A Better Way to Make the Medicine Go Down

Prodrugs may soon join the pharmaceutical arsenal for conditions as challenging as AIDS and cancer

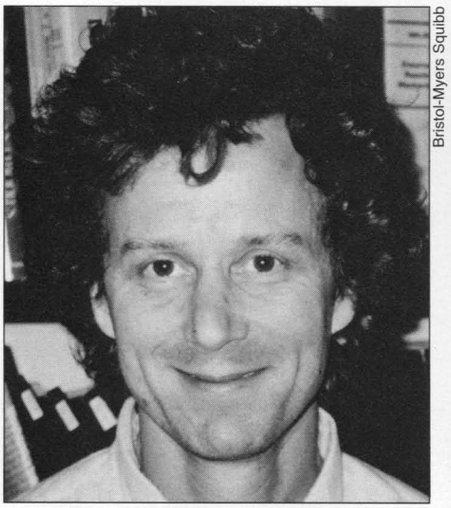

Bayer

WHAT DO CODEINE, ASPIRIN, AND A NEW form of AZT have in common? All serve to treat a symptom or disease—and none is an active drug. These pharmaceutical paradoxes, inert substances converted by the body's own chemistry into active compounds, are called prodrugs. In recent years, researchers have learned that chemically modifying a new drug to convert it into a prodrug may be the answer whenever the parent compound is hard to take or absorb or is slow to accumulate in target tissues. And now the art of prodrug design is receiving a fresh burst of attention as pharmacologists apply it to some of their most daunting challenges: AIDS and cancer.

Researchers are finding that modified, inactive versions of the AIDS drug AZT accumulate far more efficiently than the parent drug in specific tissues harboring the virus. To administer the potential new anticancer drug taxol without severe side effects, pharmacologists are converting it into a prodrug. And the prodrug strategy has given rise to an ingenious new means of targeting other anticancer drugs to the tumor cells while sparing normal tissue.

Long before anyone set about consciously designing prodrugs, pharmacists were prescribing them. Codeine, a natural morphine derivative isolated in the 19th century, is actually a prodrug: The body converts it back to morphine before it exerts its narcotic effects. And when the German chemist Felix Hoffmann discovered in 1899 that he could produce a better tolerated version of the pain reliever salicylic acid by modifying it to acetyl-salicylic-acid, he was unwittingly turning it into a prodrug. Aspirin, as the new compound was christened, is metabolized to salicylic acid in the body.

But though the concept of prodrugs was understood by the late 1950s, when chemist Adrian Albert of the Australian National University at Canberra coined the term, the notion of intentionally designing them really took hold only in the mid-1970s. That was when researchers began tracing the fate of drugs in the body—their absorption, distribution, and excretion. These pharmacokinetic studies showed that in many cases drug therapy was embarrassingly inefficient. Some drugs given orally were slow to enter the bloodstream through the intestine, requiring high—and hence wasteful and sometimes dangerous—doses; others, both oral and injectable, were degraded prematurely in the stomach, gut, or liver. Still others were distributed evenly in the body instead of being concentrated at the target organ. Says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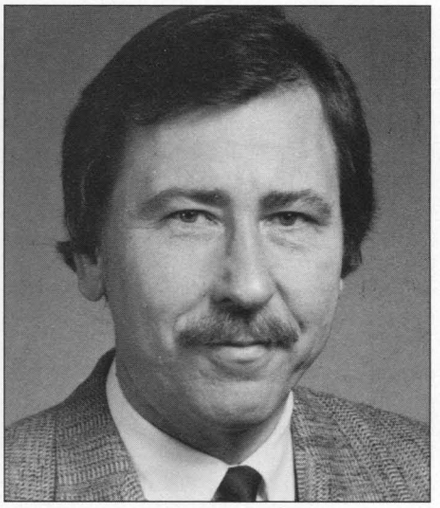


Prodrug creators then and now. *Felix Hoffmann* (top) *made a prodrug by chance, but Peter Senter* (left) *and Valentino Stella* (right) *do it by design.*

prodrug designer Valentino Stella of the University of Kansas: "We began to realize the limitations of currently used drugs and started looking for optimizations."

While pharmacologists were waking up to the inefficiency of drug delivery, they were also learning enough about the biochemistry of those compounds to do something about it. Finding a chemical precursor that was more readily absorbed and more efficiently transported to its site of action became a favorite strategy. In addition to the clinical advantages, the pharmaceutical industry also had a financial incentive to explore the potential of prodrugs, notes Stella. A natural compound can't be patented, but a modification renders the drug unique—hence patentable and potentially more profitable.

Whatever the motivations for creating a prodrug, it has to be designed with an eye on metabolism. The enzymes or reactants that convert the precursor to the active drug have to be plentiful in the body or the intended target tissue, even in patients with metabolic disorders, so that the reaction proceeds at a reasonable rate. And, most important, neither the prodrug nor the part of the molecule that is discarded along the way should wreak any havoc of its own.

What drug designers gain from all this trouble is, in some cases, nothing more than better taste in a drug that is taken by mouth. And yet, because patients certainly tend to be more "forgetful" in taking a bad-tasting medicine, that's not a trivial gain. Unmodified, the antibiotic chloramphenicol, for example, has a bitter taste that is hard to disguise in oral preparations. But as workers at Parke-Davis discovered decades ago, the drug becomes tasteless—and much easier to give to children—when it is converted to a palmitate ester. Esterase enzymes in the gut then resurrect the active drug.

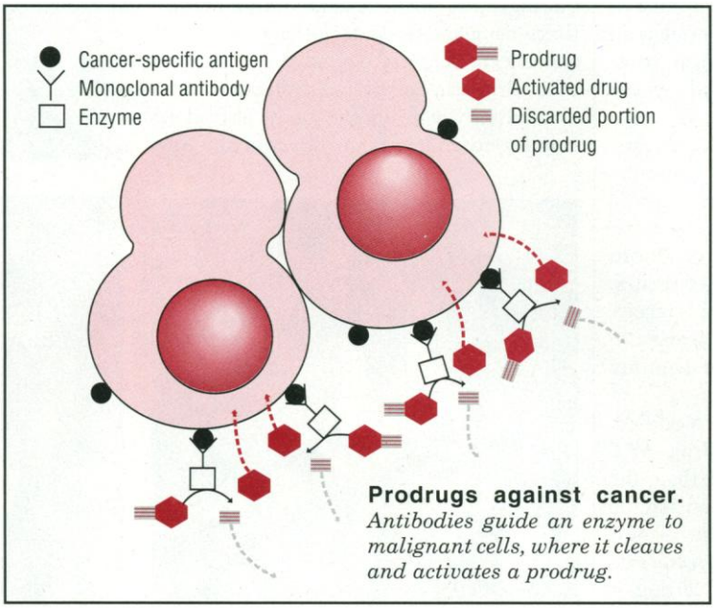
But the prodrug strategy can also surmount more serious hurdles to drug treatment than bad taste. Take taxol, the promising new cancer drug. The molecule, an alkaloid found in the bark of the Pacific Yew tree

(see *Science*, June 28, p. 1780), won't dissolve in water to make an injectable solution. In recent clinical trials of the drug at Johns Hopkins University and the University of Texas, taxol was mixed with a soapy solvent so that it could be given intravenously. But this formulation produced severe side effects in most of the patients. Stella's group at the University of Kansas is now trying another tack: modifying the drug to make it water-soluble. Converting some of the hydroxyl groups of the molecule into amino acid esters seems to do the trick. Stella and his colleagues have tested some of these taxol prodrugs in animals and have seen them break down into the parent drug. But, Stella cautions, "it will still take some time before these prodrugs are tested in humans."

Besides making a drug easier to administer, the prodrug strategy can also target it, sending it on a one-way trip to the desired organ. Prodrugs with an affinity for a specific tissue can confine drug therapy to the proper site, minimizing the risk of side effects. In the case of the drug dopamine, for example, that strategy serves to dispatch the compound on two different journeys. In the form of one prodrug—L-dopa, first introduced in the 1960s—dopamine is able to cross the blood-brain barrier. Brain enzymes reconstitute the active drug, which helps to relieve symptoms of Parkinson's disease and related disorders. But a different dopamine prodrug, gamma-glutamyl-dopamine, developed in 1979 by Jaroslav Kyncl and co-workers at Abbott Laboratories in Chicago, specifically accumulates in the kidney. A kidney-specific enzyme converts it back to dopamine, which dilates the organ's blood vessels—an effect useful in the treatment of shock.

A similar strategy may soon enable the AIDS drug AZT to infiltrate macrophages, the blood cells that are a major reservoir for the AIDS virus in the body. Macrophages are ordinarily reluctant to absorb AZT, but they can be fooled into accepting it when the parent drug is converted into a prodrug, phosphatidyl-AZT. This compound, developed by Douglas Richman of the University of California at San Diego and his co-workers, can easily be incorporated into small, membranous sacs known as liposomes. Macrophages, which are the immune system's scavenger cells, readily take up the drug-bearing liposomes. As Richman puts it, "The phospholipid compound can be integrated in the macrophage's membranes as a reservoir of the drug." In theory, the strategy could expose virus within the macrophages to a high concentration of AZT while protecting other tissues from the toxic drug.

Targeting specific tissues is especially critical in cancer therapy, where the aim is to kill the malignant cells but save the surrounding normal tissue. For years researchers have been struggling to exploit the targeting potential of monoclonal antibodies, which can be designed to home in on antigens—molecular markers—on the surfaces of cancer cells. One common strategy is to link radioactive isotopes or toxins directly to the antibody molecules. But relying on the antibody to ferry the drugs themselves to the cancer cells has drawbacks, especially in solid tumors. The antibody's target molecules may not be distributed evenly over the cells, and the cells may not take up the toxin efficiently. Now, two groups—one led by Kenneth Bagshawe at the Cancer Research Campaign Laboratories in London and the other by Peter Senter at the Bristol-Myers Squibb Pharmaceutical Research Institute in Seattle—have independently combined monoclonal antibodies and prodrugs in a strategy they think may yield both precise targeting and an adequate drug level.



Prodrugs against cancer. *Antibodies guide an enzyme to malignant cells, where it cleaves and activates a prodrug.*

Their approach uses the antibody as a vehicle not for a toxin but for a drug-activating enzyme—one that isn't abundant in normal tissue. Says Senter: "We want to create the difference between tumor cells and normal tissue, if it doesn't exist naturally." After the antibody-enzyme combination is delivered to the target tissue, a cytotoxic drug is administered in the form of an inert prodrug, which is activated specifically by the antibody-bound enzyme. Thus the active drug emerges preferentially at the tumor, which should minimize toxic side effects on the surrounding tissue.

Senter thinks the technique—a combination of magic bullet and Trojan horse—will be easy to adapt to various kinds of cancers, simply by varying the prodrug-enzyme combination and the kind of antibody. He stresses that the choice of enzyme can be as important as the choice of anticancer drug: Human enzymes are less likely to provoke an immune response in the patient, but prodrugs that respond to such enzymes may be activated before they reach the target. Nonhuman enzymes can yield more specific drug activation but are also more likely to cause an immune reaction.

Currently, several of these cancer-targeting, enzyme-prodrug combinations are being tested both in vitro and in animal models. And last year, Bagshawe's group started the first clinical trial of the system, with a small group of patients with advanced colorectal carcinoma. The patients first received a dose of the prodrug alone—a derivative of a so-called nitrogen mustard—to make sure it wasn't activated by their own enzymes. Only afterward did they get both the antibody-enzyme conjugate and the prodrug. Although the trial is still in an early stage, preliminary results are encouraging, says Caroline Springer, one of Bagshawe's co-workers: "We could detect the active drug in the patients and we do see some symptomatic relief," such as longer survival and reductions in the size and number of metastases. But she emphasizes that it's still too early to give a final verdict on the approach.

That's at the cutting edge of prodrug development. But while drug developers have been applying the prodrug strategy to some of their most daunting challenges, such compounds have been quietly infiltrating the rest of the pharmacopoeia. In a 1985 review article Stella asked: "Prodrugs—do they have advantages in clinical practice?" Since then, as many as 20% to 30% of the new drugs introduced each year have been designed from scratch as prodrugs, and old drugs are being turned into prodrugs to reap the benefits of the approach. Six years later, the answer to Stella's question clearly has to be yes. ■ SUSANNE HILLER

Susanne Hiller, a postdoctoral fellow at the National Institutes of Health, has just completed an internship at Science.