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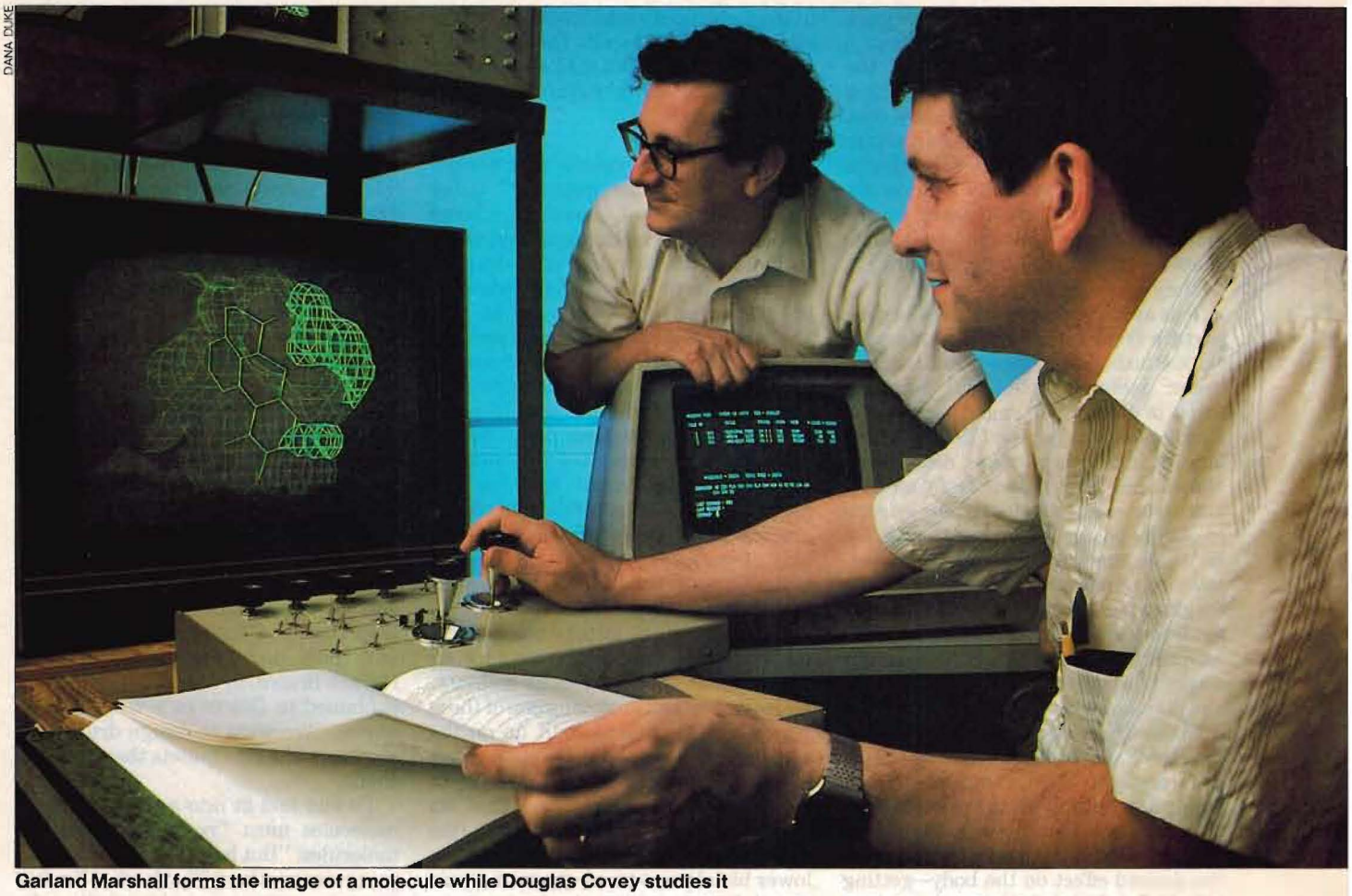

Garland Marshall forms the image of a molecule while Douglas Covey studies it

DESIGNING DRUGS WITH COMPUTERS

By creating images of molecules on the screen, chemists are learning to tailor drugs to diseases

by MARCIA BARTUSIAK

Chemist Douglas Covey felt very much at home in his laboratory at the Washington University School of Medicine in St. Louis. The maze of glass tubes, whirling centrifuges, and bubbling flasks seemed to be all he needed to carry on his work, the creating and testing of new drugs.

Then three years ago he met Garland Marshall, a professor of biophysics at Washington. Marshall told him about a totally new way to confront his molecules: face to face on a computer screen. Covey was skeptical. "Computers have absolutely nothing to do with my work," he said. Today he admits that he was dead wrong. He has become a true convert to computer chemistry.

Part of Covey's research is now done in front of a cathode-ray tube, where he manipulates a joy stick and the computer keyboard as though he were playing some sort of electronic space game. At the flick of a wrist, lines of red, yellow, and green turn and twist before his eyes, each image conveying a bit of information about the electrical charges, structure, and volume of the molecule he may later make in the laboratory.

Covey is one of many scientists in universities and drug companies across the country who use computers before turning to their test tubes. On glowing screens, they not only create blueprints for new drugs but also analyze in mi-

nute detail the way existing drugs work in the body. Says Harel Weinstein, a professor of pharmacology at the Mount Sinai School of Medicine in New York City, "Drug companies know they simply cannot be without these computer techniques. They make drug design more rational." How? By helping scientists learn what is necessary, on the molecular level, to cure the body, then enabling them to tailor-make a drug to do the job.

This approach represents a sharp departure from traditional pharmaceutical methods. Ever since primitive man began dabbling (often with fatal results) in things like snake venom and jungle plants in hopes of finding remedies for injuries or disease, drug development has been based chiefly on trial and error—and luck. Peruvians learned to eat the powdered bark of the cinchona tree to cure raging fevers. Old wives' tales recommended the leaves of the foxglove plant for heart trouble. It took modern science to determine that these medicines were not magic potions, but worked because they contained quinine and digitalis, respectively.

These drugs and others work, scientists think, by finding their way to specific receptors (such as enzymes, DNA molecules, or proteins in the membrane of a cell) and uniting with them in a kind of molecular embrace that triggers the desired effect on the body—getting rid of a headache, for example, or lowering a fever. The computer, with its lightning calculations and vivid graphics, can facilitate the understanding of this union by diagramming the receptor and the drug molecule that will fit it. To do the same thing with the unwieldy wire-and-ball molecular models in most chemistry labs would be impossible. "Besides," recalls Daniel Veber, of Merck Sharp & Dohme Laboratories, "those things were always falling apart in your hands."

The computer systems that are doing "molecular mapping" today rapidly digest incredibly large amounts of information and then use it to build a visual model of a drug or chemical. Says Robert Langridge, of the University of California at San Francisco, "I think the Chinese proverb 'One picture is worth ten thousand words' is the best way to describe why the computer is so important to pharmacology. Except that the Chinese probably underestimated the number of words." Langridge and his colleagues at the Computer Graphics Laboratory have developed what is probably the most advanced modeling system now in use (see computer model at the top of the next page).

A computer can display the molecular structure of any drug from a listing of thousands contained in its memory. By looking at and analyzing one of these stored models, or one built up on the screen from scratch, chemists can tell if a drug's particular arrangement of atoms is the molecular "key" that fits into and opens a biological "lock" (the receptor) within the body—perhaps to lower blood pressure, to prevent a pain signal from reaching the brain, or to zap an invading bacterium. "The computer is literally an idea box," says Covey. "This whole approach is helping us avoid the blind alleys before we even step into the lab."

Pharmaceutical firms are familiar with those alleys. Out of every 8,000 compounds the companies screen for medicinal use, only one reaches the market. "The computer should help lower those odds," says John Adams, of the Pharmaceutical Manufacturers Association. This means that chemists will not be tied up for weeks, sometimes months, painstakingly assembling test drugs that a computer could show to have little chance of working. The potential saving to the pharmaceutical industry: millions of dollars and thousands of man-hours.

Pharmacologists want to use computer chemistry to eliminate the annoying side-effects that drugs often produce when they act like master keys, opening more than one biological lock. For example, one drug used to combat diarrhea not only acts on the intestine but also attaches to a receptor in the brain, where it acts as a mild opiate. To avoid this dual action, chemists would like to manipulate the structure of the drug, first on the computer and then in the laboratory, to make sure it interacts with only one type of receptor. As Horace Brown, of Merck Laboratories, explained to DISCOVER's Wayne Villanueva, "We want to design drugs that are more like rifle bullets than shotgun shells."

To find and fit into a receptor, drug molecules must "recognize" receptor molecules. "But how does one molecule recognize another? That's what I'm fascinated with," says Marshall, who along with C. David Barry helped guide the development of Washington University's MMS-X (molecular modeling system) computer. Like other computer chemists, Marshall begins by studying the shapes of the drug molecule and its receptor (when the receptor is

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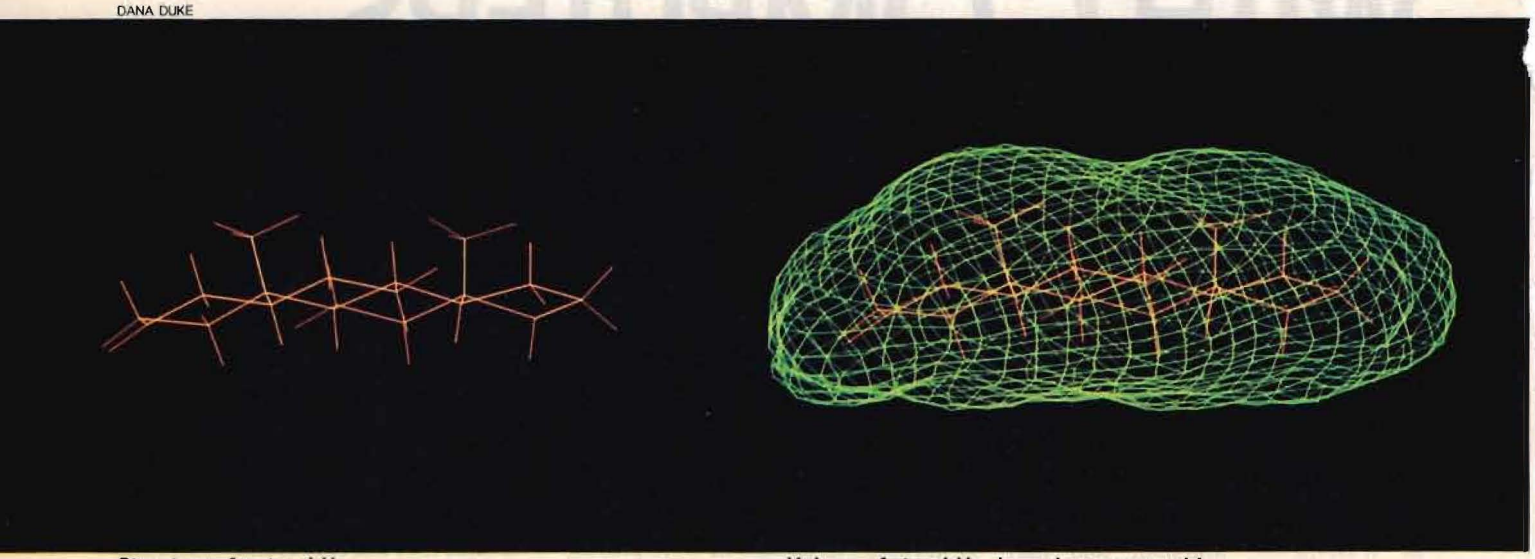


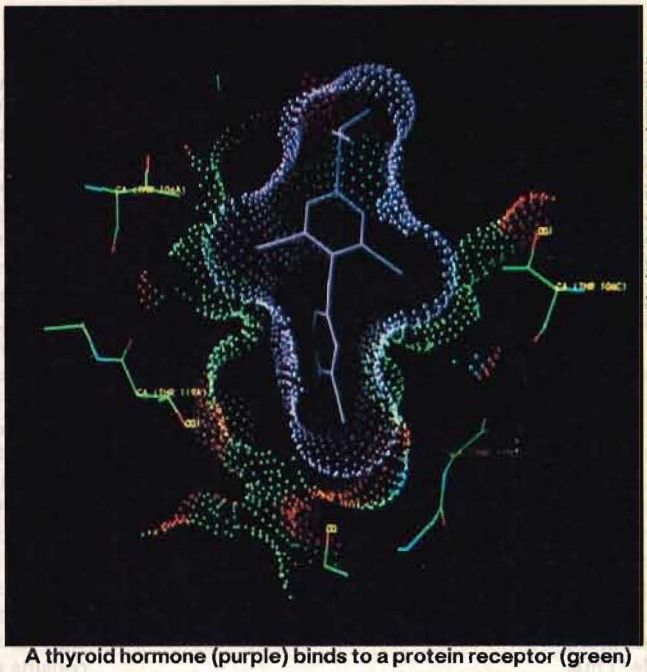
Structure of a steroid hormone

Volume of steroid is shown by a green grid

known), rotating the models on the computer screen to see them from every possible angle. On the simplest level, a drug and its receptor must fit together like pieces of a jigsaw puzzle. Beyond that, the electrical fields that surround both should attract each other, the way a magnet attracts iron. The computer allows the scientist to calculate and display those effects in graphic form.

Using this technique, scientists have figured out how a chemical agent called alloxan works. When fed to laboratory rats, the drug produces many of the symptoms of diabetes. By computing the molecular shape—actually the shape of the cloud of electrons hovering around the molecule—Washington University researchers found that alloxan resembled glucose, the sugar molecule that triggers the release of insulin. Both form a sort of four-fingered hand. Alloxan, they concluded, might be fitting into a receptor for glucose and jamming it. The resulting lack of insulin could have been bringing on the diabetes in the rats.

When a chemist wants to know why different-looking drugs act on the same receptor, he can ask the computer to superimpose them all on the screen so he can see how their atoms match up. Marshall, for example, was interested in four chemicals that act like dopamine, a natural substance in the body that helps transmit nerve signals (Parkinson's disease is associated with a lack of dopamine). Once he punched in the proper commands on his computer keyboard and the four molecules merged on the screen, he saw that they all had something in common: a ring of carbon atoms and one nitrogen atom in the same location. It seemed logical to assume that those atoms were at least part of the electronic key that opens the receptor's door—and a clue to the understanding of dopamine-related diseases.

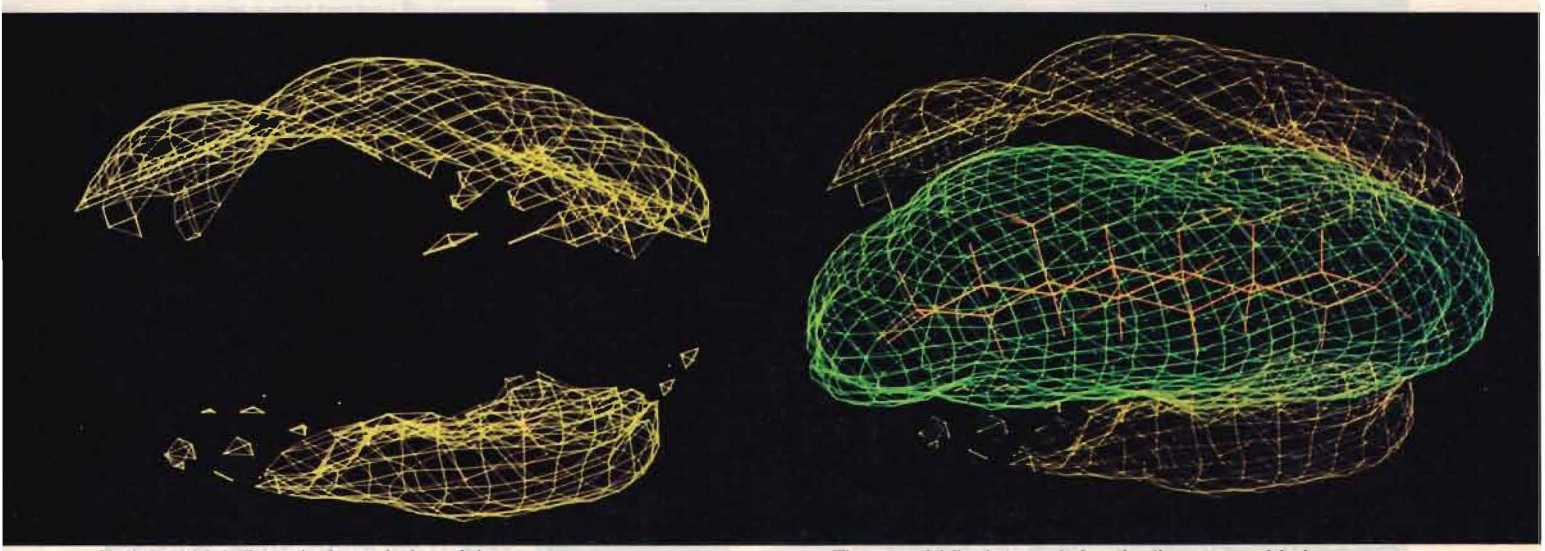


LANGRIDGE, COMPUTER GRAPHICS, UCSF

A thyroid hormone (purple) binds to a protein receptor (green)

Covey is using the computer to design a "suicide molecule" that will latch onto and destroy an enzyme (and itself in the process). He is modeling these molecules after steroids, such as the hormones estrogen and testosterone, which determine sexual characteristics. How he uses the computer for this purpose is shown at the bottom of these pages. At the left, the red lines represent the intricate links between the carbon, oxygen, and hydrogen atoms found in a steroid called dihydrotestosterone. In the next picture, the computer displays in green the volume that those atoms occupy. The green grid looks like and has been called a hamburger. To be effective, the green molecular blob must link up with an enzyme. But an enzyme will not accept just any molecule; the steroid must be able to slip between certain barriers, the yellow "hamburger buns" in the third picture. These barriers could be considered the walls of the enzyme; their shape and width are gleaned indirectly, from knowing the size of other drugs that fit into the enzyme. (Says Weinstein, "Determining the structure of a receptor is like trying to describe the beauty of a woman while only knowing what her husband and lovers look like.") In the last screen, the steroid and the enzyme combine to complete the sequence, in what Covey's colleagues call, for obvious reasons, the "Big Mac" model.

Having determined all these specifications for normal interaction between a steroid and an enzyme, Covey can design his kamikaze steroid. Like a molecular bomb expert, he varies the formula of the steroid just enough so that it will not only fit between the barriers



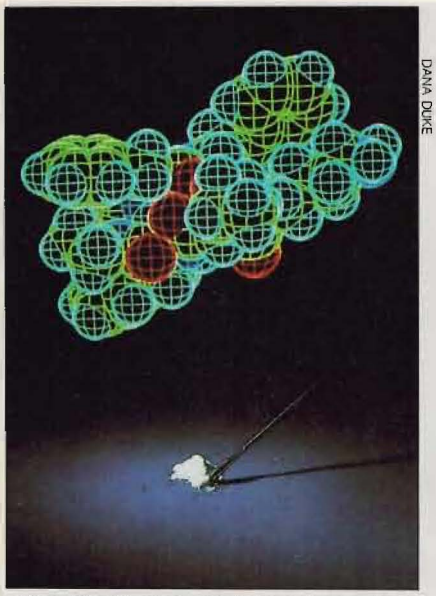
Yellow grid defines the boundaries of the enzyme

The steroid fits into and chemically reacts with the enzyme

but, once "bitten into" by the enzyme, destroy both the enzyme and itself in the ensuing chemical reaction. "This process may be helpful in treating tumors," says Covey. "Molecules could be designed specifically to seek out and kill an enzyme that keeps a tumor growing." He has already produced one of his computer-designed steroids, and it has destroyed a bacterial enzyme. His next project is to design a suicide molecule that will attack enzymes in rat tissues.

The use of computer graphics in drug design is so new that it has not yet been used to produce drugs for human use. But at Merck, one computer-designed compound has been tested on laboratory animals. It is similar to the hormone somatostatin, a long chain of amino acids that helps regulate, among other things, the release of glucagon, which controls blood-sugar levels. Thus an extra dose of this natural hormone might help diabetics—if not for one problem: it does not stay in the body long enough to be useful. With their computer, Merck scientists set out to change that.

Led by Daniel Veber, they soon found that all the useful work of somatostatin was being done by a group of four amino acids on one side of the molecule; the rest of the long chain was, in a sense, excess baggage. Using computer graphics developed by Peter Gund, they decided to snip off the section that was doing



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New Merck compound: from computer model to finished product

the work and attach it to a shorter chemical handle. The resulting compound—a fine, white powder—stays in the body anywhere from ten to 40 times as long as the natural hormone and shows nearly all the effects of somatostatin in tests on rats, dogs, and monkeys. If the drug goes into and passes clinical tests, it may be given to diabetics to improve their response to insulin. Says Veber, "The computer was instrumental in introducing new lines of thinking into our work."

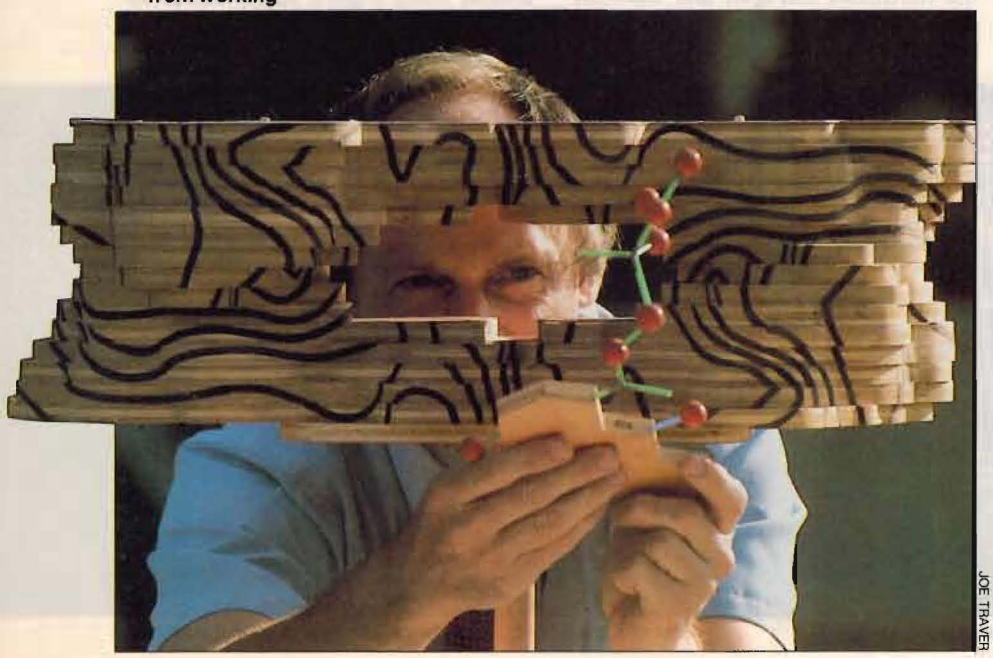
For Kenneth Miller, a theoretical chemist at Rensselaer Polytechnic Institute in New York, the computer is a means of testing and discarding ideas more quickly in his search for anti-cancer agents. Miller has been looking at ways to disrupt the function of DNA, the "double helix" molecule that resembles a spiral staircase and carries the genetic message in its steps. A drug called lucanthone has characteristics that draw it toward DNA molecules. Its approach causes two steps in the molecule to spread apart; it can then slip into the opening, where it becomes a wedge that prevents the DNA from transmitting its message. Says Miller, "If you can stop the DNA in a cancer cell from passing along its information, you may be able to stop the disease."

But lucanthone is toxic. It attacks the DNA of normal cells as well as cancerous ones. Using its structure as a starting point (it resembles three hexagonal bathroom tiles joined in a row), Miller has used the computer to design close (and, he hopes, nontoxic) cousins of the drug. With its ability to carry out millions of calculations, the computer helps Miller decide which of his candidates will single out cancer cells, get through the cell walls, open up the DNA, and bind tightly to it. "It's like writing a recipe," says Miller. His colleagues, organic chemists Kevin Potts and Sydney Archer, have made five of the computer-designed molecules and turned them over to the National Institutes of Health, which is now testing them for safety and effectiveness.

Miller has also analyzed the way one anti-cancer agent, daunomycin, works; it attacks a specific site on the DNA molecule—a certain "word" in the genetic code. He thinks this knowledge could lead to some interesting medicine: "I can imagine that in the distant future a sample of someone's tumor will be snipped off and put into a gene machine to have its code read off. Then we'll push some buttons on a computer to design and synthesize a drug that will attack only that code."

Does all this mean that the days of the pharmaceutical chemists are numbered, that they, like many others, can be replaced by a computer? Not at all, says Gund. "You can have the most beautiful picture of a molecule on the computer screen, but the big test is whether or not it actually works in the body." Adds Veber, "Sometimes the molecules the computer proposes do absolutely nothing." Electronic logic, it seems, is not infallible. Langridge also hastens to reassure his fellow chemists. "The computer is only a tool," he says. "After all, the most important thing is the person sitting in front of the screen." ◙

Peering through a large model of a DNA molecule, Miller holds a small molecule that can slip into the hole and stop DNA from working



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