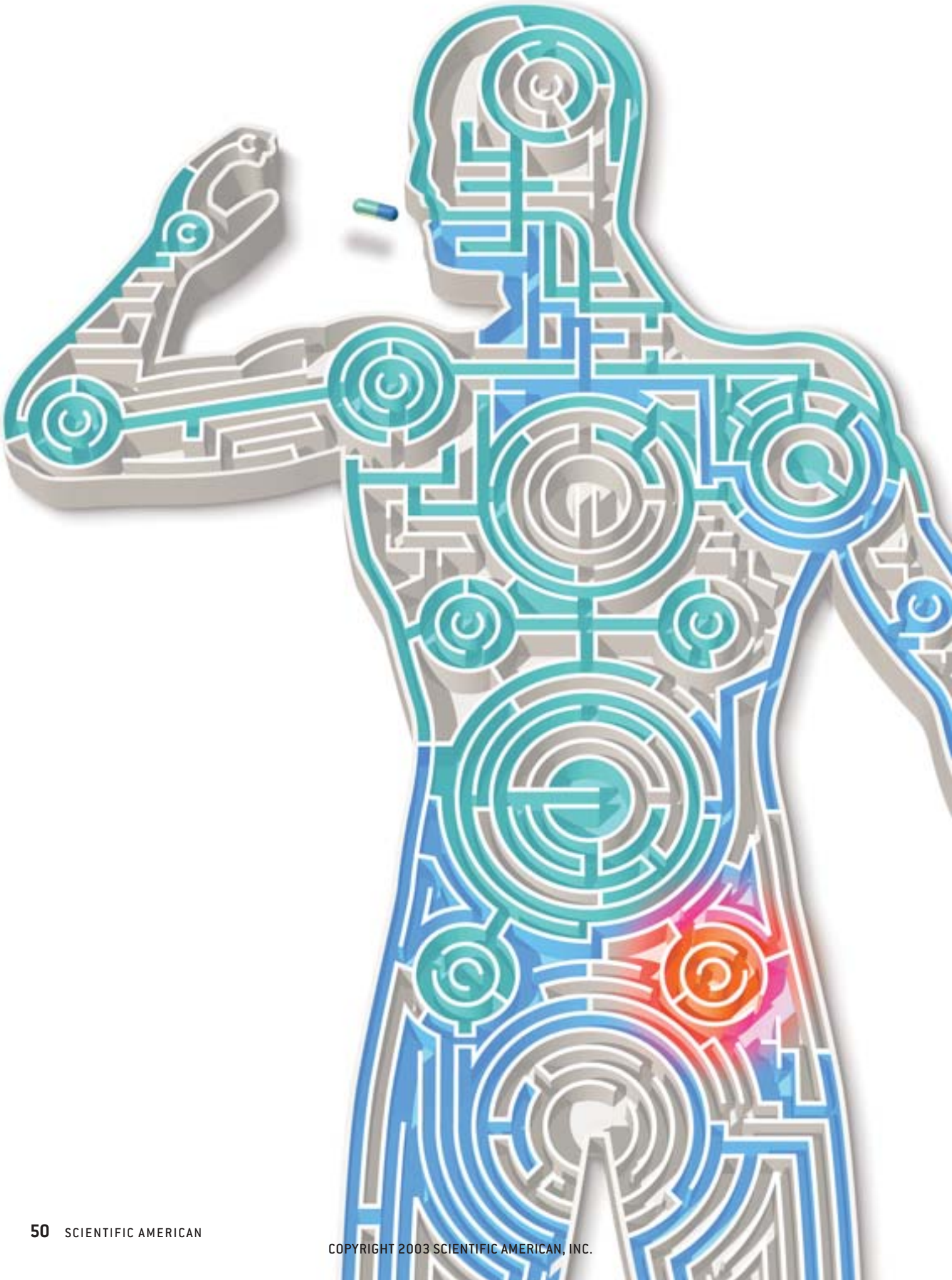


By Robert Langer

ILLUSTRATIONS BY SLIM FILMS

How to get drugs where they need to go

Where a Pill Won't Reach

From the point of view of a drug, it's a long trip

from the pill bottle to an ache or the site of an infection.

After someone swallows a medicine, the chemical must traverse a veritable maze. It has to survive a journey through the stomach and reach the intestines intact before crossing the intestinal wall into circulation. Once in the blood, it gets filtered through the liver before it can travel to the rest of the body. At each "way station," the compound must resist the acids of digestive juices, jump membrane barriers or fend off enzymes designed to chop it into useless bits.

Pharmaceutical makers have come up with various solutions to help certain medicines on the market today surpass these obstacles; however, these approaches do not work for many other drugs. One strategy, for instance, coats pills with a shell that is insoluble in stomach secretions but that dissolves readily once it hits the more alkaline environment of the small intestine. But if a drug is made of protein—as most agents produced using biotechnology are—it also has to evade the activity of protein-destroying enzymes called proteases. Packaging pills with their own bodyguards (in this case, molecules called protease inhibitors) could enable protein-based drugs to survive, but it would not aid them in crossing the gut lining; they are too big to slip into the blood as easily as more typical drugs, which generally consist of small molecules. Coatings also have a limited ability to control a drug's pharmacokinetics—the rate at which it enters circulation and the time it persists in the body's tissues and organs. A drug can be toxic if it gets into the bloodstream too quickly at high concentrations or if it sticks around too long; conversely, it can be ineffective if a protracted delay occurs before it begins circulating.

Injecting a drug avoids the obstacles posed by the stomach and the intestinal tract, but many patients are understandably reluctant to give themselves shots repeatedly or to visit a doctor every day. Accordingly, scientists have sought a better way. Over the past two decades a spate of alternative drug delivery systems have been designed: sales of drugs administered by patch, implant, long-acting injection, topical gel, controlled-release pill, or nasal or lung spray now exceed $20 billion a year in the U.S. alone. Two notable examples approved recently by the Food and Drug Administration are Nutropin Depot—injectable, degradable polymer microspheres that secrete human growth hormone for up to four weeks between shots—and Gliadel, a wafer that can be implanted into the brain to administer chemotherapy directly to brain tumors. Already available in Europe and coming soon in the U.S. will be polymer-coated, drug-releasing stents, which so far have shown remarkable results in keeping blood vessels open after a clot-clearing procedure called angioplasty.

Indeed, scientists have been exploring nearly every part of the body—the skin, the nose, the lungs, as well as the intestine—as portals for introducing drug payloads. In the process, they have devised noninvasive ways to deliver complex molecules, such as using ultrasound to blast drugs through the skin painlessly. They have also combined advances in nanotechnology and microfabrication to make implantable microchips that can deliver drugs precisely and on schedule.

Overview/*Drug Delivery*

- Many drugs—especially the protein-based pharmaceuticals made using biotechnology—are broken down quickly if taken orally.
- Accordingly, researchers are developing new means of administering medicines, including wearable devices that use pulses of electricity or ultrasound to drive drugs through the skin painlessly.
- The future promises implantable microchips that deliver drugs in preprogrammed doses and that communicate with computers in physicians' offices.

Breaching the Wall

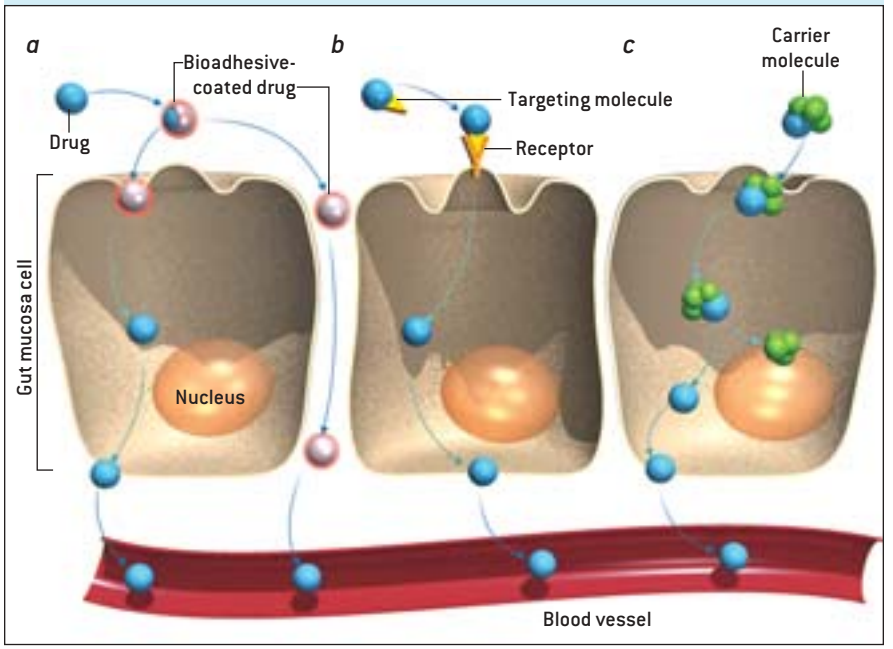
A VARIETY OF GROUPS have been using the new technologies to solve the problem of penetrating the intestinal wall. Edith Mathiowitz of Brown University and her colleagues, for example, have developed a way to entrap proteins in extremely tiny blobs of a gluey substance called a bioadhesive, which can penetrate through and between intestinal cells. The concept of using bioadhesion to enable orally administered drugs to attach to mucous membranes had its origins in work conducted in the 1970s and 1980s in the laboratories of Tsuneji Nagai of Hoshi University in Tokyo, Joseph R. Robinson of the University of Wisconsin–Madison and Nicholas A. Peppas of Purdue University (he is now at the University of Texas at Austin). Until 10 years ago the

GETTING PAST THE GUT

HURDLES: Digestive acids and enzymes degrade drugs before they can reach their targets; drugs have difficulty piercing the intestinal wall

SOLUTIONS: (*a*) Coat drugs with bioadhesive polymers that bind to the gut lining and squeeze between cells; (*b*) link drugs to targeting molecules that home in on receptors on intestinal cells that allow the drugs to be taken up; (*c*) attach drugs to carrier molecules that escort them into cells

SOME COMPANIES WORKING ON THE PROBLEM:
Biotech Australia, Roseville, New South Wales
Emisphere Technologies, Tarrytown, N.Y.



Scientists have been exploring nearly every part of the body—the skin, the nose, the lungs, as well as the intestine—as portals for introducing drug payloads.

most promising bioadhesive polymers seemed to be water-loving plastics called hydrophilic polymers and hydrogels. From these early studies, researchers inferred that the most "wettable" polymers—those with the highest concentrations of carboxyl groups—were the materials of choice for bioadhesion. Although they would stick to the intestinal mucosa, however, they did not penetrate it very well, and they released the protein too quickly.

In 1997 Mathiowitz found that hydrophobic (water-repelling) bioadhesive polymers called polyanhydrides, which expose carboxyl groups on their exteriors as their surfaces erode, can bind to the gut lining just as well as hydrophilic polymers but can cross the intestinal mucosa and enter the bloodstream more readily. One polyanhydride in particular—poly(fumaric-co-sebacic anhydride)—showed greater adhesive forces than any other material tested. The technology is now being explored to make a form of insulin that can be given orally. (Many new drug delivery approaches focus on insulin because it is a protein that must be injected regularly by people with type 1 diabetes.) In animal tests, the polyanhydride shows promise with both hydrophilic and hydrophobic proteins.

Peppas and his co-workers have also developed polymers that are not only bioadhesive but swell in response to a pH change. They are able to protect a protein drug such as insulin from the acidic pH of the stomach and then release it in the more alkaline pH of the intestine. The polymers are also able to protect the protein from proteases in the upper small intestine and can temporarily open the connections between intestinal cells, allowing the protein to pass through.

Another strategy to deliver protein-based drugs orally is to encase them in carrier molecules that can ferry them across the gut lining. Emisphere Technologies in Tarrytown, N.Y., has developed a series of molecular carriers that appear to squeeze proteins to make them smaller so they can cross cell membranes more readily. Once the carrier does its job of getting the drug inside a cell, it breaks away and allows the protein to spring back into its native—and therefore active—form. Emisphere is testing the strategy to administer insulin to diabetics and to deliver the blood-thinning protein heparin to people undergoing hip-replacement surgery, who sometimes experience blood clots.

Other scientists have been working to couple drug proteins to molecules that target specific receptors in the gastrointestinal tract. One of the early examples is the work of Gregory J. Russell-Jones of Biotech Australia in Roseville, New South Wales, who exploited the fact that cells in the intestine use receptors to grab vitamin B12 and transport it through the gut wall. He found that by linking a pro-

tein to vitamin B12, he could trick the vitamin receptors into taking up the protein as well as the vitamin. But there are only so many vitamin B12 receptors in the gut, and they might not be abundant enough to drag a given protein drug into the blood in the amounts needed for a therapeutic effect. Other scientists are now looking to harness lectins—plentiful, sticky molecules that constitute part of the connective tissue between intestinal cells—or other substances to do the job.

Patching It Up

THE INTESTINE is a fairly direct route to the bloodstream, but the skin is much more accessible. Although skin can be a relatively impermeable barrier, a few drugs have just the right physical and chemical characteristics to cross it at reasonable rates. Transdermal patches that last up to seven days are now on the market: nicotine to help people stop smoking and estradiol (estrogen) to counter the symptoms of menopause or to act as part of a contraceptive [see "Potent Patches," Working Knowledge, page 92].

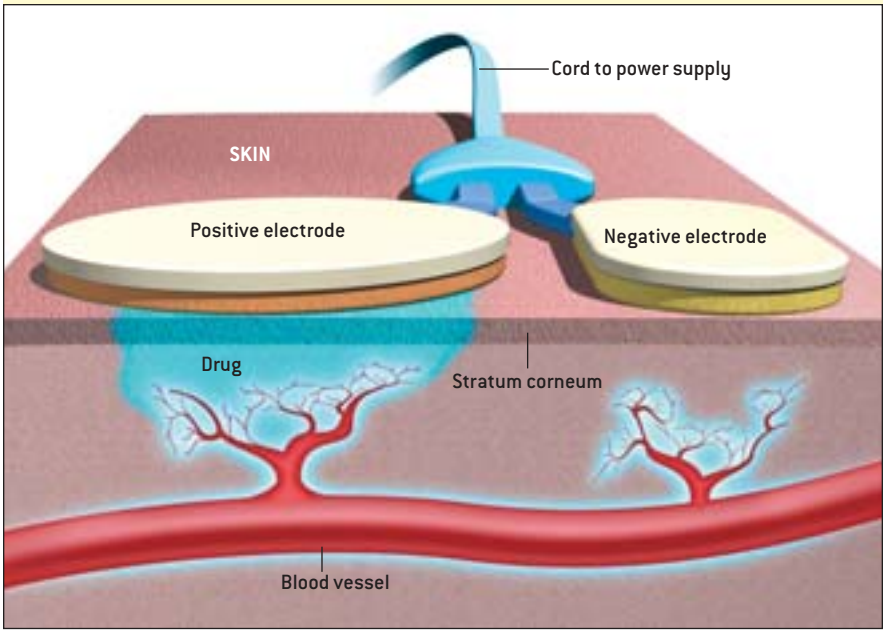
Passing a small, direct electric current through the skin can make the epidermis permeable to many other drugs—including proteins. Scientists at ALZA in Mountain View, Calif., and at Vyteris, a spinoff of Becton Dickinson based in Fair Lawn, N.J., are independently conducting advanced clinical trials using the technique, known as iontophoresis. In general, iontophoresis employs two patches—one negatively charged and one positively charged—that are linked to a reservoir of a given drug. A painless pulse of electricity can drive drugs, which tend to be charged, through the impermeable outer layer of the epidermis and into the blood vessels of the dermis. Vyteris, for example, has applied for FDA approval to market its iontophoresis system to deliver the painkiller lidocaine. The system's battery source is small enough to wear underneath clothing. The company is planning clinical tests of its device's ability to administer daily doses of parathyroid hormone to patients with osteoporosis or pulses of gonadotropin-releasing hormone every 90 minutes to women preparing for in vitro fertilization procedures.

PENETRATING THE SKIN

HURDLES: Tough stratum corneum (skin's outer layer) blocks drug entry; large molecules have difficulty crossing the epidermis to the blood vessels in the dermis

SOLUTIONS: Iontophoresis (*below*) uses painless pulses of electricity to make skin permeable; ultrasound employs sound waves that temporarily make tiny channels in the stratum corneum

SOME COMPANIES WORKING ON THE PROBLEM:
ALZA, Mountain View, Calif.
Sontra Medical, Cambridge, Mass.
Vyteris, Fair Lawn, N.J.



Ultrasound has also been harnessed to enhance skin permeability. Joseph Kost—a former postdoctoral fellow and visiting scientist in my laboratory and now a professor at Ben-Gurion University in Israel—discovered that ultrasound can temporarily disorder the skin's outermost layer, the stratum corneum, the principal barrier to drug diffusion. My M.I.T. colleague Daniel Blankschtein, Samir Mitragotri, a former graduate student in my lab, and I have used ultrasound to increase up to 5,000 times the ability of proteins the size of insulin to diffuse through the skin. Sontra Medical in Cambridge, Mass., which I co-founded and where Kost is chief scientific officer, is testing the technique for administering insulin and pain medications. The ultrasound device uses a short (15-second) burst of energy

THE AUTHOR

ROBERT LANGER is Kenneth J. Germeshausen Professor of Chemical and Biomedical Engineering at the Massachusetts Institute of Technology. He is also a director of a number of companies, including Sontra Medical and MicroCHIPS. In 2002 he received the Charles Stark Draper Prize, which is considered the equivalent of the Nobel Prize for engineering. In 1998 he was granted the Lemelson-M.I.T. Prize for being "one of history's most prolific inventors in medicine." Langer is one of the few individuals to have ever been elected to all three of the U.S. national academies: the Institute of Medicine, the National Academy of Sciences, and the National Academy of Engineering.

much weaker than that employed for diagnostic imaging to make the skin more permeable in a particular spot for up to 24 hours. The ultrasonic horn of the handheld device vibrates at 55,000 cycles a second (55 kilohertz) in a liquid medium coupled to the skin. The low-frequency ultrasonic energy creates tiny bubbles that expand and contract in the coupling medium and in the cell membranes of the stratum corneum, in effect drilling temporary miniature channels through which drugs can enter.

Inhaling the Future

LUNG DELIVERY represents another important opportunity and challenge—whether for treating lung conditions or for administering a drug to the bloodstream quickly to treat diseases elsewhere in the body. The lungs consist of microscopic sacs called alveoli that are linked directly to blood vessels. During breathing, oxygen enters the blood through the alveoli, and the waste product carbon dioxide exits. A similar process can also admit aerosols of larger molecules, such as protein-based drugs. It has been difficult, however, to design inhaler devices that can produce a sufficient number of aerosol particles small enough to penetrate deeply into the lung, without wasting the drug. (Most conventional inhalers, such as those used to treat asthma, deliver less than 10 percent of their contents.) Immune cells in the lung called macrophages can also clear most drugs rapidly.

A variety of researchers and companies are now working on improved inhaler designs that administer extremely fine mists in an efficient manner. One such inhaler, developed by Aradigm in Hayward, Calif., for liquid formulations, pushes a given drug through small nozzles that can be preprogrammed to deliver particular doses. Another approach, developed by Nektar Therapeutics (previously called Inhale Therapeutic Systems) in San Carlos, Calif., can generate an aerosol cloud from a dry powder by compressing air into it and breaking it into tiny particles capable of reaching the deepest areas of the lung. Both companies are now testing their devices in diabetics to deliver insulin without the need for injections.

Until the mid-1990s, however, scientists paid little attention to the aerosol particles themselves. At that time, David A. Edwards, who was then a postdoctoral fellow in my lab (he is now a professor at Harvard University), began to think of ways to design better aerosol mists. He reasoned that by dramatically lowering the density of aerosol particles while increasing their size and porosity, he might reduce the tendency of the particles to aggregate, thus enabling them to enter the lungs through an air stream produced by an extremely small, simple inhaler. Consider the difference between wet basketballs, for example, and wet grains of sand. The former have essentially no propensity for sticking together,

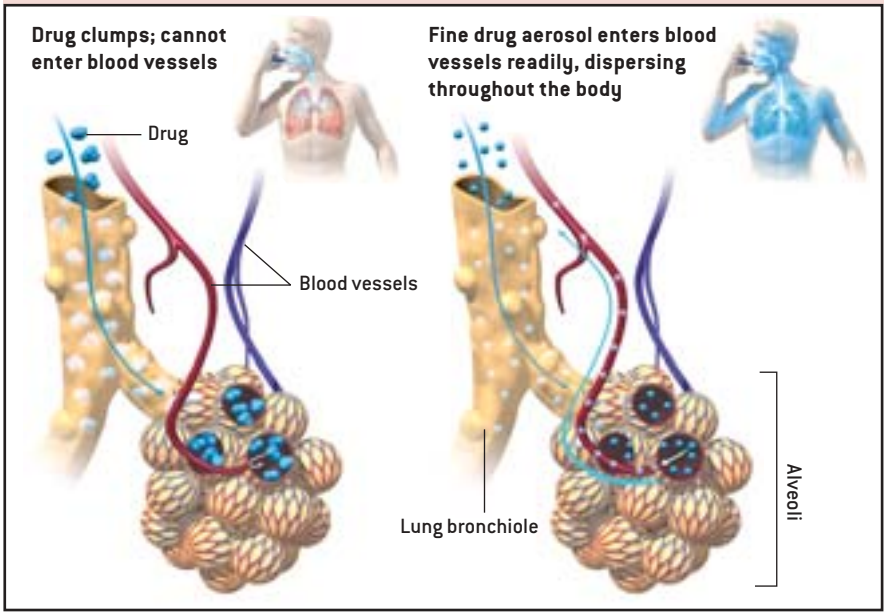
A painless pulse of electricity can drive drugs, which tend to be charged, through the outer layer of the epidermis and into the blood vessels of the dermis.

ENTERING THE LUNGS

HURDLES: Penetrating the air sacs, or alveoli; avoiding destruction by immune cells called macrophages

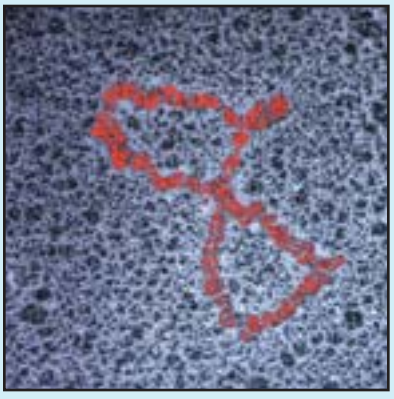
SOLUTIONS: Optimize the size of aerosol particles (liquid or powder) so they can reach deep into the lungs; prevent the aerosol particles from sticking together so they can form a fine mist

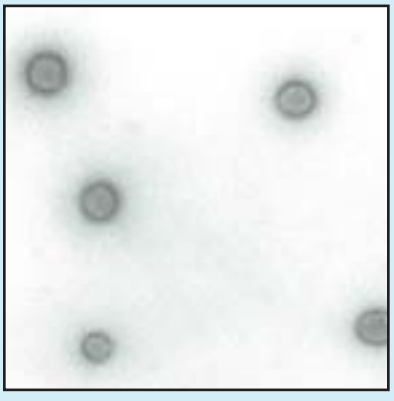
SOME COMPANIES WORKING ON THE PROBLEM:
Alkermes, Cambridge, Mass.
Aradigm, Hayward, Calif.
Nektar Therapeutics (formerly Inhale Therapeutic Systems), San Carlos, Calif.



Delivering Genes

Gene therapy depends on ferrying new genetic material into body cells





CIRCLET OF DNA, called a plasmid (*top*), must enter a cell and begin functioning to be an effective gene therapy. Most gene therapy tests in people have used viruses to introduce genes into body cells, but they have raised safety questions. Researchers are now looking to package plasmids in cages of polymers (*bottom*) that are readily taken up by cells.

As the noted biologist Inder M. Verma of the Salk Institute for Biological Studies in San Diego has stated, there are three challenges in gene therapy: delivery, delivery, delivery. To introduce a new gene into the body, scientists must condense the corresponding DNA into small packages that can be taken up by a cell. But that is not all: they must also protect the gene from the cell's destructive enzymes, deliver it to the nucleus and release it in active form. For years, scientists have harnessed viruses as vectors, Trojan horses that sneak foreign genes into cells. But even viruses that have been disabled carry risks, as the tragic death in 1999 of gene-therapy trial volunteer Jesse Gelsinger made all too clear.

As researchers work to understand and reduce the risks of viral vectors for gene therapy, they are also devising alternative means for delivering genes that are based on polymers or on fatty molecules called lipids. One interesting approach, developed by Mark E. Davis of the California Institute of Technology, involves polymers named cationic, or positively charged, B-cyclodextrins (CDs).

Davis chose CDs because they are relatively nontoxic, do not elicit an immune response and are soluble in water. He originally intended to package DNA for gene therapy into nanometer-size particles of CDs alone but found that this simple combination was unstable when administered to animals. So Davis and a graduate student, Suzie Hwang Pun, came up with the idea of altering the surface of the CD particles by adding adamantane-conjugated polyethylene glycol (PEG). The modification generates uniformly sized nanoparticles of CDs and DNA that resist clumping into useless aggregates with proteins in the blood serum.

"Decorating" the surfaces of the particles with the PEG compound also provided Davis and Pun with chemical hooks for attaching other molecules that could lead the particles to home in on, and deliver their genes to, specific types of cells. Insert Therapeutics in Pasadena, Calif.—which Davis founded and where Pun now works—is testing whether these targeted complexes can help treat various cancers and liver disease.

Specialized polymers are also being developed as gene therapy vectors by David M. Lynn of the University of Wisconsin–Madison. Lynn, who was a postdoctoral fellow in my laboratory at the Massachusetts of Technology, has synthesized sets, or libraries, of biodegradable cationic polymers called polyaminoesters. Along with Daniel Anderson, another postdoc in my lab, and David Putnam, who is now at Cornell University, Lynn has made hundreds of such polymers and has devised screening tests to identify the most useful ones according to how readily they can bind to DNA, how soluble they are in blood serum and how well they enter, or transfect, cells. Using this method, the researchers have found a number of polymers that can transfect cells more efficiently than the standard nonviral vectors lipofectamine and polyethylenimine.

Fred E. Cohen of the University of California at San Francisco has also employed the library approach. In collaboration with Ronald Zuckerman of Chiron in Emeryville, Calif., Cohen has synthesized a new class of polymers called peptoids or (more technically) cationic *N*-substituted glycine oligomers. Some of these can condense DNA into particles of between 50 and 100 nanometers in size that are capable of transfecting cells.

Lipids are also useful for delivering gene therapy, according to Sung Wan Kim of the University of Utah. Kim wraps a particular gene to be administered in a sheath of stearyl polylysine and then coats it with low-density lipoprotein. In studies using rabbits, he and his co-workers have employed this system to deliver the gene that encodes vascular endothelial growth factor (VEGF) to heart muscle damaged by a lack of oxygen (a condition called ischemia), as can occur when blood vessels are blocked. Kim plans to begin testing the approach next year in patients with ischemic heart disease. The hope is that the introduced VEGF gene will spur the growth of new blood vessels to bring oxygen and nutrients to starved areas of the heart muscle. —*R.L.*

J. L. CARSON *Custom Medical Stock Photo (top)*; MARK E. DAVIS AND SUZIE HWANG PUN *California Institute of Technology (bottom)*

"Smart" drug delivery systems would detect chemical signals in the body and release drugs in response to such signals.

whereas the latter cling together readily.

By making the aerosol particles larger, Edwards thought he could also decrease their uptake by lung macrophages, which tend to engulf smaller particles and to destroy drugs. Edwards and other scientists in our respective laboratories have shown that a single inhaled dose of insulin formulated in a large-particle aerosol can last up to four days in the lungs of animals. This approach is now being tested in humans by Alkermes, a company based in Cambridge, Mass.—in conjunction with pharmaceutical firms such as Eli Lilly—using several different drugs.

Intelligent Microchips

LOOKING FURTHER ahead, I see "smart" drug delivery systems as particularly exciting. These would detect chemical signals in the body and release drugs in response to such signals, keeping the concentration of a drug in the body at a desired therapeutic level.

A number of years ago, while I was watching a television program about how silicon chips for computers were made, I realized that the same technology might be applied to create smart systems for administering drugs. In conjunction with Michael J. Cima, an M.I.T. expert in ceramics processing, I found an undergraduate at the University of Michigan at Ann Arbor, John T. Santini, Jr., who agreed to explore the idea as a summer research project. Santini, who ended up doing his Ph.D. at M.I.T., worked out a way to create silicon microchips that contain a number of wells that can be loaded with drugs and covered with caps of thin gold foil. Applying a one-volt electrical signal to one or more of the wells dissolves the gold covers and releases the drug. Santini is now president of MicroCHIPS in Bedford, Mass., which is currently developing these systems for testing in human patients.

Microchips could be implanted under the skin or into the spinal cord or brain to deliver drugs ranging from pain medications to chemotherapies against cancer. Animal studies conducted by James Anderson of Case Western Reserve University and his colleagues have shown that the materials in the microchips are quite biocompatible and unlikely to cause side effects. Chip-based systems, which would include a small, wearable power source, would be easy to use and could keep an accurate record of how much drug a given patient is taking: data from the devices could be downloaded into a computer at home, at a doctor's office, or in the hospital, providing a permanent record of a patient's drug history. ChipRx, a drug delivery company based in Lexington, Ky., is also developing implantable devices to sense the level of a drug in the body and administer appropriate doses in response. It states that it is now preparing publications for scientific journals describing its devices.

We look forward to a day when any drug can be administered at the right time, in the right dosage, anywhere in the body with specificity and efficiency. SA

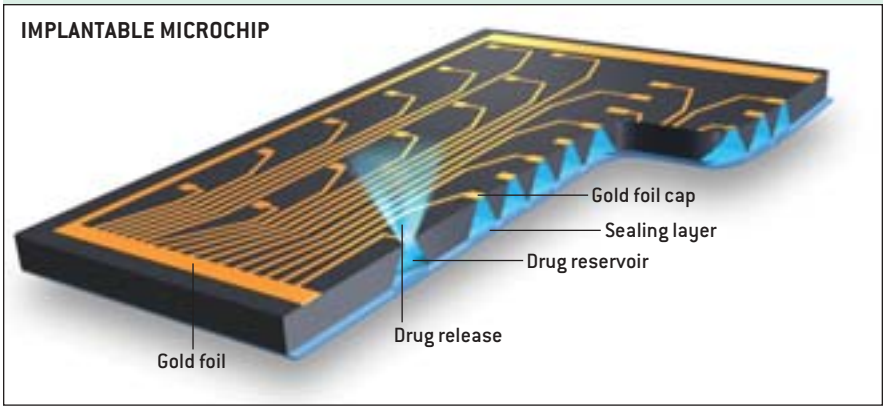
CONTROLLING RELEASE

HURDLE: Keeping the drug at a desired therapeutic level in the body while avoiding the need for frequent administration

SOLUTION: Implantable microchips with drug-filled reservoirs capped by gold foil that can be dissolved by an electrical charge to release the drug at appropriate times

SOME COMPANIES WORKING ON THE PROBLEM:
ChipRx, Lexington, Ky.
MicroCHIPS, Bedford, Mass.

IMPLANTABLE MICROCHIP



MORE TO EXPLORE

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