# Planting the Seeds for Better Drug Delivery

## Researchers are attempting to expand the versatility of controlled-release drug implants

By JANET RALOFF

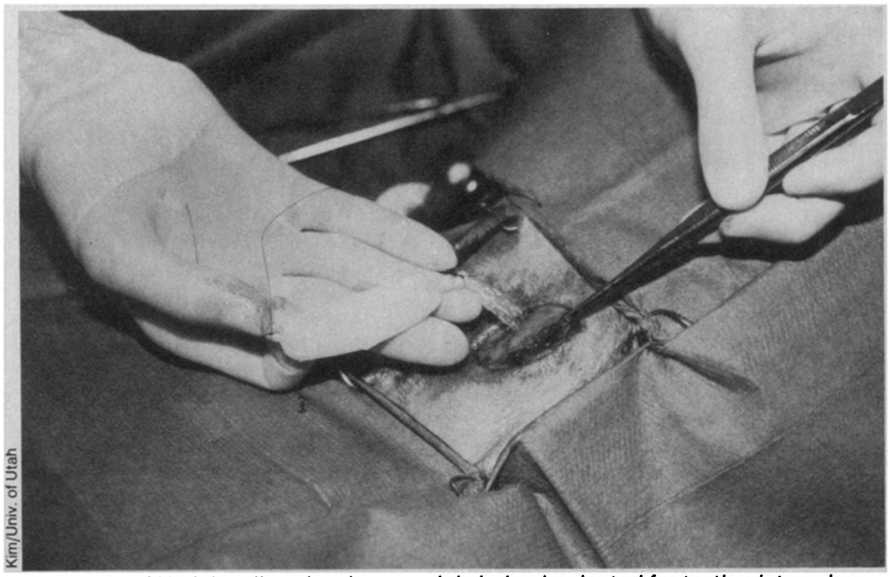
The last decade has seen the major commercial introduction of polymeric drug implants — plastic reservoirs of drugs that steadily release small, controlled doses of medicine. Though they eliminate the peak-and-valley oscillations in dose that tend to occur when medicines are taken in bulk amounts orally or by injection, they have had two serious limitations: They cannot deliver polypeptides — drugs like insulin, interferon or interleukin, which involve large molecules — and they cannot adjust dose to match a patient's changing need for a drug. Several novel implant devices now being developed, however, could overcome both problems.

These new implants, some of which were described at the recent American Chemical Society (ACS) national meeting in New York City, vary considerably — from those that can be triggered by an externally broadcast signal to those that automatically dispense a drug whenever changes inside the patient's body signal a need for the medicine.

One of the more unusual of these implant systems involves a solid, drug-impregnated plastic that biodegrades faster — and thereby releases more of its drug — when exposed to ultrasound radiation. "We can cause a 30-fold increase in the drug-release rate when we turn on the ultrasound," says Robert Langer, a biomedical engineer and co-developer of the device at the Massachusetts Institute of Technology. The ultrasound-initiated drug-release increase not only is instantaneous, he says, but also can be varied by altering the radiation intensity and frequency. When the ultrasound is turned off, the effect goes away.

Although work on the system is still in its preliminary stages, Langer envisions that the ultrasound-sensitive drug-containing polymer would be implanted under the skin as a series of microcapsules, each perhaps a few microns in size. The patient would wear either a wristwatch-style or belt-carried ultrasound generator preprogrammed to broadcast radiation at set intervals. Alternatively, the broadcast device could be manually triggered by the patient: A diabetic, for example, could turn it on at mealtime or whenever the need for insulin arose.

The key to this system is its biodegradable plastic. The present model, now being tested in rats, uses a polyanhydride — a new polymer developed by Langer's group. The drug is uniformly dispersed within the solid plastic. Already tested with three drugs, including insulin, the system "looks promising," Langer says. But as to how it works, he says, "we're really not sure . . . it appears complex." Tests have already shown that temperature increases in the polymer during irradiation are not a factor. "We do see some surface cracking of the polymer," he notes, adding that the formation of tiny bubbles in the implant may play some role in increasing drug release during irradiation.



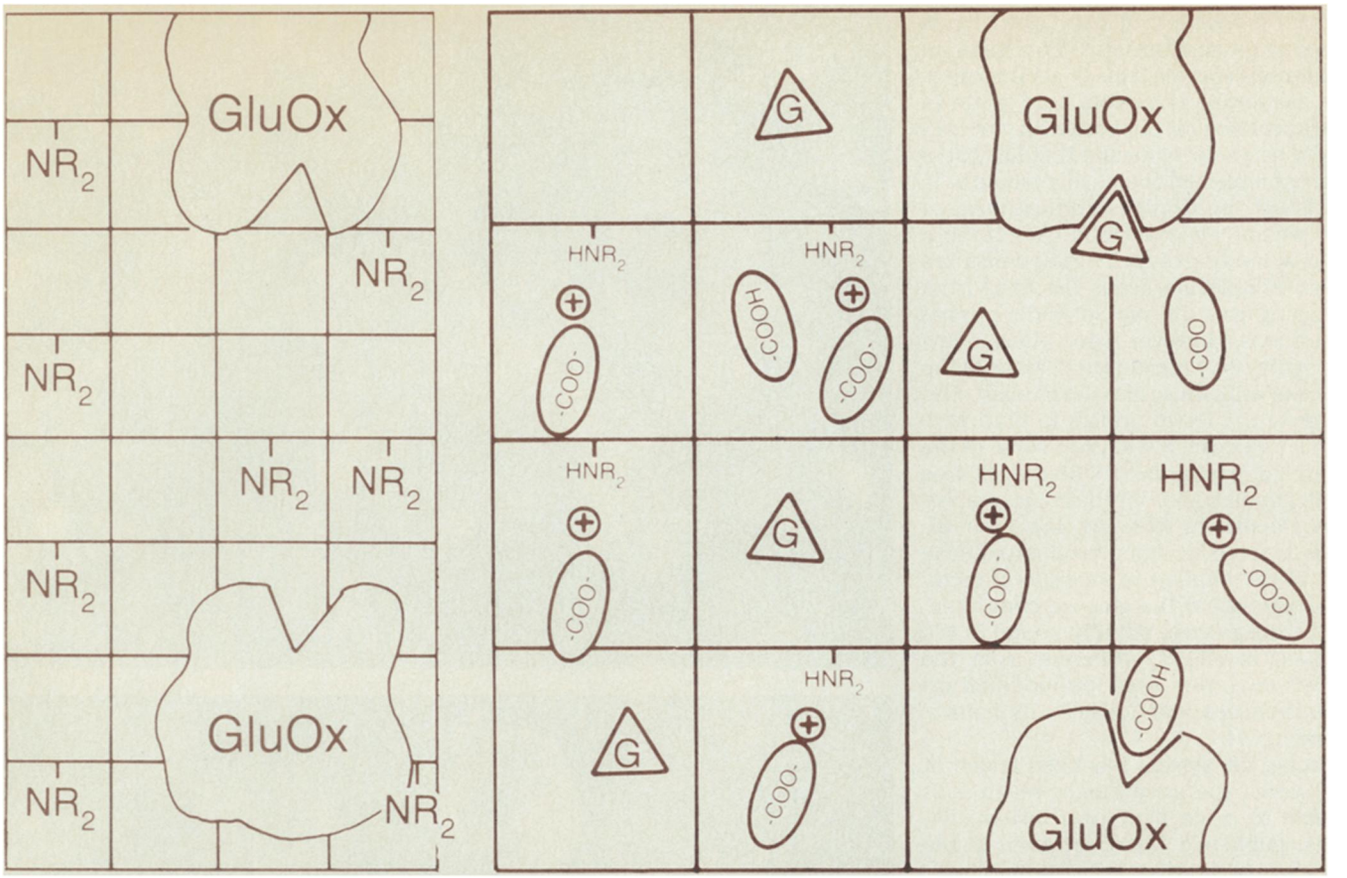
Kim/Univ. of Utah

*University of Utah insulin-releasing pouch is being implanted for testing into a dog. Because its pancreas has been removed, this animal cannot make insulin.*

Another Langer design — begun before the ultrasound research — relies on externally applied variable magnetic fields, instead of ultrasound, and an elastic polymer into which small magnetic beads and insulin are placed (SN: 4/5/80, p. 213). The idea, Langer explains, is that "when you turn on an oscillating magnetic field, the beads will move and actually squeeze pores that contain our drug, allowing it to come out." Still under development, that system "is probably much farther along than the ultrasound one," Langer says, "but we believe the ultrasound one could eventually have some advantages over it." Chief among them is the elimination of a need to periodically remove the surgically implanted device that contains the magnetic beads.

Even newer than the ultrasound system is an enzyme-based, nonbiodegradable implant Langer is developing. In contrast to his other variable-rate drug-release systems, this one would allow the patient's body to determine not only how much drug is released but also when.

Insulin, a polypeptide that allows glucose to enter cells, is one of many drugs whose solubility changes with changing acidity levels. Initially being designed for insulin, the implant "senses" the body's need for insulin using an enzyme — glucose oxidase — that Langer attaches to tiny beads of a polysaccharide (sugar) inside the device. Ordinarily, the implant would steadily emit a small amount of insulin into the body. However, as body-glucose levels rise, signaling a need for more insulin, some of this glucose diffuses into the implant, through its outer polymer membrane. Once the glucose is inside, the enzyme converts it into gluconic acid. This acid lowers the implant's internal pH, increasing insulin's solubility and diffusion out into the body. Because gluconic acid also diffuses out of the implant and into the body, the implant will return to its orig-



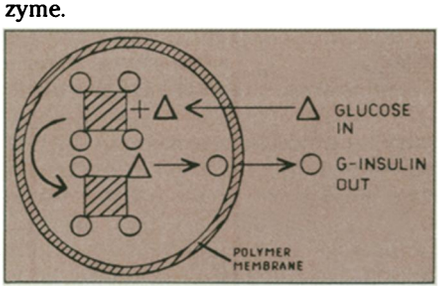

Horbett/Univ. of Wash.

*Chemistry behind University of Washington's implant. The implant's unswollen membrane (left diagram) initially contains just amine groups ($NR_2$) and glucose-oxidase enzyme (GluOx). But when glucose (G) enters (right), gluconic acid (COOH) is formed. The acid donates protons — hydrogen nuclei (H) — to the amines, creating $HNR_2$. Charge-repulsion between the now positively charged amine groups will cause the membrane to swell, releasing drug from the reservoir it encases.*

inal pH – and its original insulin release rate – when body-glucose levels diminish. Concerned that the enzyme he uses might be antigenic, causing an allergy-like reaction, Langer made this implant nonbiodegradable so that its enzyme won't be released into the body.

In preliminary tests the device was implanted under the skin on the back or belly of rats. An injection of glucose into the bloodstream – creating blood-glucose concentrations comparable to what might occur after a meal – was sufficient to double the implant's insulin release rate, Langer says. Rats unable to make their own insulin but carrying the enzyme-based implant were able to comfortably tolerate even large injections of glucose. Langer says the implants reacted to the glucose by dispensing insulin with a speed and in quantities that generally mimicked what occurs naturally in healthy rats.

A related biodegradable implant was also described at the ACS meeting. Again dependent on pH changes to release the drug, this implant contains both glucose oxidase and insulin dispersed rather uniformly through a solid polymer. Whenever glucose contacts the enzyme on the surface of the polymer, it produces the pH-lowering gluconic acid, which causes the implant's surface "to sort of peel like an onion," explains Jorge Heller, a polymer chemist developing the implant at SRI International in Menlo Park, Calif. In so doing, it releases some of the polymer-bound drug. Since it will also release some of the polymer-bound enzyme, Heller plans to counter the potential antigenicity problem by "grafting" polyethylene glycol onto the enzyme.




Kim/Univ. of Utah

*Body glucose (△) and glucose-bound insulin (○) can pass through the Utah implant's membrane; lectin (⧄) cannot.*

Yet another variable-rate insulin-delivery system using glucose oxidase is under development at the University of Washington in Seattle. In this one, the glucose-oxidase enzyme is bonded within the outer membrane of a saclike implant. One of the membrane's constituents is an amine, a compound that will take up protons and become more positively charged when the pH decreases – a situation that occurs whenever glucose contacts the enzyme. Explains biochemist Thomas Horbett, one of the system's developers, "Because we have a lot of the amine groups in the membrane, the charge repulsion [that occurs when they become positively charged] causes the membrane to swell." This allows the membrane to take up more water and become more permeable to the insulin stored inside the reservoir.

Horbett and co-developer Buddy Ratner expect an operating system would consist of a small, refillable, membrane-encased reservoir of insulin. "A 5-cubic-centimeter reservoir could easily hold a year's supply of insulin," Horbett says. However, he adds, if the implant's membrane ruptured while it contained that much, dangerously low blood sugar could result. "So in practice we'd probably fill ours with less than a year's supply."

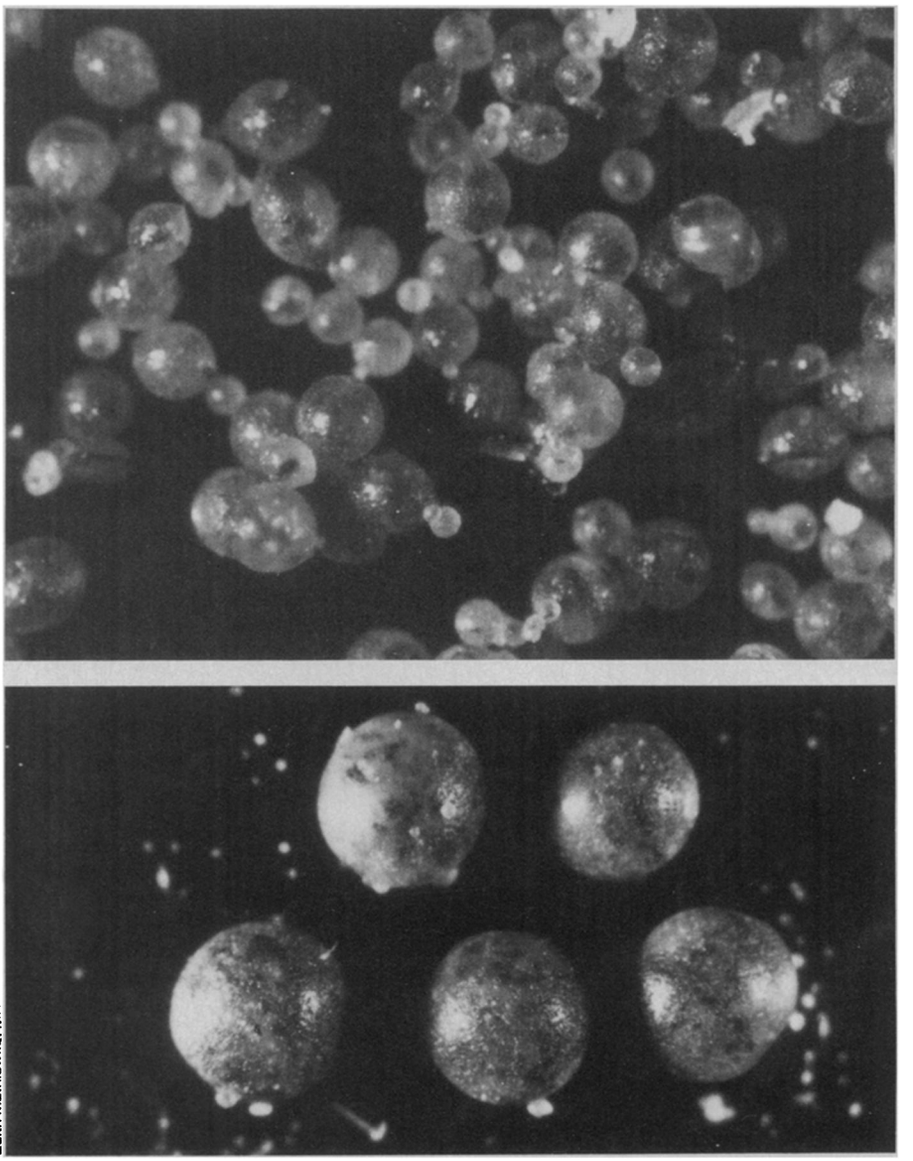
So far, the researchers have demonstrated the membrane-swelling concept. Right now they're using computer modeling to optimize the system. Once they are able to make it responsive to the full range of glucose concentrations that might occur in the body, they will consider testing it in animals.

Sung Wan Kim, director of the University of Utah's Center for Controlled

Chemical Delivery in Salt Lake City, is working on an alternative pouchlike insulin-reservoir system. A semipermeable membrane is used to hold lectin (a glycoprotein that can bind with glucose) and a reservoir of insulin that has had a glucose molecule chemically bound to it.

Though the insulin can diffuse through the membrane, the lectin cannot. So a natural binding of the modified insulin's glucose molecule keeps the drug from escaping from the implant under normal conditions. However, when glucose levels in the body are elevated, some of the glucose will diffuse into the implant. And because the lectin prefers to bind with regular glucose, it will drop some of the modified insulin that it's holding to free up its binding sites for the incoming regular glucose. In so doing, the lectin allows its freed modified insulin to diffuse out of the implant in amounts directly proportional to the glucose coming in. While the glucose initially bound in the implant is slightly different from the body's own, Kim says the modified insulin behaves identically to its natural counterpart.

So far, the system has been tested in one-week experiments using seven dogs unable to make their own insulin. Results, published last December, in the JOURNAL OF CONTROLLED RELEASE, indicate that the abdominal-cavity implants "work like a charm," Heller observes. Clearly, he says, Kim's controlled-release drug implant "is the farthest along of the self-regulating." Though Heller is somewhat concerned about the possible toxic effects of the lectin should the implant's membrane ever rupture, Kim is not. Kim told SCIENCE NEWS that because the implant uses so little – less than a tenth of a percent of the amount that might be toxic – he discounts the lectin-rupture issue as an important concern. In fact, he says, human trials of the device may begin within three years.



Edith Mathiowitz, MIT

*A number of solid polymers under development by Langer, Kam Leong and colleagues at MIT, such as those used to create the roughly 100-micron-diameter spheres pictured here, biodegrade faster during exposure to ultrasound radiation. Evenly dispersed throughout the polymer beads in the lower photo is the protein myoglobin – used in tests as a stand-in for large-molecule drugs such as insulin. The rate at which these small microspheres – administered by injection – release their bound-in drugs is determined by varying the ultrasound intensity and frequency.*

Most of these body-regulating controlled-release systems are initially being developed to deliver insulin – a drug the body uses every day. But Heller points out that the concept could just as easily be used to release a drug that might be needed only occasionally. "We are working on such an implant, one that won't do anything until a specific molecule appears in the tissue to activate the system," he says.

People being weaned from a dependency on addictive drugs such as morphine are sometimes given naltrexone – a drug that competes for the same receptors in the brain but does not elicit a pleasurable effect. Should an addict take morphine, the naltrexone would prevent the individual from obtaining the desired "high." But, Heller asks, why *continually* medicate a rehabilitating addict with naltrexone, when it may be needed only occasionally? "A better system is one that would be passive until the person took morphine. Then it would activate the naltrexone, so that one would only get as much of that drug as needed," Heller says. And with funding from the National Institute of Drug Abuse, he is working on such a system.

The same concept could be used to trigger the dispensing of a drug in a variety of situations, such as after body chemicals indicate that a heart attack has occurred, or to release a contraceptive drug only after a similar type of chemical flag indicates that egg implantation has taken place, says Heller. Such systems not only would reduce unnecessary medication but also could theoretically deliver medication as soon as the body signaled a need for it – even before diagnosis of the conditions they might be used to treat.

Smaller than mechanical pumps, these developing drug-delivery systems should prove far more comfortable to the wearer, according to Ping I. Lee, vice-president of research and development for TheraTech Inc. in Salt Lake City and an organizer of six sessions on controlled-release-technology advances at the ACS meeting. Their variable release rates are more responsive to changes in the body's needs for a drug than existing implant systems. And the fact that some are not only biodegradable but also small enough to be implanted with a hypodermic needle should reduce or eliminate the need for much implant-related surgery. Lee considers these "the ultimate delivery systems," ushering in a new era in controlled-release drug delivery. □