AIDS Therapy: New Push for Clinical Trials

Several drugs are now being tested, but no magic bullet is in sight; lifetime therapy may eventually be required

More than 4 years after acquired immune deficiency syndrome (AIDS) was first recognized as a new disease, federal efforts to develop an effective therapy are finally beginning to move into high gear. Congress has approved a massive infusion of funds, drug-testing centers will soon be established around the country, and a new committee has been formed to help coordinate and accelerate research on therapeutic agents.

At least part of the credit for this new push should go to actor Rock Hudson, whose much publicized trip to Paris for experimental therapy focused public and political attention on the desperate plight of those diagnosed with AIDS. Hudson's last-ditch, and ultimately futile, effort to halt the progress of his disease dramatically underscored the lack of effective therapy for AIDS, which has now afflicted some 15,000 people in the United States alone.

Inherent in much of the publicity surrounding Hudson's quest was criticism of the federal government for failing to move speedily enough to develop and test drugs and vaccines to combat the epidemic. The fact that Hudson had to travel to Paris for experimental treatment was held up as evidence of this alleged failure.

Federal officials have responded to this criticism by pointing out that it was not possible even to develop a strategy for testing therapeutic agents until the cause of AIDS was determined. It was only last year that a newly discovered retrovirus was firmly implicated as the cause of the disease, and many of its biological properties are only now being revealed. "The fact is," says Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID), "we are moving with unprecedented speed."

The avalanche of publicity following Hudson's trip to Paris has, however, helped move the process along. "The spasm of media attention resulted in a barrage of questions to every official and congressman who stepped out of Washington," notes Terry Beirn of the AIDS Medical Foundation in New York. As a result, Congress has come close to writing a blank check for AIDS research (see box, p. 1358). It has approved a budget of some $240 million, of which a substantial portion will be devoted to testing drugs that show some promise against the AIDS virus.

A mechanism is also being put into place to move drugs quickly into clinical trials. NIAID is establishing a network of medical centers around the country to carry out so-called phase II trials of promising compounds that have undergone limited toxicity testing. Several institutions are competing for contracts to operate these centers, and the network should be in place by spring. According to Fauci, perhaps 2000 patients could be enrolled in clinical trials by the end of 1986.

Finally, to help provide coordination and focus to the effort, a drug evaluation committee has been established at the National Institutes of Health (NIH) under the chairmanship of Samuel Broder, associate director for clinical studies at the National Cancer Institute (NCI). It will review data on individual compounds and make recommendations for moving drugs into clinical trials.

Nobody is pretending that finding an effective therapy for AIDS will be easy. "We are trying to do something that has never been done before," says James O. Mason, director of the Centers for Disease Control and acting assistant secretary for health. Among the difficulties are:

- The AIDS virus in essence becomes part of the cell it infects, which means that it may never be removed entirely from the body by drug therapy.
- The virus is now known to infect the brain, which means that to be effective, drugs must cross the blood-brain barrier.
- Even if a drug can be found to interrupt the life cycle of the virus, if it is administered in the late stages of the disease, the patient's immune system will already have been destroyed. This means that additional therapy will probably be required to reconstitute the immune system.

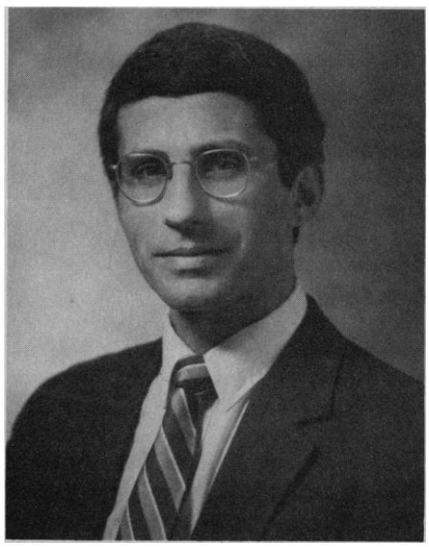
Many of these difficulties stem from the virus's complex life cycle. The virus first latches on to its target by binding to a particular molecule on the cell surface. Once inside the cell, it employs an enzyme known as reverse transcriptase to copy the RNA that makes up its genome into DNA, which is then spliced into the cell's own genes. At this stage, the integrated virus is indistinguishable from the rest of the cell's nucleus, and the viral genes are reproduced every time the cell divides.

At some point in its life cycle, the integrated virus takes over the cell's reproductive machinery to churn out RNA copies of the viral genes. Viral particles then "bud" from the cell surface, and new viruses go on to infect fresh cells. This process of viral reproduction eventually ends up killing the infected cell.

One implication of this life cycle is that, short of killing every infected cell and removing all free virus from the blood stream, the virus will not be eliminated by drugs. Moreover, since brain cells are infected, it would obviously not

The War on AIDS

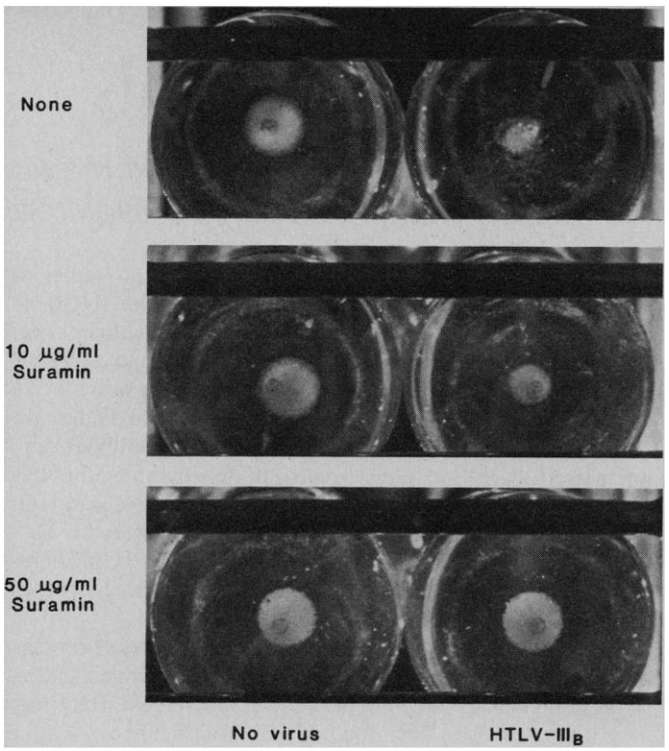
*This is the sixth and last article in a series on AIDS research.**



Anthony Fauci

NIAID head says perhaps 2000 patients may be in clinical trials by the end of 1986.

*Previous articles in this series were published in *Science*, 25 October, p. 418; 1 November, p. 518; 8 November, p. 640; 29 November, p. 1018; and 6 December, p. 1140.



Rapid assay

Infection with the AIDS virus causes pellet of T cells to break up (top right). Addition of suramin at different concentrations provides partial (middle right) and complete (lower right) protection. [Source: H. Mitsuya and S. Broder, unpublished data]

be desirable to kill every infected cell, even if such an approach were feasible.

This suggests, says Broder, that "we are probably going to have to give drugs on an intermittent basis, perhaps for the rest of the patient's life." There will also be a premium on getting drugs into people as early as possible, before the virus has wreaked havoc on the immune system. What this all adds up to is that antiviral drugs should be relatively nontoxic, preferably be administered orally, and be tolerated for long periods. That is a tall order.

The search for such an agent has at least been placed on a rational footing by the recent development of techniques that permit drugs to be screened rapidly in test tubes for activity against the AIDS virus. One such technique, developed by Broder and his colleagues at NCI, has already been used to screen some 120 compounds.

It is extremely simple. Broder has developed a highly sensitive T-cell clone that forms a pellet at the bottom of a test tube. About 4 days after virus is added to the culture, the infected cells begin to die and the pellet starts to break up. Within 10 days it is destroyed. The protective effect of antiviral compounds is assessed simply by adding them at varying concentrations to the culture before adding the virus, and monitoring what happens to the T cells (see illustration).

"We are at a point now where we can see quickly which compounds are promising, and equally important, we can see what modifications enhance the antiviral activity," says Broder. He has found, for example, that relatively minor changes in the sugar molecules of some compounds can have major effects on their ability to suppress the AIDS virus.

At least four compounds are in limited clinical trials in the United States, but so far the results have been at best mixed. In general, even though they appear to suppress the virus by interrupting its life cycle, they do not seem to offer much clinical improvement when given in the late stages of AIDS.

The most widely tested is suramin, a drug that has been used for years to treat trypanosomiasis. It clearly inhibits viral infection in lab tests, apparently by interfering with the action of reverse transcriptase, the enzyme used by the virus to make a copy of its genes for splicing into the host cell's genome.

Recent published reports indicate that it also suppresses the virus in some patients, but the drug is quite toxic and virus reappears when treatment is ended. The investigators, who come from a variety of medical centers around the country, reported that there were no significant clinical or immunological improvements in the patients, but recommended that suramin be moved into larger and longer term trials. It is now being tested at six medical centers and the NIH Clinical Center.

A second antiviral, developed by Burroughs Wellcome, is generating a little more optimism because, on the basis of limited toxicity testing, it seems not only to block the virus but also to result in some regeneration of T4 cells. According to David Barry of Wellcome Research Laboratories in Research Triangle Park, North Carolina, the compound, azidothymidine, was first considered as a potential candidate for AIDS therapy when it was found to suppress the activity of a retrovirus that causes leukemia in mice. Because Wellcome lacked necessary high-containment facilities to test it against the AIDS virus, Barry sent samples in February to Dani Bolognesi at Duke University and Broder at NCI.

In vitro tests looked promising. The compound appeared to suppress the virus by inhibiting reverse transcriptase activity, and it was also found to block synthesis of the virus's major core protein. The Food and Drug Administration (FDA) took just 5 days to approve an application for limited human testing, which began in July. The drug has so far been given to about a dozen patients at NCI and Duke.

It appears to be bioavailable when given orally and has been found to penetrate the central nervous system and suppress the virus in patients. Barry says a clinical trial involving some 200 patients in 10 to 15 centers should get under way in January.

Studies of a third drug, ribavirin, have been conducted in Europe and at the New York University–Cornell Medical Center in New York. Like suramin and azidothymidine, it suppresses viral replication in laboratory tests and appears to do so in patients. It was the first drug to be considered by NIH's new drug evalulation committee and should be moved into broader clinical trials early in 1986.

The fourth drug under clinical investigation is HPA-23, the compound used to treat Rock Hudson. When Hudson was forced to go to Paris for his therapy, FDA came in for some criticism for not permitting HPA-23 to be used in the United States. However, Harry Meyer, chief of FDA's Center for Drugs and Biologics, noted recently that clinical testing had not been approved because no application had been filed. When Rhône-Poulenc, the manufacturer of HPA-23, did submit an application last summer, there were insufficient toxicity data on which to base a review. When the data were finally assembled, the application was approved within a week.

Some 50 patients have received HPA-23 in France, and although the drug appeared to suppress the virus at least transiently, no clinical improvement was noted. The drug is now being administered to some 80 patients in the United

AIDS Virus Presents Moving Target

Every few weeks, a dozen or so virologists meet in Bethesda, Maryland, often over dinner at a local restaurant, to share information and plan the next steps in a coordinated campaign to develop an AIDS vaccine. They are members of an unusual ad hoc task force put together by Peter Fischinger, deputy director of the National Cancer Institute (NCI). Together with a handful of other investigators around the country who are involved in similar studies, they face an enormous challenge.

In April 1984, Health and Human Services Secretary Margaret Heckler predicted that a vaccine would be ready for testing within 2 years. However, it is not even certain that any of the strategies now being pursued will work, and the official target date for getting a vaccine ready for general use has been put back to 2000.

The more sober, and realistic, assessment of the task ahead reflects several major difficulties:

- The retrovirus widely believed to be the prime cause of AIDS is highly variable. Its genetic structure changes rapidly, which means that a vaccine that protects against one strain may not provide immunity against others.
- AIDS patients generally have high levels of antibodies against the virus circulating in their blood, yet these antibodies do not seem to provide protecion. Some patients do, however, have low levels of so-called neutralizing antibodies, and this gives researchers some hope that a protective antibody response can be induced.
- The virus may be transmitted directly from cell to cell, in addition to being released into the blood stream. Direct transmission would evade detection by antibodies. "That's the problem that scares me the most," says Dani Bolognesi of Duke University, a member of the NCI task force. Moreover, Jay Levy of the University of California at San Francisco (UCSF) says the problem is compounded by the fact that the virus probably enters the body integrated into cells in fluids such as semen, rather than as free virus.
- Although rhesus monkeys can be infected with the AIDS virus and show symptoms of the disease, the response is variable. The only really good animal model for testing vaccines is the chimpanzee, which is a protected species and is in short supply for medical research.
- Many vaccines are produced by inoculating people with a strain of virus that is not pathogenic. But most investigators are extremely wary of using such an approach with the AIDS virus because there is a possibility that the virus could activate cancer genes or become pathogenic through changes in its own genetic material. Recent findings by a group headed by Max Essex of the Harvard School of Public Health, indicating that a monkey virus very similar to the AIDS virus may have infected people without causing disease, have, however, raised speculation about the possibility of producing a vaccine strain from this virus. Although such a possibility is dismissed by many researchers, if antibodies to the monkey virus do protect against infection with the AIDS virus, an understanding of the mechanism could advance other vaccine approaches.

The first approach being pursued is to see whether the protein that forms the outer coat of the virus will produce protective antibodies when injected into animals. According to Fischinger, NCI researchers have now purified milligram quantities of this envelope protein from virus grown in culture and it is being tested in monkeys.

If this approach works, large quantities of envelope protein will be required, which means that they will have to be produced by genetic engineering. The NCI program is already moving in this direction. "We are trying every approach you can put down on paper," says Robert C. Gallo, whose lab at NCI is carrying out much of the vaccine work. Under contract to NCI, Dupont and Centocor, a small Pennsylvania-based biotechnology company, are producing proteins using bacterial systems; Hoffmann–La Roche is working with yeast; and Biotech Research Laboratories of Rockville, Maryland, and a subsidiary of Smith Kline in Belgium are using mammalian cells.

Researchers are concentrating on the envelope protein because is seems to evoke the most powerful immune response. However, the region of the virus's genome that codes for the envelope protein is highly variable, which means that changes in the protein may evade immune surveillance. There is, though, a ray of hope in a recent finding that parts of the envelope genes do not change: antibodies to proteins produced by these constant regions might protect against a wide range of variants of the virus.

The envelope protein bristles with sugar molecules, and a debate is currently going on over whether an antibody response will be enhanced or diminished if these molecules are stripped off. The outcome is important, because envelope proteins produced by genetic engineering using bacterial systems will not contain the sugars.

The NCI groups are not alone in taking these approaches. A group at Chiron, a biotechnology company based in Emeryville, California, in collaboration with researchers at UCSF and San Francisco General Hospital, is producing envelope proteins using yeast and mammalian systems. And another group at Genentech, in South San Francisco, is believed to be working along similar lines.

A different approach is being pursued by a group headed by Bernard Moss at the National Institute of Allergy and Infectious Diseases. Moss is using recombinant DNA techniques to splice parts of the AIDS virus genome—chiefly those that code for envelope proteins—into vaccinia virus. He has already found that the genes are expressed, and the hope is that such a recombinant virus will provoke an immune response to the AIDS virus.

Finally, a technique that does not involve injecting viral antigens at all, but relies instead on the use of so-called anti-idiotype antibodies (*Science*, 12 April, p. 162), is being pursued by some researchers, including Hilary Koprowski of the Wistar Institute in Philadelphia. This approach first requires the production of monoclonal antibodies to the envelope protein, which is currently being attempted by workers at NCI.

Some researchers are arguing that a major federal initiative should be launched, not only to develop an AIDS vaccine but also to clear away some of the financial and legal risks in vaccine production and testing. Robert Pollack of Columbia University suggests, for example, that legal requirements for extensive animal testing of genetically engineered proteins may be unnecessary. The need for a vaccine is too urgent for business as usual, he says.—**C.N.**

States at NIH and four other clinical centers. One investigator who asked not to be named says he has found that HPA-23 has little or no clinical effect.

In addition to these four compounds, which are already in human trials, several other antiviral agents are currently in laboratory testing. They include Foscarnet, an antiherpes drug developed in Sweden; a compound known as AL 721, which in tests by Prem Sarin at the NCI appears to disrupt the virus's envelope protein; and ansamycin, an antibacterial agent that has been used to treat some opportunistic infections in AIDS patients. Investigators are also likely to take a closer look at cyclosporine, a drug that showed some initial promise in the treatment of advanced AIDS cases in France but which was prematurely ballyhooed at a press conference on the basis of only one week's therapy involving just six patients.

Further down the road, it may be possible to use some of the knowledge that is now being accumulated about how the virus works to fashion drugs that are targeted toward specific features of its life cycle. In particular, work by William Haseltine at Harvard University's Dana-Farber Cancer Center and Robert Gallo of the National Cancer Institute has indicated that a small gene, which they have called the *trans*-activating, or *tat*, gene, codes for a protein that plays a central role in viral replication (*Science*, 5 July, p. 37). The *tat* gene product "offers an additional target" for drug therapy, says Haseltine.

The hope is that if a safe and effective antiviral drug can be developed and given to patients before their immune systems are destroyed by the AIDS virus, their immune functions may regenerate spontaneously or be reconstituted through additional drug therapy. Several drugs known to boost the immune system, such as isoprinosine, α-interferon, and interleukin-2, have been tried in AIDS patients but with little or no clinical success. The next step is to test them in combination with antiviral agents.

A more drastic approach is bone marrow transplantation. This was attempted at the National Institutes of Health in 1983 using marrow from an AIDS patient's identical twin. Although there was transient restoration of some immune function, the virus quickly overwhelmed the system. Fauci says the procedure is being repeated with another set of twins, using an antiviral agent in addition to the marrow transplant.

With perhaps 2000 people enrolled in clinical trials by this time next year, there will at least be a sense that the federal government is finally moving with a concerted effort on AIDS therapy. However, since the incidence of the disease is roughly doubling each year, there are likely to be 15,000 new cases of AIDS next year. With little to offer the bulk of these patients, frustration will remain high.

Since AIDS, at least in its advanced stages, is a terminal disease, should experimental drugs not be made available beyond controlled clinical trials? In a recent interview with *New York Native*, a gay publication that has provided extensive coverage of AIDS research, Fauci answered this way: "If you start throwing drugs out in haphazard ways, with no scientific basis of whether [they] will be effective, the horrible thing that could happen is that five years from now, we'd still be . . . running in circles. Whereas, if we do it in an orderly fashion, then we'll be able to eliminate something that definitely isn't worthwhile and go on to the next thing." Fauci also added that AIDS patients respond to drugs differently, and there is a danger that administering unproven drugs "might start killing AIDS patients right off the bat."

There is clearly a long way to go before an effective therapy is developed for AIDS. It is also clear that there is unlikely ever to be a "magic bullet" that will eliminate the virus from a patient's system. Given these difficulties, there has been some despondency in the medical community about the prospects for therapeutic intervention. However, some drugs are showing promise and, says Broder: "I think it is important to start with a working assumption that AIDS is a curable disease. . . . If a doctor believes that any given patient is incurable, that doctor will always be proven right."—COLIN NORMAN

An Avalanche of New Cash

Congress has put the finishing touches to legislation that will boost federal spending on AIDS to more than $240 million in fiscal year 1986, which began on 1 October. This is more than double the amount spent last year.

This avalanche of new money is mostly contained in an appropriations bill for the Department of Health and Human Services (HHS), which was approved by a House-Senate conference committee just before Thanksgiving and sent to the President on 6 December. Although the measure could still be derailed by the antideficit fever that is currently gripping Washington, AIDS funding is unlikely to be reduced.

The total amount is more than was originally approved by either the House or the Senate in their individual versions of the HHS appropriations bill. In essence, the conference committee simply approved the highest figure in either bill for each agency. Thus, the final version contains $140 million for the National Institutes of Health (NIH), $65 million for the Centers for Disease Control (CDC), $13 million for the Alcohol, Drug Abuse, and Mental Health Administration, and $16 million for a new demonstration program to test various ways of delivering health care to AIDS patients. A second appropriations bill currently working its way through Congress includes an additional $6 million to $10 million for AIDS programs sponsored by the Food and Drug Administration.

Included in the $140 million for NIH is a $70-million dollop of cash that will go to NIH Director James Wyngaarden to apportion among institutes as he sees fit. In effect, Congress is letting NIH determine its own priorities in the distribution of AIDS funds. The conference report notes, however, that Congress has placed "a high priority on vaccine development, for which $14,000,000 would have been provided in the Senate bill."

Congress is, however, not too enamored with the direction of the AIDS effort by top management of HHS. A whole year has now gone by since Edward Brandt departed as assistant secretary of health, and the post has been filled on a part-time basis by James O. Mason, who has been doubling as director of CDC. The conference committee has instructed HHS "to take whatever steps [are] necessary, including the appointment of a coordinator, to develop and implement a comprehensive, planned research strategy" for AIDS. It also instructs the assistant secretary to report directly to Congress—a device intended to bypass the Office of Management and Budget, which in the past has failed to submit to Congress requests for additional AIDS resources identified by HHS.—**C.N.**