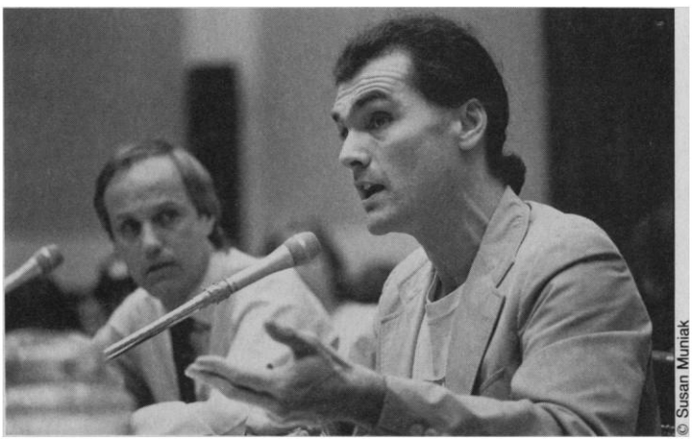
Quick Release of AIDS Drugs

In response to lobbying by patients, U.S. health officials agree to distribute experimental AIDS drugs before testing for effectiveness is complete; "parallel track" to be ready by the fall

THE HIGH COMMAND in the war against AIDS filed into Representative Henry Waxman's (D–CA) health subcommittee hearing room on 20 July to make a public concession.

You can't run a war without troops, they acknowledged, and their own troops—the AIDS victims who serve as volunteers in drug testing clinics—are in revolt over the tight federal rules that limit who gets new AIDS drugs and when. The patients want faster access to drugs as they come off the laboratory bench, before they go through time-consuming "Phase II clinical trials" that test their effectiveness.



Changing the rules. *AIDS activists Jim Eigo (right) and Martin Delaney argue that drugs in clinical trials should be widely available.*

The nation's top health officials say they are ready to yield on this point and that they will relax the rules in a significant way this fall. The plan is to make drugs more widely available before Phase II tests, a major shift in policy that could have long-term consequences in the research and pharmaceutical communities. If exceptions are made for AIDS, the same arguments would hold for cancer and other currently incurable diseases afflicting millions of people.

Some researchers and clinicians have been calling for just such a policy shift for years. Others are skeptical, fearing that this will make clinical data harder to interpret and slow down the ultimate licensing decisions.

Several scientists who run AIDS studies worry that if experimental drugs are distributed early to people outside the clinic, this could make it impossible to control the patients' medication. This, they argue, will make it difficult, if not impossible, to determine whether a new drug is in fact responsible for clinical improvements.

The AIDS activists' response: too bad. Jim Eigo, a leader of the New York gay advocacy group ACT UP, told Waxman that AIDS victims are not in awe of the "strange and abstract god, clean data." Eigo claimed that, contrary to what researchers fear, patients will be more likely to comply with clinical test requirements if they perceive the rules as fair—which is not the case today. Martin Delaney, founder of Project Inform, an advocacy group in San Francisco, says, "I argue that it is the FDA restrictions that are polluting the clinical trials," because patients desperate to get access to drugs lie about their medical history. With more lenient rules that would not happen.

The specific concession the activists want, and will get this fall, according to U.S. health officials, is a new structure for distributing experimental drugs called the "parallel track." It means essentially that an AIDS patient will be able to receive the latest drugs that appear safe, whether or not they have been licensed for sale, without having to be part of a clinical trial. Normally, a drug that is not approved for sale by the Food and Drug Administration (FDA) cannot be obtained except by people in an FDA-sanctioned test. In the past, FDA has allowed case-by-case "compassionate" or "emergency" exceptions. It also permitted a broader exemption (called "group C" drugs) for some cancer patients. But what is being proposed now is a much bigger reform.

Anthony Fauci: *"We can be humanitarian and do good science."*

The new procedure "could change ground rules on research, clinical care markets, and insurance," Waxman said. "If it works, it could revolutionize drug development," but if it fails, it could "cripple AIDS research."

The parallel track will open a kind of second supply window, providing experimental drugs routinely to "persons for whom there are no satisfactory alternative drugs or therapies available . . . and who for some reason are not eligible for or not able to participate in a clinical trial." So declared James O. Mason, the assistant secretary for health of the Department of Health and Human Services, the top health official at Waxman's hearing. Mason was flanked by Anthony Fauci, chief of the National Institute for Allergies and Infectious Diseases, Samuel Broder, director of the National Cancer Institute, and Frank Young, commissioner of FDA, all of whom spoke in favor of the reform.

However, before the new plan can go forward, Mason said, critical details must be worked out. He has asked Young to assemble an advisory committee quickly and submit a report no later than 21 August. Among other duties, the committee will define procedures for identifying toxic effects among patients not in clinical trials, review liability issues and develop standards for informed consent. Young hasn't decided who will sit on the new committee as yet, but he may use an existing FDA advisory group that reviews antiviral medicines.

The FDA has been broadly criticized by the activists for its slowness in making new drugs available. (See comments of Vincent DeVita, former National Cancer Institute director, p. 346.) But Young argued that it was FDA that began the reform in June 1987 when it proposed a "fast track" for drugs that may alleviate serious illnesses. Young claims FDA was denounced in Congress at the time for moving too fast, then, 1 year later, for moving too slowly.

At the hearing, Delaney of Project Inform blamed the FDA's staff, not its chief, for delay. An innovation of last year designed to

cancer trials has been published, although a report of the first has been accepted by the *Journal of Clinical Oncology*.

The cancer institute has taken another step with regard to the levamisole–5-fluorouracil data, and it touches on an issue, namely the use of placebo controls, that is no less sensitive in cancer research than it is in AIDS research. NCI is now requiring that its grantees tell any colon cancer patient who is considering participating in one of their clinical trials about the promising levamisole results.

The idea is to give them the opportunity to opt for the levamisole–5-fluorouracil treatment, instead of entering a new study, especially if that study is comparing an experimental therapy with an inert placebo. "If it were me I would demand to know all the information, and I would be madder than a hornet if the information hadn't been explained," Broder asserts.

DeVita thinks that placebo controls are no longer justified in colon cancer studies and that any new therapy should be compared to the levamisole–5-fluorouracil combination. He suggests that Moertel is reluctant to announce the results of the levamisole–5-fluorouracil studies because this might interfere with the recruiting of patients for a placebo-controlled trial that he is conducting on another drug combination, Leucovorin and 5-fluorouracil.

Moertel takes strong umbrage at that suggestion. "We're trying to defend that study because we feel it is in the best interest of cancer patients," he maintains. The Leucovorin combination has already proved effective in prolonging the survival of patients with advanced, recurrent colon cancer, and Moertel thinks it may hold even greater promise than the levamisole combination as an adjuvant to colon cancer surgery. In any event, Broder says, the informed consent form for the Leucovorin trial is in compliance with the requirement to inform prospective participants about the levamisole results.

The dispute over the levamisole therapy has a positive side. It carries a strong implication that cancer researchers are at last beginning to make headway against a major killer, even if they do not agree over the current status of the research. Equally apparent, however, is the conclusion that the long-standing issue of when to make experimental drugs available to people with life-threatening illnesses is not likely to be resolved anytime soon. ■ **JEAN L. MARX**

allow greater access to investigational new drugs or INDs—called "Treatment IND"—was judged a failure by Delaney because the staff made little use of it. Delaney charges that the FDA has not delivered on promises made by Commissioner Young.

It was Fauci who gave the latest bureaucratic innovation—the parallel track—its notoriety. He endorsed it publicly on 23 June at a San Francisco meeting on AIDS treatment. (Fauci coordinates a national effort to test new AIDS drugs and talks often with AIDS activists.)

Events added urgency to the proposal. As Fauci, Young, and the AIDS activists were discussing the parallel track this spring, the Bristol-Myers Company revealed that its new compound DDI is less toxic than existing AIDS drugs and is proving reasonably effective for patients in clinical trials (see story this issue, p. 353). AIDS patients will want to use it as soon as possible, which could be in September, if the parallel track is working by then.

Fauci said during the hearing that he recognizes that some AIDS patients could be "disenfranchised" from the benefits of DDI under the traditional research rules. Distribution of the drug would be limited to people in clinical trials, and the trials would randomly give participants either DDI or AZT, an older AIDS drug. The catch is that AZT is quite toxic and has a limited period of usefulness (about 2 years). Patients who have gone beyond that limit, or who cannot take it for other reasons, would be excluded from the trials. Yet, as Eigo and Delaney point out, "AZT-intolerant" people most desperately need the new drug.

Fauci told the committee, as he told his own clinical research chiefs, that "we can be humanitarian and do good science" as well. Mason echoed the sentiment: "We have a responsibility to be compassionate," and the parallel track "might even enhance our ability to get people to participate" in clinical trials.

On the other hand, some researchers worry that the parallel track will be unmanageable. Several who spoke with *Science*—Martin Hirsch of Harvard, Douglas Richman of the University of California at San Diego, and Lawrence Corey of the University of Washington, Seattle—have such concerns. One question is whether the benefits of this new approach will outweigh the risks, even in the short term. Toxic effects not apparent in small Phase I reviews could surface when the drug is distributed on a wider scale, doing unexpected harm. Second, as each new drug appears, there may be a faddish tendency for patients to begin taking it in place of or in addition to those in a clinical trial. Some clinicians say this will make it hard to control the research data.

Finally, because the parallel track will be open to patients who live far from a test clinic, some researchers worry that this geographical exemption will divert patients from major medical centers, adding to the growing problem of recruiting patients for trials.

Similar criticism, though with a different slant, came from Ralph Nader's Health Research Group. Speaking across town on 20 July as a witness before a meeting of the presidential advisory panel on AIDS and cancer drugs, director Sidney Wolfe said the parallel track could create "an extraordinary conflict between researchers and patients." Wolfe and a senior attorney of the group, William Schultz, worry that a fast track plan will jeopardize the conduct of more rigorous clinical trials."Nothing will happen [in validating therapies] if science isn't applied" to the proper testing of an experimental drug, Wolfe said. "The parallel track is fraught with that possibility."

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In addition, Wolfe argues that manufacturers should be required to show that a drug has some efficacy before it is allowed into the parallel track. However, defining a minimal threshold of effectiveness will be difficult. A year ago, many AIDS patients were scrambling to buy dextran sulfate, which had shown biological activity in test tube experiments. The drug was only available in Japan, so AIDS patients formed buying clubs and used a Canadian clearinghouse to purchase it overseas. Scientists soon discovered, however, that dextran sulfate wasn't even absorbed by the body. One way to discourage quack therapies in the future, Wolfe said, would be to prohibit a manufacturer from making a profit on a drug while it is distributed under the fast track system. No guidelines have yet been developed on matters of profit or liability.

Many things remain undefined, and this is what makes the clinic directors so nervous. Richman puts it this way: "People say, here's the concept; we'll fill in the blanks later. But what you put in the blanks will determine whether it succeeds or not."

■ **ELIOT MARSHALL**

With reporting by Marjorie Sun.