Where Are All Those Antiviral Drugs?

Certainly not on the American market. Some blame the FDA, others the pugnacity of viruses and the difficulty of destroying them without hurting cells as well.

BY JOAN AREHART-TREICHEL

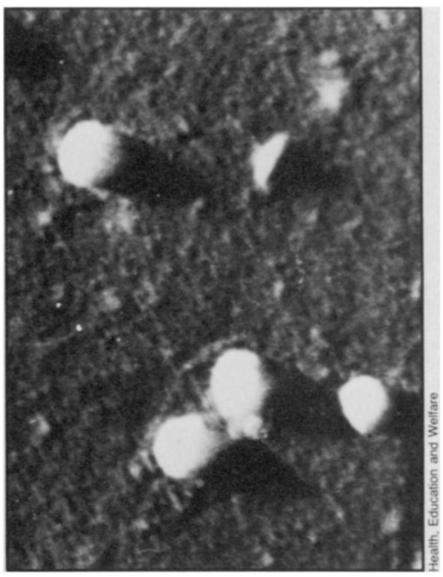
If there was ever a glorious age of medical research, it had to be the 1940s and 1950s when deadly bacterial diseases fell like tenpins before the isolation of antibiotics. Public hopes were thus raised that the common cold, flu, hepatitis, herpes simplex infections, cytomegalovirus infections and other viral diseases that inflict Americans a billion times each year with misery might also fall before the discovery of antiviral drugs.

Alas, it hasn't happened. There are only two antiviral drugs on the American market—amantadine (marketed by DuPont as a preventative against one strain of flu) and idoxuridine (marketed by Allergan Pharmaceuticals and Smith, Kline and French Laboratories for herpes infection of the eye). Some scientists blame the government, specifically the Food and Drug Administration. Others blame the complexity of viral infections and the difficulty of killing viruses without harming the cells that house them. Knocking viruses, in brief, is a different game from knocking bacteria.

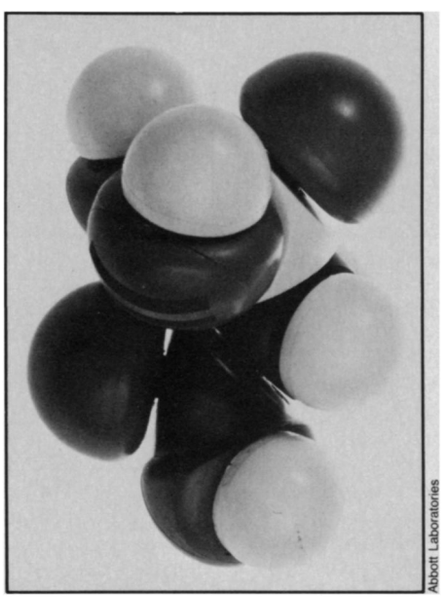
One of the scientists who blames the government is Ernest C. Herrmann Jr. of the University of Illinois and chairman of the recent Conference on Antiviral Substances sponsored by the New York Academy of Sciences. Whereas the government heavily supported antibiotic research, he says, it has not done so for antiviral research. Hence, drug companies have had to go it alone. And where companies have tried to go it alone, the FDA has been overzealous about effectiveness and safety, so many drug companies have shelved their antiviral programs.

"I've been to the FDA and have told them flatly that they have had a depressing effect," Herrmann declares. Amantadine, for example, is allowed on the market for only one strain of flu that hasn't been seen since 1967 "except in my icebox," he says. Yet the drug, he insists, is active against other strains of flu as well. So why isn't it allowed on the market for use against them, too? Such restrictions, Herrmann believes, have "had a dramatic effect on the health of the American people."

The situation is not as simple as Herrmann says, counters J.L. Melnick of the Baylor College of Medicine. Theodore Ginsberg of Newport Pharmaceuticals International in Newport Beach, Calif., agrees: "I would say that much of the difficulty is due to scientific problems as well." Antibiotics, Ginsberg explains, were discovered by hit-and-miss approaches. Only after they were shown to be effective and safe against bacteria did the reason for their actions become apparent. For example, those of the penicillin type attack bacteria in the bloodstream, and they go for the bacteria's cell walls. They do not attack human cells. Viruses, on the other hand, are not self-contained organisms. They are parasites that live inside cells. They have no cell walls and little machinery of their own. Consequently, a serendipitous approach to finding antiviral drugs did not produce anything that selectively attacked viruses without attacking cells, too.



Influenza viruses, magnified 110,000 times.



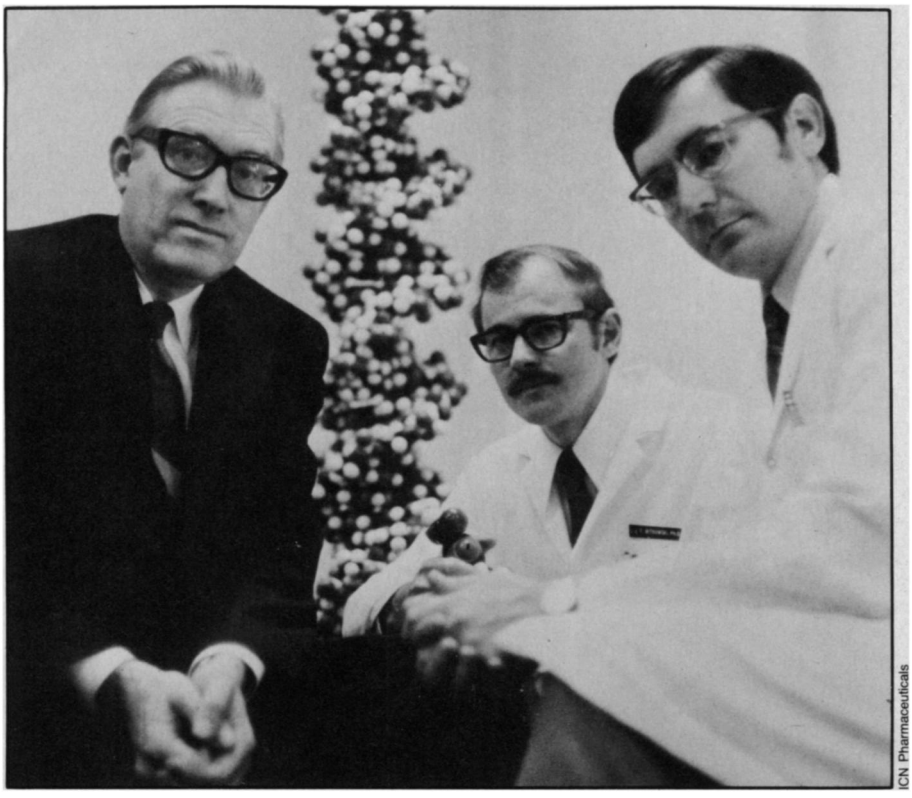
Model of virus drug phosphonoacetic acid.

Thanks to the arrival of the brave new scientific specialty known as molecular pharmacology, scientists are now finding some promising antiviral drugs. They're rationally designing drugs so that they will attack viruses but not cells.

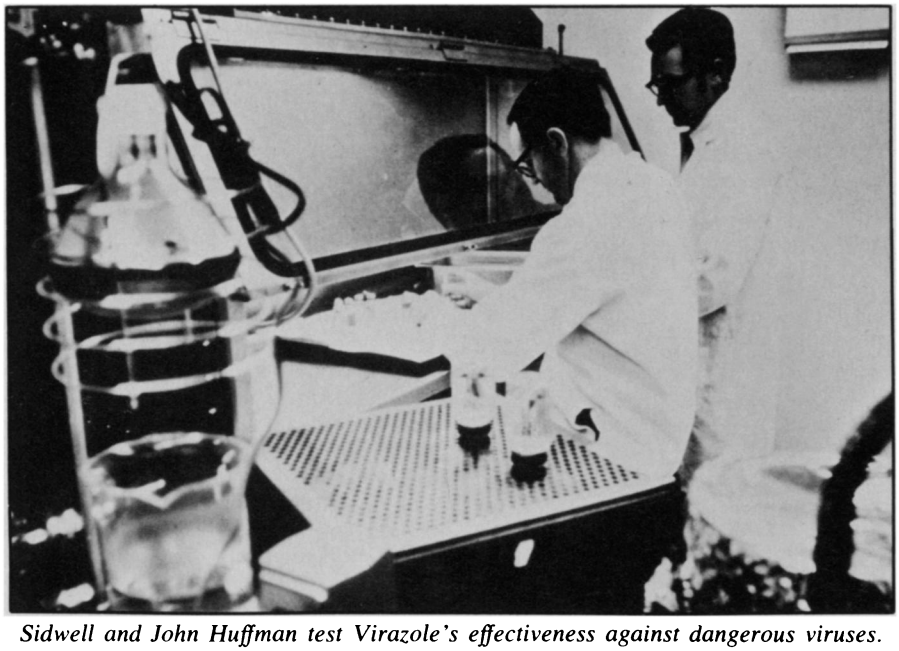
A prime example of the rational approach to finding antiviral drugs comes from scientists at the ICN Nucleic Acid Research Institute, ICN Pharmaceuticals in Irvine, Calif. Seven years ago R.K. Robins felt that scientists knew enough about viruses and viral infections to attack viruses rationally. So he gave up the position of professor of medicinal chemistry at the University of Utah and, with other scientists of similar views, organized the ICN Nucleic Acid Research Institute to map out a strategy for designing antiviral drugs.

The first requirement was preparing a drug that could get into a cell. "It was a big problem," Robins says. Another problem was designing the drug so that it would remain inside the cell for six hours at least. During this time it would do its work as assassin. Specifically, it would interfere with an enzyme that is common to both DNA and RNA viruses, one involved in the synthesis of new viral RNA. If such synthesis could be altered, then new viral proteins couldn't be made. And new cores of viral nucleic acids wouldn't have protein coats to cover them. Thus, there would be no new, complete viruses to leave the cell, and infection would be terminated.

The ICN scientists then made a drug to fit these needs. It is a totally synthetic



Robins, J.T. Witkowski, R.W. Sidwell—three of the scientists who made Virazole.



Sidwell and John Huffman test Virazole's effectiveness against dangerous viruses.

ribonucleoside known as Virazole (the generic name is ribovirin). A ribonucleoside was selected because it is most likely to act as an inhibitor of viral messenger RNA synthesis, especially binding to enzymes involved in such synthesis. Studies to date indicate that Virazole is transported into the cell by a facilitated transport mechanism. Once in the cell, it is phosphorylated to an active form, which remains in the cell about 12 hours. During this time it inhibits the synthesis of new viral RNA within the host cell without permanently altering cellular RNA synthesis. "It appears that we have been thus far successful," Robins says.

Even more impressive, their rational attack at the molecular level leads to disease eradication in animals and people. For instance, L.B. Allen and her coworkers at ICN infected mice tails with herpes virus cold sores. Then they applied Virazole topically to the sores. The sores healed considerably faster than those in the control mice. Next, they applied Virazole to herpes infections of the genital area in mice. The drug also helped reduce these infections. Salido Rengell of the Institute of Virology in Mexico City undertook a double-blind trial with Virazole among girls in a boarding school during a flu outbreak: 21 girls received Virazole, 24 received a placebo pill. Virazole reduced flu symptoms considerably; the placebo did not. Flu virus was isolated from 22 out of 24 placebo subjects, and from only 3 out of 21 subjects receiving Virazole. Then P. Galvaõ from São Paulo, Brazil, used Virazole against acute viral hepatitis in 33 patients; 33 other hepatitis patients got a placebo. Both groups improved, but especially the one receiving Virazole.

Virazole, in fact, is already on the market in Mexico for treatment of viral respiratory infections and is sold in Brazil for the treatment of viral hepatitis.

Vira-A (alias adenine arabinoside) is another antiviral drug designed to attack viruses but not human cells. It was formulated by scientists at Parke, Davis and Co. in Ann Arbor, Mich. They have found that it significantly inhibits the replication of herpes virus in cells by inhibiting a DNA polymerase enzyme made by the virus. This inhibition improved the condition of mice with herpes infections.

Still another drug that has been found to attack viruses and not cells is phosphonoacetic acid. It was made by scientists at Abbott Laboratories in North Chicago. According to R.G. Duff and J.C. Mao of Abbott, it inhibits herpes virus's specific DNA polymerase, just as Vira-A does. So they consider it to be "a promising candidate for an antiherpes virus chemotherapeutic without the extensive inhibition of noninfected cells associated with other antiviral agents."

And then there is Isoprinosine (alias inosiplex), designed by scientists at Newport Pharmaceuticals, Inc. to combat viral diseases by stimulating the body's natural immune defenses against them. Isoprinosine has shown antiviral activity in tissue culture, animal and clinical trials. For instance, Robert H. Waldman and Rama Ganguly of the University of Florida tested it in a double-blind clinical trial. Thirty-nine volunteers were randomly chosen to receive either Isoprinosine or a placebo tablet. They were then challenged with a cold virus. Of the 19 volunteers receiving Isoprinosine, 5 became ill, whereas 14 out of 20 in the placebo group did. Luis Mayo Lao of the Philippines used Isoprinosine on patients with viral pneumonia. The drug provided good, if not excellent, relief from their symptoms. Isoprinosine is already being marketed in South America, Southeast Asia and the Middle East for herpes infections, flu, measles and mumps.

Even with all this progress, a number of questions press for answers. First, there is a need to make sure that the drugs don't cause serious side effects. How specific are they really in attacking viruses but not cells? Virazole, for example, has been

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shown to trigger certain birth defects in rodents. But it did not induce them in rabbits, and ICN investigators are now attempting to see whether such birth defects are caused in baboons. Vira-A, J.C. Drach of the University of Michigan reports, does inhibit viral DNA synthesis, but it still inhibits cellular DNA synthesis to some degree. And what are the drugs doing to the body's natural immunity against viruses? Isoprinosine has been shown to enhance the body's natural immunity against viruses, but how about the other drugs? "We are in a state of gross ignorance about how antibodies attack viruses," one scientist admits, "and how we can manipulate them to fight viruses."

Then there is the question of whether antiviral drugs could completely eradicate viruses from the body, or whether they only have to reduce the virus level enough that the body's immune system can take over from there. Herrmann believes that it may not "be necessary to get completely rid of viruses in people as is the case with bacteria."

The efficacy of antiviral drugs also needs further confirmation through double-blind clinical trials in the United States. But as R.W. Sidwell of ICN admits, such trials are indeed costly ($30,000 to $100,000 a trial), and a drug company can spend $2.5 million on clinical trials beyond all the basic research costs and animal studies. Such costs are especially prohibitive for smaller drug companies like ICN Pharmaceuticals, and that is why they do their initial clinical testing in other countries. "Yet if we're going to have antiviral drugs," Herrmann points out, "they have to be made by drug companies in this country, and they have to make money from them."

Finally, there is the need for the FDA to better educate itself to viruses, viral infections and how drugs fight them. As one drug company investigator explains: "The FDA wanted proof that our drug reached a high concentration in the bloodstream. But we told them that the important thing is that the drug attacks viruses inside cells."

"Although our drug has been shown effective and safe if given by mouth," another investigator complained, "the FDA now wants us to take two more years to show that it is effective and safe if given topically. That seems like a waste of time and money to me. If it was the other way around, I would understand."

Even with all these hurdles, though, scientists in the field are convinced that more antiviral drugs will eventually reach the American market. For instance, double-blind clinical trials in the United States will be getting underway soon to find whether Virazole is effective against flu, hepatitis and herpes infections. Vira-A, Virazole and Isoprinosine may even make it on the market in the next several years, some researchers predict. □