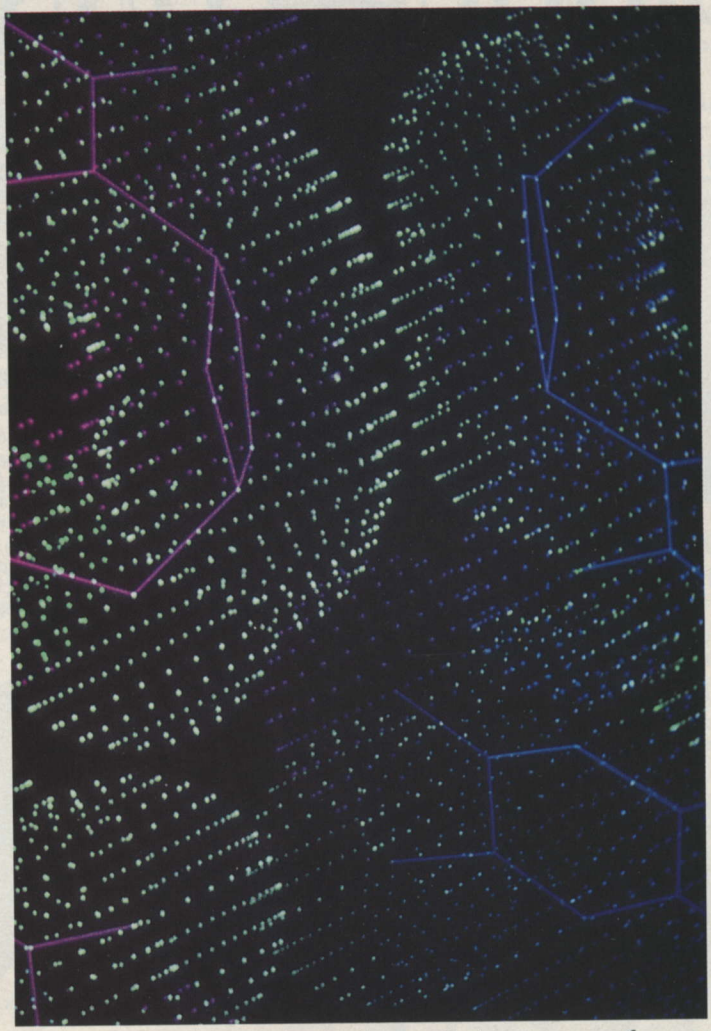
Margie Patlak

The Arsenal Gets Larger

IN 1983, WHEN THE cause of AIDS was found to be a virus, the pharmaceutical industry was openly gloomy about the prospects for treating the disease. It hadn't had much success with drugs aimed at viruses—only five antiviral drugs had been developed. A large part of the problem was—and is—the sheer intimacy of the relationship between viruses and the cells they infect. The challenge lies in making drugs that attack the virus without harming the cell. HIV, the AIDS virus, presents a particularly tough problem. It not only takes up residence in cells but slips its genes right into their DNA, making it even more difficult for a drug to distinguish between the two.

Now, six years after the AIDS virus was identified, the horizon looks a little brighter. More than 25 potential anti-HIV compounds are in various stages of testing. No single drug can promise a cure—none can actually rid the body of HIV. But researchers speak more hopefully about using combinations of drugs to keep the virus in check. "We used to say everybody with AIDS is going to die and there's nothing we can do about it," says Mathilde Krim of the American Foundation for AIDS Research. "Now we say AIDS is a treatable disease. How well it can be treated remains to be seen."



Computer modeling is being used to study the structure of the compound d4T. Like the AIDS drug AZT, d4T prevents the AIDS virus from taking over a cell's genetic machinery and reproducing. But d4T, it is hoped, will be less toxic.

PHOTOGRAPH COURTESY BRISTOL-MYERS COMPANY

The progress in AIDS drug development stems in part from advances in understanding the virus's biology. Basic research has shed light on the key events in the virus's life cycle—from the time it first introduces itself to a cell to when it co-opts it into becoming a virus factory. Each of these steps offers drugmakers an opportunity to intercept the virus and cut short its path of destruction. The very first step involves the binding of the virus to a cell. Cells targeted by the AIDS virus have molecules called CD4 receptors on their surface. The AIDS virus, for its part, is studded with proteins that serve as the binding site for these receptors. Attachment gains the virus entry into the cell and launches the infection.

The most intriguing of the drugs developed to block this process is a synthetic, free-floating version of the receptor, called soluble CD4. It essentially acts as a decoy: it sticks to all the binding sites on the virus before they have a chance to bind to the real CD4 receptors on the cells. Smothered by the drug, the virus can't get a fix on the cells and therefore can't infect them. "It's a very exciting, promising new drug," says Paul Volberding, director of the AIDS program at San Francisco General Hospital and one of several investigators now testing CD4 in AIDS patients.

The strategy just described uses CD4 to keep virus out of healthy cells. But in an interesting twist, the drug could be used to search out virus-inhabited cells as well. When the AIDS virus lurks inside a cell, it apparently "marks" the surface of that cell with the very same protein that acts as the binding site for CD4. So to attack the virus in these cells, researchers at the National Institutes of Health and the University of Texas have linked soluble CD4 to lethal poisons. In the laboratory dish at least, the drugs act as guided missiles, carrying their poisonous cargo right to the infected cells, while sparing healthy ones.

"These drugs are more likely to get to the right cells than any other substance we have to date," says John McGowan of the National Institute of Allergy and Infectious Diseases. But it remains to be seen if the toxic bullets perform in humans as well as they do in the laboratory.

Another drug that appears to stop HIV from binding to cells—at least in

the laboratory—is a sugarlike compound called dextran sulfate. This drug, which is imported from Japan, made headlines last summer when AIDS patients pressured the Food and Drug Administration into relaxing import restrictions on it. Exactly how dextran sulfate works is still unclear, but the drug is known to carry a strong negative charge. Flossie Wong-Staal of the National Cancer Institute speculates that the compound somehow comes between HIV and its target cells and uses its negative charge like an electronic shield to repel the virus, which is also negatively charged. The drug has "striking activity" in the laboratory, says Volberding, and it is now being tested in patients.

Once HIV enters a cell, it sheds its protein coat, revealing its naked thread of genetic material. In HIV that genetic material is in the form of RNA. Using its RNA as a template, the virus must then transcribe its genetic message into DNA, to make it compatible with the cell's own genetic machinery. It is this transcription process—without which the virus cannot reproduce—that is targeted by zidovudine, better known as AZT. The drug tricks the virus by providing a compound that looks like one of the building blocks HIV needs to build its DNA chains. But the building block is a fake; it lacks the attachment point for the next block in the sequence, so the chain can't be completed.

AZT is still the only anti-HIV drug approved by the Food and Drug Administration. But it has been dogged by its toxicity. About half of all patients with advanced AIDS have to give up the drug because of severe anemia, liver problems, and other side effects. The hope is that a second generation of AZT-like drugs—compounds designated by abbreviations like ddI, d4T, and AZDU—will turn out to be less damaging. "It would be a major step forward to find a drug that equals AZT in action with less toxicity," says Volberding.

After the AIDS virus has inserted its genes into a cell, it's in the driver's seat. It can now turn the cell into a factory that churns out viral proteins and then assembles them into new virus particles. Eventually these offspring burst forth from the cell to seek out and infect new targets.

Interferons, substances normally made in the body in response to infection, are known to thwart these steps in the life cycle of certain viruses. Now it's hoped that they will also stop the AIDS virus in its tracks. National Institutes of Health immunologist H. Clifford Lane recently tested alpha interferon on a small group of patients and found the results promising for those who were in the early stages of infection. The drug boosted their white blood cells and lowered amounts of an HIV marker, a protein made by the virus that circulates in the blood. Both these findings suggest that interferon is stemming the tide of new virus escaping into the bloodstream.

Polarized light reveals jewellike colors in the feathery structure of a crystal of AZT photographed under high magnification.

PHOTOGRAPH BY DENI McINTYRE, BURROUGHS WELLCOME

Moreover, studies suggest that combining alpha interferon with AZT works better—and at lower, less toxic doses—than using either alone. "If I had an HIV infection today," says Krim, who pioneered interferon research in the 1970s, "I'd treat myself with alpha interferon and AZT." All AIDS investigators may not share her conviction that the combination of these two drugs is the answer. But most do agree that a multipronged attack on HIV, using several drugs with different targets, probably offers AIDS patients their best shot at a normal life span. "In AIDS no single therapy is going to work," says McGowan, "so we need to have as many different kinds of drugs as possible in the arsenal."

There's no guarantee, of course, that the drugs now being tested will pan out: results that look spectacular in the lab may not translate into real improvements in the clinic, or a drug's side effects may prove to be intolerable. But these drugs are only the first to be examined—numerous others are waiting in the wings. Many of these compounds attack quite different stages in the virus's life cycle. Some appear to prevent the virus from uncoating when it enters a cell, for example. Others seem to work further along the assembly line—they stop infected cells from making and trimming the proteins prior to assembling them into new viral packages. "We're just beginning," says McGowan. "There are many important drugs in development with equal or better potential than the ones we see now." ❑