Chemotherapy: Antiviral Agents Come of Age

The era of the antiviral agent is upon us. Just as the use of antibiotics revolutionized the treatment of bacterial disease in the 1940's, new antiviral agents promise to revolutionize the treatment of viral diseases in the 1970's and 1980's. For the first time, man will be able to combat viral infections, halting the replication of viruses and preventing their spread. The advent of this era may well be one of the most important milestones in the continuing battle against infectious diseases.

The genesis of the antiviral era has been quite different from that of the antibiotic era. The latter was launched by the discovery of penicillin, a relatively broad spectrum antibiotic whose value was readily apparent. The antiviral era is being launched with a number of narrow-spectrum agents whose value has been more difficult to establish. Antibiotics were introduced at a time when only a limited amount of testing was necessary to introduce a new drug to the market and when the need to treat wounded soldiers during a major war greatly accelerated that testing. Antiviral agents are being introduced at a time when consumer safety is the paramount concern, necessitating a great deal of expensive, time-consuming clinical testing. The development and testing of antibiotics was largely subsidized by the federal government because of the national emergency, and the first antibiotics were quite profitable for the companies that put them on the market. The development of antiviral agents, in contrast, has been financed by the drug companies with only limited support from the government, and no company has yet made a profit on one. In some ways, it is remarkable that the antiviral agents have been developed as rapidly as they have been.

Just 11 years ago, when the New York Academy of Sciences sponsored one of the first conferences on antiviral agents, according to Ernest C. Herrmann, Jr., of the Peoria School of Medicine (he organized all three academy conferences), there were no more than a half-dozen scientists in the United States who had faith that safe and effective antiviral agents could be produced. Most of the scientific community, he says, then believed that the replicative cycle of viruses was so similar to that of the mammalian cell that it would be nearly impossible to find agents that could interfere with the viral cycle without also killing cells.

By the time of the academy's second conference 6 years ago, investigators had identified many differences between the replicative cycles, and perhaps half the participants believed that these differences could be exploited. But by the time of the academy's third conference, held in February of this year, investigators had found a number of agents that are safe and effective against a variety of viral diseases and agreed that the concept of chemotherapy of viral infections is a sound one. The major questions in the minds of most of the participants at the conference seemed to be how soon the agents could be brought onto the market and how soon even better agents could be found.

There are, in fact, already two antiviral agents on the market in this country, one in England, and several others in those countries that require very little testing before a new product is marketed. The first commercial antiviral agent was idoxuridine (5-iodo-2′-deoxyuridine), sold as Stoxil by Smith Kline & French Laboratories of Philadelphia. Idoxuridine was the first agent shown to be effective when applied topically against herpes keratitis, a rather severe eye infection that is responsible for an estimated 18,000 cases of blindness in the United States each year. Idoxuridine has many side effects when administered parenterally, however, and these effectively preclude its use against other types of infection. This agent may fall by the wayside as safer and more effective anti-herpes agents are introduced.

The second major antiviral agent is methisazone (*N*-methylisatin-β-thiosemicarbazone), sold in England as Marboran by the Burroughs Wellcome Company. Thiosemicarbazones were the first family of compounds found to exhibit antiviral activity—more than 20 years ago. That activity was inexplicably ignored until the development of methisazone, which is quite effective against one major type of smallpox virus and against vaccinia (cowpox) virus, which is used to vaccinate against smallpox. Unfortunately for the manufacturers of methisazone, smallpox has been virtually eradicated throughout the world and they have been left with the proverbial cure looking for a disease.

The most important of the antiviral agents now on the market is amantadine hydrochloride (1-adamantanamine hydrochloride), sold as Symmetrel by Endo Laboratories, a subsidiary of E. I. du Pont de Nemours & Company, Wilmington. Amantadine hydrochloride is now generally regarded to be effective prophylactically against influenza A, the most commonly encountered form of the virus and the only one thought to be capable of initiating pandemics. But the Food and Drug Administration (FDA) has not permitted Du Pont to make such a broad claim (see box). Consequently, amantadine hydrochloride has been a commercial failure as an antiviral agent.

This commercial failure, in the opinion of Herrmann and other observers, has had a chilling effect on the development of antiviral agents. Du Pont's problems, Herrmann argues, were a major factor in the decisions of some companies to abandon their antiviral programs or not to seek FDA approval for their own antiviral agents. The most beneficial thing that could happen now, he argues, would be for some company to make a large profit on a new antiviral agent. Once this occurs, he contends, other companies will accelerate their own testing programs and many more antiviral agents will reach the market, to the net benefit of the consumer. This line of reasoning seems both simplistic and overoptimistic to many investigators, but it is apparently accepted by a large number of individuals both within and outside the drug industry. That acceptance in itself might make the prediction self-fulfilling.

A number of compounds are strong candidates for becoming commercially successful agents. Three of them, ribavirin, vidarabine, and phosphonoacetic acid, are antiviral agents in the strictest sense of the term—that is, they interfere directly with viral replication. Two others, levamisole and isoprinosine, appear to act by potentiating the activity of the recipient's immune system. And several others are thought to stimulate production of interferon, a naturally occurring antiviral agent. The presumed mechanism of action and spectrum of activity of the immunopotentiating agents and the interferon inducers are quite different from those of the antiviral agents, however, and their efficacy is somewhat more doubtful. The following discussion is therefore to be restricted to those

agents that directly interfere with viral replication.

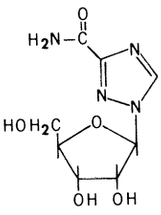
The widest spectrum of antiviral activity is claimed for ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide), which has been registered under the trade name Virazole by ICN Pharmaceuticals Inc. of Irvine, California. Virazole is already being marketed in Mexico for viral respiratory infections and in Brazil for viral hepatitis. It is also being sold in other countries in Latin America and Africa. ICN hopes that it can obtain FDA approval of the drug for certain uses within 2 years.

Ribavirin appears to be effective against three different families of disease—herpesvirus infections, hepatitis, and influenza. The first U.S. approval of the drug will probably be for use against herpesviruses. These are a large family of DNA viruses that are the causative factor of diseases, such as cold sores of the mouth, genital lesions, eye infections, varicella (chicken pox), and shingles. Herpesviruses are one of the most common causes of viral disease. By some estimates, as many as 10 percent of all Americans over the age of 18 have recurrent herpes infections three or more times per year. And more than 70 percent of Americans are thought to have antibodies in their blood that indicate a prior herpes infection. Some types of persistent herpes infections are thought to be associated with initiation of cancer.

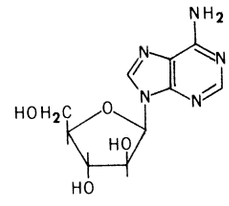
Herpesviruses are particularly susceptible to chemotherapy. Isolated herpesviruses can be killed by various agents, ranging from common vinegar to sophisticated nucleoside analogs. For this reason, herpesviruses are generally among the first to be studied when new antiviral agents are developed, and much time and effort are devoted to them. The problem, of course, is finding an agent that can safely cross the cellular membrane and attack the virus without disrupting cellular metabolism.

Ribavirin is one of the many agents that can achieve this goal. It does it, according to Jon P. Miller and David G. Streeter of ICN, by inhibiting an enzyme, inosine monophosphate dehydrogenase, that has an important function only in cells infected by viruses such as herpes. By inhibiting this enzyme, the drug interferes with the biosynthesis of guanine nucleotides, and thus with the biosynthesis of viral DNA. This inhibition can be reversed in cell cultures by the addition of guanosine and certain other naturally occurring nucleosides.

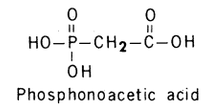
Ribavirin has been found to be effective against herpes zoster (shingles), an infection characterized by painful inflammation of the skin along the paths of nerves, in double-blind studies conducted by R. Diaz Perchez and Humberto Fernandez Zertuche of the ICN subsidiary in Mexico City. In their studies, neither the patient nor the physician knew which patients received placebo and which received the drug until the code was broken at the end of the trial, hence the term double-blind. Double-blind studies are necessary for definitive proof that an agent works in humans.



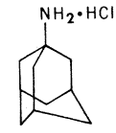
Ribavirin



Vidarabine



Phosphonoacetic acid



Amantadine hydrochloride

Perchez and Zertuche found that topical application of ribavirin reduced pain and the severity of inflammation and shortened the course of the disease. ICN is planning further trials to demonstrate the efficacy of topical application against herpesviruses, according to Robert W. Sidwell of the same company. Thus topical application in shingles will probably be the first use for which the company will seek FDA approval for ribavirin.

The second major application of ribavirin is against hepatitis. There are at least two major forms of this disease. Hepatitis type A or infectious hepatitis is a mild form believed to be caused by an RNA virus; hepatitis type B or serum hepatitis is a more severe form that is probably caused by a DNA virus. The blood of victims and carriers of the B type contains a glycoprotein known as hepatitis B antigen (HBAg). The presence of this antigen is generally considered to be proof of infection.

Ribavirin significantly reduced the symptoms of type A hepatitis in double-blind studies conducted by Paulo A. A. Galvao of the Emilio Ribas Hospital in São Paulo, Brazil. The recuperation of 33 patients treated with the drug was significantly faster than that of the controls, and various biochemical tests indicated a marked reduction in symptoms. Three other controlled studies in Brazil have shown similar success against type A hepatitis.

James W. Mosely of John Wesley Hospital in Los Angeles has demonstrated that treatment of type B hepatitis with ribavirin has little significant effect on that disease. Trials conducted in Brazil by M. P. Vilela of the Gastroenterology Clinic in São Paulo, however, indicate that the drug therapy may lead to the disappearance of HBAg from the blood of patients who are chronic carriers of it. This suggests that ribavirin may be able to halt the infectivity of carriers of the disease. ICN has recently begun double-blind trials in England to find out if this, in fact, occurs. They have also begun similar trials against type A hepatitis in the United States and are preparing to begin trials in Canada against both forms of the disease.

The third class of disease against which ribavirin appears to be effective is influenza, which is caused by a family of RNA viruses. John Oxford of the Medical Research Council in England has reported that ribavirin specifically inhibits the synthesis of influenza viral proteins while having no discernible effect on the synthesis of the host's protein. Francisco Salido-Rengell of the National Institute of Virology in Mexico City has conducted a trial of ribavirin against influenza A during a natural outbreak of the disease at a girls' school in Mexico City. He observed a marked decrease in symptoms and severity of illness in the girls who received the drug. Furthermore, he was unable to isolate the virus from the majority of the 21 girls who received the drug, whereas it could be isolated readily from 22 of the 24 controls.

Two studies of the use of ribavirin against influenza A were conducted by Yasushi Togo of the University of Maryland School of Medicine and Albert Cohen of Peninsular Testing Corporation, Miami. Both studies produced negative results. A later study in which Togo tested ribavirin against influenza B did show a definite reduction in the serious signs of the disease. ICN is planning additional studies in the United States and Canada.

Ribavirin appears to produce very few side effects. The most important is anemia, which occurs only with about three times the normal dose of the drug, and which disappears when drug therapy is halted. But many investigators are concerned about its potential use because it is a teratogen—that is, it has been shown to produce birth defects when ingested by female rodents during the early stages of pregnancy. Teratoge-

nicity seems to be characteristic of antiviral agents that are nucleoside analogs, and this is not unduly surprising. The rapid cell division that occurs during gestation is accomplished by certain enzymes that are different from those in mature cells, and many of these may be similar to virus-specific enzymes. The ultimate solution to this problem will be the development of antiviral agents that are not nucleoside analogs; but in the meantime, the danger of birth defects

Amantadine: An Alternative for Prevention of Influenza

An example of the problems that can be encountered in marketing a new drug, particularly when the drug and the disease it is targeted against are out of the ordinary, can be found in the efforts of E. I. du Pont de Nemours & Company to market amantadine hydrochloride (Symmetrel) during the epidemic of Hong Kong influenza of 1968–1969. Even though amantadine hydrochloride is not the ideal anti-influenza agent, argue Fred M. Davenport of the University of Michigan Medical School, Ernest C. Herrmann, Jr., of the Peoria School of Medicine, and many other investigators, its use during the epidemic might have prevented a substantial number of the 40,000 influenza-related deaths in this country.

The history of these problems is illustrative of the reluctance of some scientists to accept new scientific developments, of the obstinancy of special interest groups whose interests might be threatened, and of the maxim that successful science does not necessarily ensure successful business. The history is also particularly pertinent because of the recent isolation of the new swine variant of influenza A virus, which many scientists believe to be the harbinger of another epidemic next winter.

The anti-influenza activity of amantadine hydrochloride was first reported in 1963 by George Gee Jackson, Robert L. Muldoon, and Loren W. Akers of the University of Illinois Hospital in Chicago. They found that ingestion of the drug inhibited the infection of volunteers inoculated with the Asian A_2 strain of influenza virus. Subsequent studies by them and other investigators indicated that use of the drug would reduce the incidence of infection by at least 50 percent. It was also found that amantadine hydrochloride and its analogs share an apparently unique mechanism of action. The details of the mechanism are not yet completely understood, but Conrad E. Hoffmann and his associates at Du Pont and Nobuo Kato and Hans J. Eggers of Justus Liebig Universitat in Giessen, West Germany, have shown that the drug prevents the infectious virus RNA from initiating new growth either by blocking penetration of the virus into the cell or by inhibiting removal of the protein coat of the virus particle.

Du Pont filed a new drug application for amantadine hydrochloride the following year and, on 18 October 1966, FDA approved its use "in the prevention (prophylaxis) of respiratory infections caused by influenza A_2 (Asian) virus strains . . ., especially for high influenza-risk patient groups or close contacts of index cases in whom respiratory illness is thought to be due to susceptible influenza A_2 (Asian) virus strains." By the time FDA issued this approval, however, the Asian A_2 strain was little more than a laboratory artifact.

Influenza A viruses display a genetic plasticity that is unique among the major disease-producing viruses (*Science*, 8 June 1973, page 1042). Their genetic complement is carried in five to seven discrete pieces of RNA rather than in the one piece that is found in most other viruses. Each of these pieces is thought to be an intact gene that controls at least one characteristic of the virus. Genetic plasticity arises from the ease with which these genes are interchanged among different viral strains.

If a host cell is simultaneously infected by two different strains of influenza A virus, the genes from these strains can undergo a random reassortment in the cell to produce one or more hybrid strains. The hybrids differ primarily in the nature of the glycoprotein antigens on their surface—the molecules that permit recognition in an immunological system. This so-called antigenic shift enables the hybrid to bypass the immunity to the parent strains which has built up in a large population, thereby rendering that population once more susceptible to infection and making possible the initiation of epidemics. (Influenza B and C viruses do not undergo antigenic shift, and thus are thought not capable of initiating epidemics.)

Antigenic shift is of critical importance in the manufacture of influenza vaccines, which must reflect precisely the antigenic determinants of the target virus. It should, however, be irrelevant to the chemotherapy of influenza infections since antiviral agents owe their activity to something other than interaction with the antigens. But FDA has regulated Symmetrel on the basis that antigenic shift produces a distinctly new virus.

When the Hong Kong strain of A_2 influenza virus was first detected in Europe in 1968, Du Pont sent scientists to bring back samples. Tests in tissue culture systems, in eggs, and in laboratory animals convinced company officials that the new strain was at least as susceptible to amantadine hydrochloride as the old strain. Du Pont then issued a press release suggesting that Symmetrel could be used for prophylaxis of the Hong Kong strain.

FDA objected that there had been no clinical trials of the effects of Symmetrel against the new strain in man—even though similar clinical trials are not required for vaccines against new influenza strains. The agency required Du Pont to send a "Dear Doctor" letter to every physician in the country stating that "Until such time as these tests are completed, we are not in a position to claim that 'Symmetrel' is efficacious in man for the prevention of influenza due to A_2/Hong Kong/68 strain." The clinical tests had, in fact, been begun as soon as possible, but they were not completed until the epidemic was practically over.

Du Pont subsequently submitted a revised application to FDA providing evidence from the clinical trials and other investigations which showed that laboratory studies of amantadine hydrochloride in tissue cultures and eggs are valid predictors of its effect against new influenza strains in man. In this manner, the company hoped to avoid conducting expensive ($2 to $3 million) and time-consuming (a year or longer) clinical trials for each new strain of the virus—trials that could not be completed before an epidemic was already over. This concession had already been given to vaccine manufacturers. Such tests have already shown, for

can probably be largely avoided by careful selection of drug recipients to avoid those who are pregnant. It should be mentioned that there are already drugs on the market, such as aspirin, which are suspected of producing birth defects when ingested by pregnant women.

Another important new antiviral drug is vidarabine (9-β-D-arabinofuranosyladenosine, also known as adenine arabinoside or ara-A); this drug was given the trade name Vira-A by its primary devel-

example, that the drug is effective against the new swine virus. This application was returned by FDA as "incomplete," for reasons that are still not clear.

Some investigators, such as Herrmann, have charged that FDA's rejection of the application was influenced by advisory groups with a strong stake in the use of vaccines. Such allegations have been vigorously denied by FDA, and would, in any case, be exceptionally difficult to prove. But Herrmann's concern is, perhaps, understandable. The advent of sulfa drugs, penicillin, and streptomycin virtually destroyed research on bacterial vaccines. It requires little imagination to foresee that effective antiviral agents could have a similar effect on research involving viral vaccines. The stakes that are involved are perhaps best illustrated by current arguments that some $150 million should be invested to produce 200 million doses of a vaccine against the new swine influenza virus. It should be noted that vaccination and chemotherapy are complementary. Drug treatment does not interfere with the development of immunity to influenza, and the drug is actually more effective in individuals with some immunity to the virus.

The objection to antiviral agents by those with an interest in vaccines is perhaps best exemplified by Albert B. Sabin, developer of the oral polio vaccine, who is now at the Medical College of South Carolina. Sabin has consistently argued that chemotherapy is not a viable approach to either the prevention or the therapy of viral disease, and he publicly and vigorously castigated FDA for issuing even limited approval for Symmetrel. Some scientists think that FDA overreacted to these attacks in its subsequent decisions about Symmetrel.

In June of 1967, Sabin published a Special Communication in the *Journal of the American Medical Association* that was highly critical of amantadine hydrochloride. Even some vaccine scientists concede that the article was blatently biased. Sabin summarized all the negative aspects of the first studies with the drug and concluded not only that it was ineffective, but also that it had potentially dangerous side effects. This article, combined with the subsequent "Dear Doctor" letter, apparently produced such a negative impression on physicians that hardly any of the drug was prescribed and used during the Hong Kong influenza epidemic.

Symmetrel would, in fact, probably have been taken out of production in the United States shortly thereafter had not the late Robert Schwab of Massachusetts General Hospital in Boston inadvertently discovered that it is effective against Parkinson's disease. (Parkinsonism is probably not caused by a virus, and in this disease the mechanism of the action of the drug is different from that against viruses.) FDA approved this use of Symmetrel in April 1973 after clinical trials showed that it was both effective and safe.

Meanwhile, according to Jackson, scientists in other countries began to investigate amantadine hydrochloride and found it effective. By 1971, controlled trials involving more than 20,000 subjects had been conducted in the U.S.S.R., Great Britain, Czechoslovakia, the Netherlands, and Sweden. Typical of these trials are those of A. A. Smorodintsev and his associates at the State Research Institute for Influenza in Leningrad. They found that amantadine hydrochloride is 51 percent effective in preventing disease after individuals are exposed to the Asian A_2 strain of influenza virus and at least 73 percent effective against the Hong Kong variant. As in the clinical trials with Parkinsonism, they observed no significant side effects. The most important is an amphetamine-like stimulus at high doses, although some patients may experience drowsiness. Furthermore, they observed that the severity and duration of influenza was greatly reduced in those individuals who contracted the disease despite drug treatment. Similar results were obtained in the other countries.

Amantadine hydrochloride was, in fact, used extensively in the Soviet Union during the Hong Kong influenza epidemic and subsequent outbreaks, and Soviet officials attribute a substantial reduction in disease and mortality to its use. American critics such as Sabin, however, argue that clinical trials conducted in other countries do not incorporate the rigid scientific protocols required in the United States, and that results obtained in such trials should not influence decision-making in this country.

Part of the problem of distinctions among the strains of influenza viruses may have been resolved in 1972 when the World Health Organization adopted new nomenclature for influenza viruses. The gist of the semantic change was that different strains of the virus—such as A_1, A_2, and so forth—should henceforth all be classified simply as influenza A. This decision reflected the view long held by scientists that the strains differ only in their antigenic determinants. In response to this change and to evidence from the foreign trials that was presented at a National Institutes of Health seminar in 1974, José Canchola of FDA asked Du Pont to submit a supplemental application for Symmetrel. This application, sent on 14 February 1975, would allow the drug to be marketed for prophylactic use against all strains of influenza A. The application is still under review by FDA, but Canchola says the chances are good that it will be approved.

Amantadine hydrochloride is by no means the perfect drug for use against influenza. It has, says Jackson, inherent limitations that make it less than ideal from both a clinical and logistical point of view. But the most important point, he contends, is that amantadine hydrochloride can provide an effective holding operation and supplemental therapy until such time as reliable vaccines against the new strains have been prepared or ideal chemotherapeutic agents have been developed.

Potentially better agents are already on the horizon. Du Pont and other investigators, for example, have found that analogs of amantadine hydrochloride—such as α-methyl-1-adamantanemethylyamine hydrochloride (rimantidine hydrochloride) and *N*-methyladamantanespiro-3′-pyrrolidine hydrochloride—are more effective for both prophylactic and therapeutic use against influenza A. But these and other agents will probably never reach the market until the problems encountered by amantadine hydrochloride have been fully resolved.—T.H.M.

oper, Parke, Davis & Company of Detroit. Vidarabine exhibits activity against poxviruses, oncornaviruses, and rhabdoviruses, but it seems to be most effective against herpesviruses, including herpes varicella. Vidarabine is converted to a triphosphate ester within the cell, according to Paul E. Borondy and his associates at Parke, Davis. This ester, says Werner E. G. Muller of Johannes Gutenberg University in Mainz/Rhein, West Germany, inhibits a herpes-specific DNA polymerase, and thus blocks replication of the virus.

Vidarabine is apparently quite effective against herpes keratitis. Studies conducted separately by Peter R. Laibson of the Wills Eye Hospital in Philadelphia and Deborah Pavan-Langston of the Massachusetts Eye and Ear Infirmary in Boston, for instance, demonstrated that vidarabine is at least as effective as idoxuridine against the eye disease, and that it perhaps has fewer side effects. Studies by Pavan-Langston and other investigators have also shown that vidarabine is effective against herpes keratitis in patients who are allergic or resistant to idoxuridine therapy. The FDA is reviewing the results of these and other studies, and Parke, Davis hopes to receive approval sometime this year to market vidarabine for topical use against herpes keratitis.

The National Institute of Allergy and Infectious Diseases (NIAID) is cooperating with Parke, Davis to sponsor studies of the use of vidarabine against herpes zoster, herpes encephalitis, neonatal herpes, and progressive mucocutaneous herpes (which includes the venereal disease herpes progenitalis). There are now four separate studies of these effects being conducted by 20 investigators under the leadership of Charles Alford and Richard J. Whitley of the University of Alabama. Results from these first studies suggest that the drug is effective against herpes zoster. Studies conducted by James Luby of the Southwestern Medical Center in Dallas, however, indicate that the drug is not effective against herpes progenitalis.

Vidarabine has few side effects—although it is also teratogenic—but it has at least two liabilities. The first is that it is quite insoluble in water. This can make it difficult to administer. The second is that it is rapidly degraded by a commonly occurring enzyme called adenine deaminase. Deamination of vidarabine renders it much less effective. Monkeys, for example, have very high concentrations of the enzyme, so the drug is almost completely useless against viral infections in them. Humans have lower concentrations of adenine deaminase, but the concentrations are great enough to require high doses of the drug.

One approach to the second problem is to use vidarabine in combination with specific inhibitors of adenine deaminase. A nucleoside analog isolated from *Streptomyces antibioticus*, for example, has been found by Bernard J. Sloan and his associates at Parke, Davis to be a very effective inhibitor of the enzyme. A combination of vidarabine and the inhibitor is effective, for example, against many viral infections in monkeys where vidarabine alone is not. In other species, small doses of the combination are as effective against viral infections as much higher doses of vidarabine alone.

But this approach also presents a problem. FDA may not approve, and physicians may not be willing to prescribe, a compound that inhibits an enzyme with a normal function in the body. By far the better approach, then, may be the use of vidarabine derivatives that are not as readily deaminated. Some of these have the additional advantage of being more soluble.

One such compound is vidarabine 5′-monophosphate, also known as ara-AMP, which is freely soluble in water. Tests at Parke, Davis indicate that it is deaminated less readily than vidarabine in tissue culture and animal systems, and thus may be effective at somewhat lower doses. Parke, Davis, NIAID, and the National Institute of Dental Research are planning trials at three clinics to study use of the drug against mucocutaneous herpes. The FDA has just given permission to test the drug in humans, and the trials will begin in June. If these trials are successful, ara-AMP will be tested in a similar fashion against herpes progenitalis.

A similar type of compound is 9-β-D-arabinofuranosylhypoxanthine 5′-monophosphate, which is also water-soluble. ICN claims that this drug is at least as effective as vidarabine against viruses, and the company has received permission from FDA to test the drug for oral applications in humans. Filing for topical applications is in progress. Other derivatives of vidarabine are being tested at various institutions.

The third major new antiviral agent is phosphonoacetic acid, which is being studied by Lacy R. Overby and his associates at Abbott Laboratories in Chicago. Phosphonoacetic acid may be the most effective of the new agents against herpesviruses, Overby says, but so far it has been tested only in animals. It has one great potential advantage in that it is not a nucleoside analog, which should reduce the potential for teratogenicity. Like vidarabine, phosphonoacetic acid inhibits the herpes-specific DNA polymerase, but it appears to bind at a different site and work through a different mechanism. Experiments in animals so far indicate that it has very few side effects.

The major liability of phosphonoacetic acid, some investigators believe, is that it is not a patented drug, but rather is in the public domain. These investigators suggest that Abbott thus may not be willing to spend the $2.5 to $3 million necessary for clinical testing to acquire FDA approval of the drug, since the company would not have exclusive rights to the drug after approval. Indeed, Abbott's research on the drug has so far been very low-keyed. But it should be pointed out that vidarabine is also in the public domain, and that fact has not stopped Parke, Davis from sponsoring clinical testing. It may be, though, that clinical testing of such agents will require extensive government support if they are to reach the market. The first trials of phosphonoacetic acid in humans, in fact, will be cosponsored by the government: it will be tested against mucocutaneous herpes in the same trials as ara-AMP.

Many other agents have been observed to have potential antiviral activity. Douglas L. Swallow and his associates at Imperial Chemical Industries Ltd. in Macclesfield, England, for example, have found that *N*-*p*-chlorophenyl-*N*′-(*m*-isobutylguanidinophenyl)-urea hydrochloride inhibits the growth of at least 15 strains of rhinoviruses, which are among the many causative agents of the common cold. Paolo La Colla and his associates at the University of Cagliari, Italy, have found that several bichlorinated pyrimidines are active against enteroviruses, poxviruses, and herpesviruses. Angel S. Galabov of the Medical Academy of Sofia, Bulgaria, has shown that many *N*,*N*′-disubstituted thioureas are effective against some picornaviruses, which also cause colds. And Ilona Béládi and her associates at the University Medical School in Szeged, Hungary, have found that flavonoids are active against many DNA viruses.

Many investigators have observed similar effects with other compounds, and it seems likely that at least some of these compounds will be among the second and third generations of commercial antiviral agents. But it seems fair to say that these later generations will never reach the market—or that their arrival will, at least, be substantially delayed—unless there are some strong commercial successes among the first generation.

—THOMAS H. MAUGH II