemical factory. More than 2000 people died immediately and thousands more later on, while tens of thousands continue to suffer breathing problems and other illnesses as a result.

MIC, a highly reactive compound, was stockpiled at the plant for use in creating the pesticide carbaryl. Shipping and storing hazardous intermediate compounds are routine in the chemical industry, because not every ingredient in a process can be made on site. But physicist Jim Ryley and his colleagues hope to do away with this practice.

Ryley's team, at DuPont's central research facility in Wilmington, Delaware, is developing tiny microchip-based chemical reactors that could be installed wherever a chemical such as MIC is needed, eliminating the need for stockpiles. Much like other "microfluidic" chips (see main text), these tiny reactors are typically just centimeters in size and etched with a series of micrometer-sized channels, valves, and chambers. Because they are often made with the same microfabrication techniques as those used in the computer-chip industry, they have the potential to be both cheap and small, making it easy to scale production up or down as needed. Portability, says Ryley, "lets you make your hazardous chemicals at their point of use."



Scaling up. Microreactors (left) can easily be combined to form small assemblies (middle) and even mini–chemical factories (right).

At the time of the Bhopal disaster, no one had dreamed that you could carry out complex chemical synthesis in a device the size of a compact disc. But nearly a decade later, in 1993, the DuPont team members took advantage of microelectronics technology and the chemical inertness of silicon to make one of the first chemical plants on a chip. They demonstrated that they could synthesize MIC in a three-layer microreactor assembled from a trio of the standard silicon wafers (100 millimeters in diameter) used to make computer chips. The precursor gases oxygen and monomethylfomamide were mixed together in channels etched in the top layer, before passing down to the middle layer; there, they were preheated to about 300 degrees Celsius with a heat-exchange liquid that carried waste heat from the final-stage reaction. Last, in the bottom layer, the hot gases hit a silver-based catalyst and reacted to create MIC. Such a reactor, they calculated, could churn out 18,000 kilograms of MIC a year.

The DuPont team has produced chips to synthesize other compounds as well, such as hydrogen cyanide, a toxic intermediate compound used in drug synthesis. And although the field of microchemical reactors is still in its early stages, several other groups are also exploring the technique to create everything from specialty compounds used in drug synthesis to fuels.

At the Pacific Northwest National Laboratory in Richland, Washington, for example, Robert Wegeng and his colleagues have already built miniature heat exchangers and chemical separations devices; among other projects, they are currently working to build a miniaturized fuel reformer to extract hydrogen from gasoline to power automobile fuel cells. And at the Institute of Microtechnology in Mainz (IMM), Germany, Wolfgang Ehrfeld and his colleagues have focused on devices that can oxidize numerous compounds, such as converting alcohol-based precursors to aldehydes, widely used in food flavorings and perfumes.

For those reactions, the microreactors have advantages that go beyond low cost and portability, says IMM microreactor expert Claudia Gärtner. Oxidation reactions generate such large amounts of heat that industrial reactors are often run well below their optimum temperature, to prevent the development of hot spots that cause unwanted side reactions and to stop the main reaction from spinning out of control. "Microreactors have a large surface-to-volume ratio," says Gärtner. So heat that builds up is quickly transferred to the walls of the chip, where it can be conducted away.

Still, Ryley cautions that microchips have their limits when it comes to chemical synthesis. One problem, he says, is control. Running a single large-scale reactor is fairly straightforward: You need only one set of control valves, circuitry, and sensors to monitor the reaction. But when you string 10 or 100 microreactors together, "you have one very large control problem," says Ryley. Chip-based reactors also don't make sense for producing commodity chemicals—such as adipic acid, involved in making nylon—that are used by the trainload.

"Clearly you're not going to replace all large reactors," says Klavs Jensen, a microreactor expert at the Massachusetts Institute of Technology. Perhaps not. But the chemical industry is sure to find niche applications for these factories on a chip, and preventing future Bhopals may turn out to be one of them. **–R.F.S.**

CREDIT: KLAVS JENSEN/MIT PHOTO: FELICE FRANKEL/MIT

The effort to make labs on a chip has been under way for several years (*Science*, 7 April 1995, p. 26). Past efforts showed it was possible to etch tiny systems of channels and valves on chips to control the flow of liquids and run reactions. But a number of researchers remained skeptical that the complexity of many chemical processes could ever be handled by such micromachines. Sequencing DNA, for example, requires several steps, all needing different equipment and chemical reagents and reaction conditions. "Early on, we were asking whether all this integration was possible," says Jed Harrison, a analytical chemist and chipmaker at the University of Alberta in Edmonton.

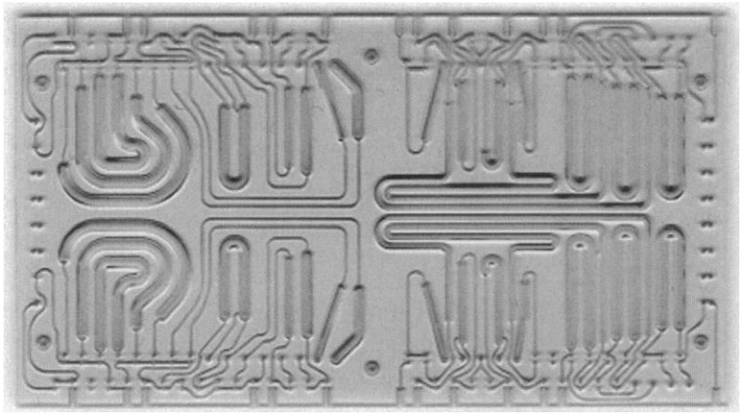
Today, the picture has changed, says Harrison. "Not only is it possible, but it's being done." At Affymetrix, Anderson and his colleagues jumped into the field 3 years ago in an effort to prepare nucleic acid samples for the company's microarray tests, in which unknown DNA or RNA strands are identified by allowing them to bind onto chip-bound DNA fragments (see p. 396). At a meeting last year, Anderson reported one of the most complex microfluidics instruments to date. At its heart is a plastic cartridge smaller than a credit card which, when plugged into a workstation that provides the needed reagents, carries out seven different processes to extract DNA from blood; amplify, prepare, and dilute it; then send it to the DNA array.

To use the system, researchers start by mixing a blood sample with a salt compound that breaks open the cells and releases the DNA. This mixture is then injected into a storage chamber on the chip, and its computer-controlled system takes over from there. The chamber contains a tiny glass wall that uses a charge interaction to bind the sample's nucleic acids, while the rest of the sample is ejected. Then three separate samples of an ethanol and water mixture wash into the chamber to rinse the DNA. Another buffer solution is then piped in to release the DNA from the glass and carry it to a neighboring chamber, where it's combined with a cocktail of enzymes and other reagents piped in from an adjacent storage alcove. This mixture is then sent on to the next chamber, where the genetic material is amplified. During this step, a tiny heater pressed against the back of the chamber provides the cycles of hot and cold needed to carry out the reaction. Additional steps then convert the DNA to RNA, slap on numerous fluorescent tags, chop up the RNA, and combine it with a buffer, before sending it on to the DNA array.

The key to the system, says Anderson, is a strategy for moving fluids around on a chip with pressure-backed air bubbles and strategically located membranes that allow air bubbles to pass through but halt liquids in their tracks. "We're able to move fluids around at will, position them in different chambers, and control the temperatures of different reaction chambers independently. When you have all that, you can do lots and lots of things." The Affymetrix chip is "very impressive," Harrison says. "If it works, it will be a major sales item, because it will eliminate all the different fluid-handling steps needed just to prepare a sample for analysis."

When speed counts

Piling as much complexity as possible into one device isn't the only way to go. Other companies are churning out simpler chips that perform just one or two reactions very quickly, and often in parallel. Here, the driving force is coming from the drug industry, which is facing the challenge of screening the vast numbers of drug candidates made by combinatorial chemistry, a scheme that links a handful of chemical building blocks together in all possible combinations.



Tortured path. This credit-card-size chip handles seven separate reactions.

CREDIT: ROLFE ANDERSON/AFFYMETRIX

Several microfluidics companies and pharmaceutical firms are working on chip-based drug-screening systems capable of analyzing thousands of drug candidates at once. Caliper, for example, is developing glass and plastic chips that use electric fields to steer different drug compounds along a drug-testing assembly line, in which drugs are combined with their targets and allowed to react, and the results monitored. "For the most part, we are trying to take the conventional assays used in the drug industry and put them on a chip," says Caliper's Parce.

They are certainly not alone. Aurora Biosciences of San Diego, California, has teamed up with SmithKline Beecham and other big pharmaceutical companies to create its own fluidic devices, capable of screening 3456 compounds at once in tiny microwells. And other companies, such as Aclara BioSciences of Hayward, California, and PerSeptive Biosystems of Framingham, Massachusetts, are also working on related systems.

Meanwhile, researchers at Orchid Biocomputer in Princeton, New Jersey, are aiming to take a somewhat different path: Rather than carrying out a series of complex reactions on a small number of samples (like Affymetrix) or thousands of simple reactions (like Caliper), they're looking to run numerous ones of moderate complexity in parallel. One Orchid project, for example, aims to synthesize numerous analogs of a drug compound all at once—in effect, combinatorial chemistry on a chip.

Orchid's chips look something like chemical factories shrunk down to credit card size, complete with internal piping, conduits, and reaction chambers. Electric fields and pressure send reagents through a series of channels laid out in rows and columns. Near the intersections, valves then open and close to carry these reagents down to a reaction chamber located on another level of the chip. Inside each chamber, the reagents react on the surface of a tiny plastic bead to create the first building block of a newly forming drug candidate. Leftover reagents are piped away, and new reagents are sent into the reaction chambers to continue the process. At the end of the synthesis, the newly minted drug candidates are cleaved from the beads and tested offchip for activity. Already, the company has built 2.5-centimeter-square chips containing 144 minireactors to synthesize compounds simultaneously. And Dale Pfost, Orchid's chair and chief executive, says the company is currently working on 10,000-chamber systems for its partner, SmithKline Beecham.

Which—if any—of these miniaturization strategies will succeed commercially is still uncertain. Remaining challenges include loading tiny samples onto chips and ensuring that they contain a representative mixture of compounds in a starting sample. But microfluidics are improving rapidly, say Harrison and others, because they are building on the foundations of the stunningly successful microelectronics industry. The huge accumulated expertise in etching tiny patterns in ceramics and mass-producing chips gives these little labs a big advantage that competing technologies just don't have.

–ROBERT F. SERVICE