Delivering the Goods

Designing a new drug is one thing; getting it to the disease is another.

By RICK WEISS

Drug development is entering a remarkable era. With advances in molecular biology proceeding at breakneck speed, "gene jockeys" are engineering bacteria and yeast to produce specialized drugs that can alter human biological processes with unprecedented precision. Immunologists are purifying a variety of peptides critical to white blood cell activity. And chemists are becoming increasingly adept at designing therapeutic molecules from the most basic ingredients.

Many of these promising products, however, are rapidly broken down by digestive enzymes and therefore cannot be administered as pills. Injections, too, offer a less-than-ideal route of delivery; hypodermic needles are expensive, inconvenient and are especially unpopular when patients require frequent doses.

In such cases, the technology for getting drugs to their destination in the body is becoming an art unto itself. As researchers develop increasingly potent, site-specific drugs for everything from cancer to contraception, biomedical engineers and materials scientists are racing to provide carrier molecules and time-release mechanisms appropriate to each drug's particular requirements.

Biodegradable plastic wafers that release neurotransmitters in the brain, glass beads that emit measured doses of radiation and contact lenses steeped in antibiotics are but a few of the novel approaches now in clinical trials. These and other pending products stress timing and targeting. And the variety of experimental strategies that scientists are employing is testimony to a new blend of biomolecular savvy and old-fashioned ingenuity.

The ability to produce highly specific drugs having virtually no side effects — once only a dream — "has become a real possibility," says Wei-Chiang Shen of the University of Southern California in Los Angeles. "With technical advances and developments in immunology and cell biology, we are now on the threshold of drug targeting."

Already, transdermal patches that deliver a slow, continuous dose of medication through the skin have received Food and Drug Administration (FDA) approval for motion sickness and heart disease. Their use to administer painkillers after surgery and to provide a combination of female hormones capable of preventing pregnancy appears likely to win approval soon.

Recently, however, scientists added an innovative twist to transdermal drug delivery with the creation of so-called microsponges. Developed at Advanced Polymer Systems in Redwood City, Calif., these synthetic, highly porous sponges are tiny enough to be individually invisible. A sprinkling of microsponges feels as dry and soft to the touch as talcum powder. But each microsponge harbors a complex network of miniature tunnels and pores that drug-makers can fill with anything from skin lotion to insect repellent to a topical antibiotic.

Each time one rubs the skin where the powder has been applied, a dose of the stored substance is squeezed from the sponges and absorbed into the skin. Already, four nonprescription, microsponge-delivered cosmetics are on the market — including a men's aftershave and a variety of moisturizing powders.

According to the developer, 1 gram of microsponges contains about 240,000 *miles* of pore length. Pore size can be altered depending on the substance to be carried, and the sponges can be custom designed to respond to a particular cue. For example, they can release their product at a predetermined temperature or when moisture levels rise. A lip balm can be released with every kiss and deodorant ejected in direct response to perspiration.

In West Germany, scientists are performing clinical tests on another novel means of transdermal delivery — this one aimed specifically at eye infections. Massimo Busin of the Universitaets-Augenklinik in Bonn reported last fall successfully delivering therapeutic doses of the antibiotic gentamycin through the use of gentamycin-saturated contact lenses. Busin told the annual meeting of the San Francisco-based American Academy of Ophthalmology that sustained and effective doses were delivered over a three-day period in 10 healthy volunteers, and that the technique has potential applications for treating glaucoma and other eye diseases.

Other researchers, including some at USC, are taking a somewhat different approach to treating glaucoma, a potentially blinding disease caused by a buildup of pressure inside the eye. According to USC researcher Vincent Lee, glaucoma therapy has traditionally centered upon eyedrops, a notoriously inefficient means of getting drugs into the eye.

"At best, only 5 to 10 percent of most eyedrops gets into the eye," Lee says, adding that the rest typically gets absorbed into the bloodstream, where it may lead to serious complications. Indeed, he notes, the most commonly used drug for glaucoma, timolol maleate, can cause breathing problems and slower heart rates when absorbed by the blood.

To increase the amount of the drug that actually gets into the eye, Lee is experimenting with a tiny piece of drug-satu-

rated, slowly dissolving plastic that a patient can place under his or her eyelid. Lower doses can be used because the drug is targeted more efficiently. In addition, Lee says he recently altered the drug molecule so that very little is absorbed by the conjunctiva, a membrane lining the eyelid. Thus, more medication is absorbed by the transparent cornea, where the drug works best.

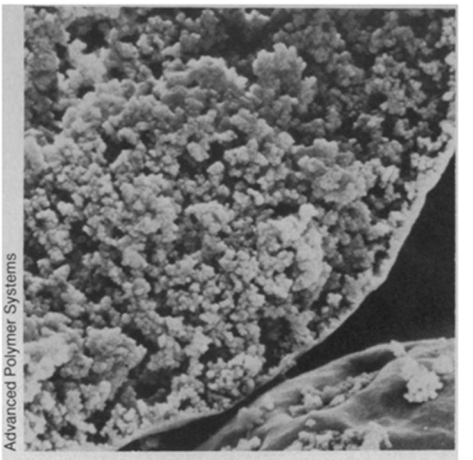
Another biodegradable polymer implant – this one designed to treat brain tumors – is under joint development by scientists at Johns Hopkins University and the Nova Pharmaceutical Corp., both in Baltimore, and the Massachusetts Institute of Technology in Cambridge. The 1-inch-diameter implant resembles a small wafer with layers of slowly dissolving plastic infused with cancer drugs.

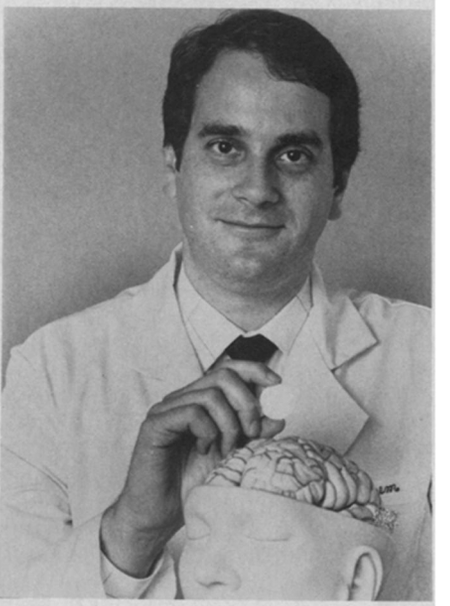
"The polymer biodegrades naturally, from contact with brain fluid, slowly releasing chemicals to kill the malignant tissue," says Henry Brem of Johns Hopkins, who is overseeing a coordinated study of the implant at three universities. The researchers say the technology may prove useful for other applications, including augmenting dopamine levels in the brains of patients with Parkinson's disease.

In a particularly fascinating bit of related research, scientists at MIT and the Deutsches Wollforschung Institut in Aachen, West Germany, are trapping insulin – along with a sugar-sensitive enzyme – inside small polymer wafers and implanting them into diabetic rats incapable of producing their own insulin. As the rats' blood-sugar levels rise, the sugar-sensitive enzyme is activated, causing a slight increase in acidity. The change in acidity increases the solubility of the trapped insulin, allowing increased amounts of the hormone to diffuse into the blood. Later, when blood-sugar levels drop, acidity decreases and insulin release slows. Thus insulin is released only when needed, in response to rising blood-sugar levels – just as insulin normally would be released by the pancreas in response to increased sugar levels, such as after a meal.

The researchers conclude in the April PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (Vol.85, No.7) that their system of natural feedback control "offers an approach that could be readily incorporated into different existing controlled-release systems to achieve self-regulated drug delivery."

Nasal sprays, too, may soon deliver insulin and other drugs that require rapid absorption into the bloodstream or that can't withstand the digestive actions of intestinal enzymes. Scientists at California Biotechnology in Mountain View, among others, are developing a new generation of nasal sprays that make old-fashioned decongestants look primitive by comparison.


Advanced Polymer Systems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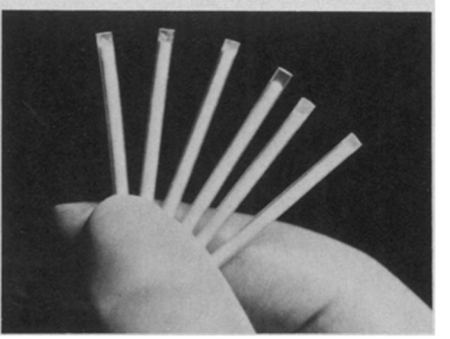

Hank Morgan/DISCOVER

A few of the novel drug-delivery mechanisms now in clinical trials. Top: Cross-section of a microsponge sphere, magnified 2,040 times. Its porous internal structure includes thousands of miles of drug-filled canals. Middle: Johns Hopkins researcher Henry Brem holds a biodegradable wafer designed to release cancer-killing chemicals as it dissolves in the brain. Similar wafers, loaded with different kinds of drugs or neurotransmitters, may prove useful in the treatment of Parkinson's disease or other neurological disorders. Bottom: Norplant capsules prevent pregnancy for five years when implanted beneath the skin of a woman's arm. When the implants are removed, the woman returns to her normal level of fertility.

Cal Bio's nasal sprays make use of specially designed "permeation enhancers," mild detergents that make therapeutic proteins more soluble, speeding diffusion of the drug through the nasal mucosa and into the bloodstream. Without such an enhancer, nasal membranes cannot absorb large molecules such as insulin.

The company is about to begin Phase II (efficacy) trials of an insulin spray it says may someday replace the injections diabetics must regularly take. In addition, Cal Bio researchers are investigating the potential for nasal administration of such compounds as human growth hormone, atrial natriuretic peptide (used experimentally in the management of high blood pressure), cholecystokinin derivatives (useful as appetite suppressants) and hormonal analogs with potential in contraception and in the treatment of endometriosis (SN: 3/5/88, p.148).

Although nasal-spray contraceptives are still experimental, other innovative approaches to birth control are already approved in many parts of the world and are undergoing clinical trials in the United States. The National Institute of Child Health and Human Development (NICHHD) in Bethesda, Md., is supporting research into transdermal contraceptive patches, some of which are under development at the Controlled Drug-Delivery Research Center at Rutgers in New Brunswick, N.J. The patches, smaller than a Band-aid, contain a blend of hormones and hormonal analogs that includes estrogen and progestin. "A woman would wear it for a week, replace it with another patch, and then repeat this procedure continuously," says Center Director Yie W. Chien.

Other novel means of contraception at various stages of development include:

- *Norplant implants.* These matchstick-sized capsules, implanted under the skin of a woman's arm, can prevent pregnancy for five years. Developed by the Population Council in New York City, the implants are already approved for use in 12 countries. FDA approval will be sought this summer.
- *Capronor.* Developed by the Research Triangle (N.C.) Institute, this biodegradable implant, unlike Norplant, never needs to be removed. It may prevent pregnancy for 18 months or more. Phase II clinical trials are being coordinated by NICHHD and the World Health Organization in Geneva, Switzerland.
- *Vaginal rings.* Developed with support from the World Health Organization, these devices release low doses of contraceptive chemicals for three months and can be removed at any time. The rings are in Phase III (large-scale efficacy) trials in several countries.
- *Injectable microspheres and microcapsules.* Once injected, these gradually release their contraceptive contents into

the blood, preventing pregnancy for up to six months. Family Health International in Chapel Hill, N.C., is coordinating clinical trials in five countries, including Phase III trials in the United States.

In recent years pharmaceutical manufacturers have grown increasingly enthusiastic about the potential uses for various kinds of specialized, drug-containing microspheres. Perhaps the most promising of the drug-bubble products are the so-called liposomes.

Made from either synthetic molecules or natural ingredients such as egg yolks and soybeans, liposomes are tiny, fat-soluble spheres with watery interiors. Water-based drugs can be trapped inside, or fat-soluble drugs can be trapped in the fatty membrane itself. In either case, the drug remains in reserve until the liposome finally dissolves or is ingested by a cell.

No liposome-based drug delivery system has yet won FDA approval, but several have advanced to clinical trials. Among the more promising applications for liposome technology are a number of cancer-drug delivery systems. In conjunction with the University of British Columbia, for example, Canadian Liposome Co. (a subsidiary of the Princeton, N.J.-based Liposome Co.) has encapsulated the cancer drug doxorubicin into preformed liposomes. Doxorubicin is highly toxic and can irreversibly damage heart muscle. But experiments show that when the drug is encased in liposomes, its cardiac toxicity can be reduced to one-fifth its original level.

In related research, Liposome Co. and Syracuse (N.Y.) University researchers have successfully packaged Cytochalasin B – a potential cancer drug – in liposomes so that it is released gradually and its toxicity to healthy tissue is reduced. Cytochalasin B appears to halt the spread of malignant cells. To do so, however, it must be present at all times. The researchers hope to fine-tune their liposomes to maintain a therapeutic dose of the drug over long periods.

Anesthetics offer another potential application for liposome time-release mechanisms. One system, developed by scientists at the University of Illinois in Chicago and the University of Miami, traps the long-acting anesthetic methoxyflurane in liposomes made of lecithin and sugar water. Lecithin, a fatty substance found in human tissue, spontaneously arranges itself into tiny microcapsules when agitated in water with high-intensity sound waves. The water-soluble methoxyflurane is trapped inside the capsules and, once injected, is gradually released over several days. The system is now in human trials.

What about targeting the liposomes for specific destinations? Researchers at the University of California at San Francisco recently reported successfully attaching liposomes to monoclonal antibodies. The antibodies guarantee that the liposomes will bind only to specific target cells, such as cancer cells. There, the liposomes are engulfed and digested, and their poisonous contents released.

Finally, liposomes may prove valuable as vaccines. Last December, the U.S. Department of Agriculture approved the first field test of a liposome-based vaccine – one designed to control a fatal disease in chickens. The vaccine, developed by IGI, Inc., in Vineland, N.J., uses especially slow-dissolving liposomes that remain in the animal for several weeks, significantly boosting the immune response.

With such a wide variety of carrier systems working their way through clinical trials, and with researchers learning how to design drugs that work in extremely specific ways, the science and art of drug delivery is reaching unprecedented heights. But a final hurdle remains: to directly target the DNA inside specific types of cells. Instead of convincing a cell, tissue or organ to change its activity in response to some outside cue, scientists would like to permanently change a cell's genetic predisposition in ways that are more suited to a person's individual medical needs.

Ideally, "We could deliver something to the cell, to the DNA, that would regulate gene expression," says Karl Hwang, a USC research pharmacologist. For example, in diabetics whose pancreatic cells fail to produce insulin, "A liver cell could be turned into a cell that excretes insulin . . . . We would make a liver cell into a pancreatic cell."

Scientists at the University of Tennessee in Knoxville reported last fall that they had done something very similar to that. They injected mice with pieces of DNA encapsulated in antibody-coated liposomes. The circulating liposomes attached themselves to mouse cells, which recognized the antibodies coating the liposomes. Once ingested by the cells, the liposomes released their load of DNA, which was then incorporated into the DNA of the cell. There it stimulated the production of an enzyme the cell previously had been unable to make.

"This work clearly demonstrated the gene-delivery potential of liposomes *in vivo*," the authors reported in the November 1987 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (Vol.84, No.22), adding that it should be equally possible to load liposomes with toxicity genes that might trigger cell death after they are incorporated into the DNA of cancerous cells. The implications of these results for cancer therapy are important, they say, "because by selecting appropriate control mechanisms, the delivered toxic gene may be expressed only in tumor cells."

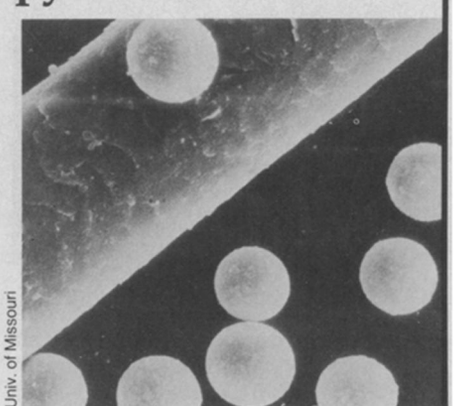
Performing gene therapy through the use of novel drug delivery techniques "may seem far-fetched now," says USC's Hwang. "But with all we're learning about how to regulate cell expression, I think it's likely in the future." □

Teaching an old therapy new tricks

Researchers are finding that radiation, too, can be carried to cancer sites on customized vehicles.

Materials scientists at the University of Missouri at Rolla have developed tiny ceramic spheres that can be bombarded with neutrons to make them radioactive, then injected into a liver cancer patient's hepatic artery. The beads become lodged in the liver near the tumor and emit their deadly dose, destroying malignant cells and causing far less damage to surrounding, healthy tissue than typically occurs when a cancer patient undergoes external beam irradiation.

"You can give the liver four or five times the dose that you could give safely with an external beam," says Delbert Day, the ceramic engineer who designed the beads. He says the beads – roughly one-third to one-half the diameter of a human hair – remain radioactive for about a month. Millions are injected in a single dose and remain in the liver indefinitely after that, apparently with no side effects.



Univ. of Missouri

These tiny radioactive, ceramic spheres, shown next to a human hair, offer promise for the treatment of liver cancer.

Clinical trials, now underway in Canada and at the University of Michigan at Ann Arbor, have been "extremely positive," Day says, adding that external beam radiation for liver cancer is not very helpful since the large doses needed would destroy too much surrounding tissue. – *R. Weiss*