An Underground Drug for AIDS

Under pressure from AIDS activists, the Food and Drug Administration will now allow patients to import unapproved drugs; researchers fear this means the end of scientifically sound drug trials

DETERMINED NOT TO GO DOWN in history as the heartless bureaucrat who robbed AIDS patients of hope, Frank Young, commissioner of the Food and Drug Administration (FDA), recently decided to allow individuals to import small quantities of unapproved drugs for their personal use. The policy applies not only to AIDS patients, who fought to receive shipments of an experimental AIDS drug called dextran sulfate, but to any person suffering from any ailment.

The new directive stunned some AIDS researchers. One official in the federal government's AIDS Program went so far as to suggest that the FDA commissioner had gone "temporarily insane."

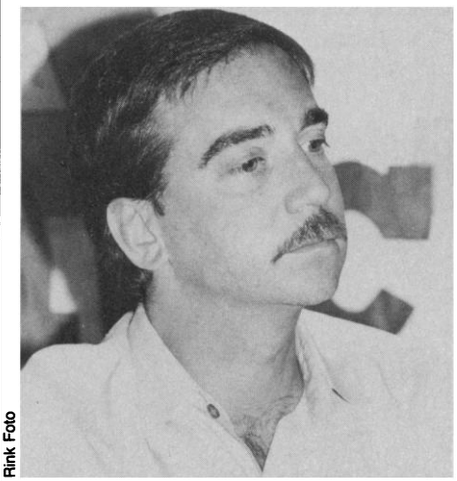
There are grave concerns among investigators that if the government allows unapproved drugs to circulate freely, it will make rigorous drug testing far more difficult to do. They fear that if patients are allowed to take a variety of unproven drugs in unknown combinations, it will be impossible to untangle the subtle signs of either efficacy or toxicity. Critics of the FDA policy say they sympathize with the need for compassion, but add that in the long run, Young's decision will only prolong the time needed to develop new AIDS drugs, while sending a confused message to patients and opening the door to charlatans selling snake oil.

Young maintains that the policy simply recognizes the fact that a large number of AIDS patients and people infected with the human immunodeficiency virus (HIV) are smuggling experimental drugs into the country from Mexico, Europe, and now Japan.

"Desperately ill people are going to be searching for anything that might offer hope. It's a fact of life and clinical trials should take this into account," says Young. The only drug approved by the FDA for AIDS is azidothymidine or AZT, which extends life but extracts a heavy price both in cost and toxicity.

Young adds that the new policy is not really new, but only makes official a long-standing but informal system for allowing patients to bring small quantities of drugs with them when they enter the country from abroad. Young stresses that the FDA will not allow the importation of dangerous drugs or drugs that are being actively marketed as cures for AIDS or other illnesses.

Young asks researchers what they would do if they were in his shoes? "We're not prepared to march into people's homes like the Gestapo and take drugs away from desperately ill people," says Young. But it is one thing to march into someone's home and quite another for the government to allow people to receive parcels of drugs about which virtually nothing is known.



Rink Foto

Donald Abrams: *"FDA turned its back on us. They're making clinical trials impossible."*

"I can't see how having an unevaluated and unapproved drug floating around is good for anybody," says Thomas Merigan, an AIDS researcher at Stanford University and a member of the government's AIDS drug development committee.

"People must remember that individual self-experimentation is extremely unlikely to yield meaningful results," says Samuel Broder of the National Cancer Institute. "The only way to know whether or not a drug really works is to put it through a series of carefully controlled and scientifically sound clinical trials."

"The FDA is saying: 'We can't regulate anymore. So who cares? Let the patients take whatever they want! Just get them off our backs,' " says Donald Abrams, an AIDS researcher at San Francisco General Hospital.

At the center of this storm is the experimental AIDS drug dextran sulfate, a potential antiviral agent that has shown promise in a test tube. In many ways, the story of this drug tells much about the roiling world of AIDS today, where emotions and politics continue to play as large a role as science, and where a sophisticated but desperate patient population composed of gay men is changing the way that drugs move through the scientific and regulatory pipeline.

The story of dextran sulfate begins with a Japanese investigator named Ryuji Ueno, the son of a food additive mogul who owns a company called Ueno Fine Chemicals Industry in Osaka, Japan. In the summer of 1986, the young Ueno told Abrams of San Francisco General that dextran sulfate could stop the AIDS virus from binding with its target cell in a laboratory dish. Impressed by the simple elegance of Ueno's data and the potent antiviral effect of dextran sulfate in vitro, Abrams agreed to test the drug for Ueno's company in a small number of patients with AIDS and HIV-related illness.

While Abrams sought approval from the FDA to do a small Phase 1 clinical trial to gauge the maximum tolerated dose of the drug, he also convinced Ueno to publish something in the scientific literature. Why? Abrams knew that any news of a potential AIDS drug would travel quickly around the network that joins AIDS patients with researchers and physicians sympathetic to their plight. An article in a scientific journal would help Abrams accrue the patients he needed.

It was a move that Abrams and Ueno may have come to regret. For Ueno's publication did far more than help Abrams attract a few patients to his study. It set in motion the whole series of events that led to the change in the FDA's approach toward unproven AIDS drugs.

On 13 June 1987, Ueno and his colleague Sachiko Kuno published a letter in the British medical journal *Lancet* that reports that dextran sulfate blocks the binding of HIV to the white blood cells called T lymphocytes. Old hands in retrovirology were not completely surprised by the news. In fact, Erik De Clercq of the Rega Institute for Biomedical Research in Belgium had suggested in 1986 that a large negatively

charged molecule not unlike dextran sulfate might inhibit the absorption of retroviruses.

How the drug accomplishes this neat trick is not yet known. Dextran sulfate is basically a big polymer of glucose that contains about 20% sulfur. Ueno suspects that the negative charge of the marcomolecule and the amount of sulfur play a critical role in inhibiting infection, perhaps interfering with the virus particle as it tries to attach itself to the surface of its target cell.

More tantalizing to patients, however, was the passing mention in the *Lancet* paper that dextran sulfate has been used in Japan for 20 years as a drug to repress coagulation and to lower cholesterol in the blood. It is assumed that the drug is relatively safe. And because the Japanese Ministry of Health does not regulate drugs in the same way that the FDA does, it was possible for patients or their loved ones to simply step up to the counter at a pharmacy in Japan, slap down their yen, and buy the drug for about 20 cents a pill.

Aided by FAX machines, national hotlines, a dozen "buyers clubs," and several newsletters, word spread quickly on dextran sulfate. Within weeks of Ueno's scientific publication, the first AIDS patients began flying to Tokyo to purchase the drug. Airline stewards flying in the Orient began mailing it to friends in the United States. One AIDS patient convinced a chemical company in the United States to manufacture 80 pounds of the stuff, which he then coated in pill form and distributed up and down the West Coast. Soon, a male nurse from Los Angeles with the nickname "Dextran Man" began smuggling the drug back to the United States in bulk.

A group of AIDS patients being treated by a physician in Los Angeles named Michael Scolaro were getting their pills from Dextran Man. Scolaro is one of a growing number of physicians who aggressively treat AIDS and HIV infection with a variety of drugs. While Scolaro did not prescribe dextran sulfate, he was willing to monitor the first patients who took it on their own. "I cannot honestly say whether dextran sulfate makes any dent in this disease," says Scolaro. "But the patients who take it do seem to be doing better."

Scolaro's patients were also telling their friends that they were feeling better. And for AIDS patients, this is enough. Soon, trips to Tokyo for dextran sulfate became so routine that detailed subway maps to certain pharmacies in Tokyo began to circulate around New York City, San Francisco, and Los Angeles.

Martin Delaney of Project Inform, a San Francisco based AIDS education and advocacy group, estimates that as many as 700 shipments left Japan for the United States and that as many as 2500 people were taking dextran sulfate before the FDA changed its mail policy.

International smuggling of dextran sulfate was a development that Ueno had never dreamed of. Not only did Ueno fear that the sudden popularity of dextran sulfate in the AIDS underground would disrupt his clinical trials, but his company had nothing to gain from it. The Ueno Fine Chemicals Industry does not even make dextran sulfate. A large pharmaceutical company in Japan does.

For reasons that are not entirely clear, dextran sulfate suddenly became extremely difficult for Americans to buy in Tokyo in the early spring. In January, Ueno's U.S. representative had notified the FDA that someone in Los Angeles was bringing in at least $10,000 worth of the drug every month. That someone was Dextran Man. Ueno himself expressed concern to the Japanese Ministry of Health that too many Americans were buying the drug through the underground.

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Martin Delaney: *"People with AIDS can't wait forever for a drug. It's now or never."*

Not only was the drug getting difficult to buy in Japan, but the FDA was detaining packages of dextran sulfate at Customs. The combination of events caused the gay community to start howling. FDA Commissioner Young was told by gay advocates that the more vocal groups in the community would be used to stage "political funerals" outside the FDA's office in suburban Maryland.

"We were talking real coffins with real bodies inside," says Curtis Ponzi, a San Francisco attorney who represents a club that buys AIDS drugs. Ponzi told FDA officials that he himself would try to bring back a large supply of dextran sulfate, and that he would alert the media of his intention. If the FDA or Customs stopped him at the airport, Ponzi would read off the names of every patient who was being denied the drug. It would have made for dramatic footage.

"I take the simple position that it's unethical and immoral to deny this drug to terminally ill patients," says Ponzi. Apparently, Ponzi and his allies got their point across. Young agreed to allow patients to receive small quantities of the unapproved drug from overseas and the Japanese agreed to allow Americans to buy dextran sulfate at three pharmacies in Tokyo as long as they showed their passport and bought only enough for a 3-month supply.

Because of the intense interest in the drug among AIDS patients and their allies, dextran sulfate has also become an issue for legislators. It was a hot topic for congressional hearings held in April and July by Representative Ted Weiss (D–NY) and Senator Ted Kennedy (D–MA), who keep asking officials from the National Institutes of Health (NIH) why it is taking them so long to get an experimental drug like dextran sulfate into their sick and desperate constituents.

Why indeed? Anthony Fauci, head of NIH's AIDS Program, admits that the government should have moved faster on dextran sulfate. But Fauci adds that part of the problem is that dextran sulfate is being developed as an AIDS drug by a small Japanese firm more familiar with producing food additives than with taking a product through the bureaucratic jungle of Washington. Ueno Fine Chemicals is represented in the United States by one person.

Staffers from Fauci's AIDS Program did meet with Ueno in August 1987, 3 months after his paper appeared. At that time it was agreed that Ueno's company would sponsor the Phase 1 clinical trial under way at San Francisco General Hospital. If things looked promising, the AIDS Program would then take dextran sulfate through larger, more extensive Phase 2 trials at a number of institutions.

In November, the AIDS drug development committee at NIH awarded dextran sulfate a high priority, based on Ueno's in vitro experiment and a few details provided by Paul Volberding of San Francisco General Hospital, who was following the work of his colleague Abrams.

But the drug committee identified several problems in November that continue to plague the development of dextran sulfate today. The group discovered that even though the drug has been used for 20 years in Japan, there are virtually no data on whether or not dextran sulfate is absorbed by the blood stream when taken orally. "The committee wanted to know what happened to the drug after people ate it," says Mau-

reen Myers of NIH's AIDS Program. "And nobody seemed to know."

Producing an answer has not been easy. Until very recently, there has been no good assay to detect dextran sulfate in blood. Yet this is a critical piece of information, because some researchers suspect that the large size of the dextran sulfate molecule means that the drug is not absorbed from the stomach, making oral doses of dextran sulfate about as efficacious against AIDS as drinking a glass of water.

In December and again in March, various AIDS committees at NIH kept pressing Ueno and Abrams about the assay. Where were the data? Abrams told NIH he was drawing blood and sending it to Japan. On questions about the assay, Abrams deferred to Ueno, who replied that he was developing a more sensitive way to analyze the drug in the blood, and that as soon as he had the data, he would submit them.

Unfortunately, Abrams was required to heat-treat the blood specimens before shipping them to Japan, because Japanese lab workers refuse to handle the live AIDS virus, says Armond Welch, the U.S. representative for Ueno Fine Chemicals. In turn, this made developing an assay in Japan even more difficult, since during heat treatment, dextran sulfate has a nasty tendency to precipitate.

Ueno now says that he finally has an assay that will settle once and for all the question of whether or not dextran sulfate is absorbed—even in blood that has been heat-treated. He is busy analyzing samples now and expects results in the coming weeks. Frustrated with the lack of data on bioavailability, the FDA recently developed another assay that will be used to confirm Ueno's data.

If dextran sulfate is indeed absorbed, there is still the question of whether or not the drug works. Of the 29 people in Abrams' clinical trial who took dextran sulfate for 8 weeks, Abrams observed no statistically significant changes in T cell counts or other markers of disease progression, such as the production of p24 antigen, a sign that the virus is active. "I saw no demonstrable effect for this agent," says Abrams.

Still, Abrams has agreed to pursue the investigation of dextran sulfate in a larger, federally sponsored Phase 2 clinical trial that is just now getting under way. With more patients, Abrams and his colleagues hope to get a clearer answer about any efficacy dextran sulfate may have for people with HIV infections and AIDS.

But whatever effect dextran sulfate turns out to have in the human body, it has certainly had a profound effect on the body politic. ■ **WILLIAM BOOTH**

NASA Delays Space Telescope

Faced with delay after delay in its first post-Challenger space shuttle launch, and concerned about overcrowding in the subsequent flight schedule, the National Aeronautics and Space Administration (NASA) has decided to relieve the pressure by postponing the launch of the Hubble Space Telescope by some 7 months: from 1 June 1989 to February or March 1990.

From all reports it was a classic case of choosing the least unpleasant alternative. "Everybody was number one in line," says NASA spokesman Charles Redmond, "but somebody had to go first." Indeed, the constraints on the launch schedule seem to have left NASA with very little room to choose otherwise. In particular:

■ Although the shuttle Discovery was rolled out to the launch pad months ago, a long string of glitches has pushed back the lift-off from August until late September at the earliest. Taken together with the post-Challenger requirements for exhaustive inspection and refurbishment of the orbiters in between flights, these delays have made it impossible for NASA to maintain even a semblance of its previous schedule. The sequence of launch dates was beginning to topple like a line of dominoes, says Jerry J. Fitts, director of NASA's transportation services office. "If it hadn't been for the delays, we wouldn't have had a problem."

■ The 1989 launch schedule contains two points that cannot be moved. The Magellan radar mapping mission has to begin its journey to Venus sometime within a 3-week period beginning on 28 April 1989; otherwise it will have to wait another 19 months before the planets are again in the correct alignment. The Galileo orbiter/probe mission to Jupiter is likewise constrained to a launch window starting 12 October 1989. Space Telescope, by contrast, does *not* have any critical time for launch.

■ Of the seven flights scheduled for 1989 in the new manifest, three will carry classified payloads that the Defense Department has claimed as top priority. (Among them there is said to be one of the Pentagon's flagship intelligence-gathering satellites, the KH-12.) The Defense Department has always had the right to preempt other missions on national security grounds, although it seldom if ever had to exercise that right in the pre-Challenger days. In this case, Lennard Fiske, head of NASA's Office of Space Science and Applications, argued long and hard to get one of those three slots for Space Telescope. So did Riccardo Giacconi, director of the Space Telescope Science Institute. They lost.

■ Even though NASA technically has a three-orbiter fleet, most of the work will actually be done by two orbiters: Atlantis and Discovery. The third, Columbia, is both older than the other two, and heavier by 4 tons. It thus lacks the edge of performance needed for Space Telescope, the planetary missions, and most of the classified missions. Indeed, Space Telescope will stretch even the lighter orbiters to the limit: because of concern over atmospheric drag during the upcoming maximum of the solar cycle, mission planners want to get the telescope into as high an orbit as possible. Current plans call for an altitude of about 600 kilometers. In any case, the fact that NASA will effectively have to operate with a 2½-shuttle fleet means that the constraints on between-flight refurbishing and preparation are even more severe than they might have seemed.

The upshot was that something had to give, and the something was Space Telescope. Reaction at the Space Telescope Science Institute was predictably downbeat. "Psychologically, just falling into the next decade really hurts," says institute spokesman Ray Villard. Many of the staff scientists have been waiting for the launch since the institute was founded in 1983. "No matter how hard you work," says one, "you can't control your own destiny."

Of course, optimists can point to a few silver linings, such as they are. For example, NASA will now be able to conduct one more full-scale test of the telescope and its control systems, similar to a very successful test held this past June. Also, the delay gives NASA time to outfit an Air Force C5A transport aircraft to fly the telescope directly from its current storage place—a clean room at the Lockheed Corporation's research facility in Sunnyvale, California—to the launch site at Cape Canaveral. The previous plan had been to take the telescope by barge through the Panama Canal, something no one was very comfortable with; even leaving aside the prospect of storms at sea, it was all too easy to imagine terrorists attacking the telescope and/or holding it hostage.

One possibility now being seriously considered is to fly Space Telescope out to the Cape this coming spring, so that it will be available to take the place of one of the other missions if any of them is unable to make it. This is what NASA's Redmond calls "the vulture-on-the-fence mode."

■ **M. MITCHELL WALDROP**