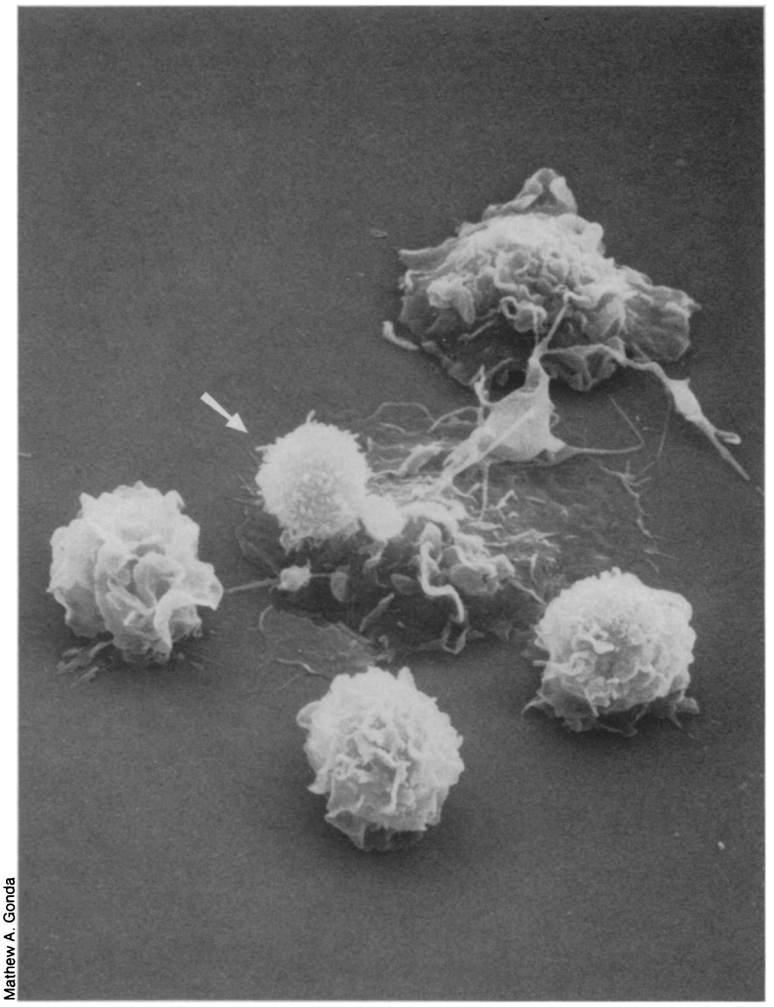
AIDS Predictors

Can new laboratory markers speed the approval of AIDS drugs?

By KATHY A. FACKELMANN



Mathew A. Gonda

This scanning electron micrograph shows the key targets of the AIDS virus — a T4 cell (arrow), macrophages and other white cells, magnified 9,000 times.

Scott Shaeffer, a 30-year-old New Yorker with AIDS, took a desperate gamble last July and enrolled himself in an underground study of "compound Q," an experimental AIDS drug derived from the root of a Chinese cucumber. Soon after taking the drug, Shaeffer suffered temporary blindness, paralysis and agitation. He recovered from the initial reaction but died suddenly at the end of August, leading some to blame his death on the unorthodox trial, which was organized by an AIDS advocacy group without the approval or oversight of the Food and Drug Administration.

AIDS activists and some researchers believe the FDA must accelerate its drug approval system so that people with AIDS, cancer and other life-threatening diseases can get new treatments without resorting to underground studies that lack the safety checks of federally sponsored research.

Under FDA's current system, clinical investigators give experimental drugs to diseased volunteers to see if the treatment alleviates symptoms or prevents disease progression in a significant number of cases. But the FDA's requirement that such trials use traditional study "endpoints," such as death rates, can keep promising AIDS drugs in clinical trials for years. To shorten the testing period, scientists are seeking surrogate endpoints — measures of specific "marker" substances in blood or urine that reflect early disease progress and can help shave years off the drug evaluation process.

Most scientists now agree that a laboratory count of certain white blood cells called CD4-positive T-lymphocytes (T4 cells for short) can serve as an important measure of an AIDS drug's efficacy. They say declines in T4 cell counts signal the onset of the steady immune system destruction caused by the AIDS virus, or HIV.

That scientific consensus is likely to pressure FDA to put more weight on a drug's ability to boost T4 cell levels in evaluating AIDS drugs in the future. However, FDA officials and some scientists say clinical investigators should not yet rely on this marker in assessing new drugs. While they concur that T4 counts do offer one measure of a drug's ability to curb disease progression, they say investigators should continue to use death rates until further research confirms the link between very low T4 counts and grim survival prospects for people infected with HIV.

T4 cells emerged as the best current predictor of HIV progression at a September meeting of scientists, AIDS activists and federal officials, held in Washington, D.C., and sponsored by the National Academy of Sciences' Institute of Medicine. Participants discussed several other surrogate markers that most scientists regard as less reliable than T4 counts as signs of AIDS progression.

Scientists say successful surrogate endpoints must faithfully mirror the patient's clinical status—changing when the disease progresses and when it remits. Perhaps the strongest evidence bolstering researchers' faith in T4 counts comes from Margaret Fischl of the University of Miami/Jackson Memorial Hospital Medical Center. At the meeting, Fischl described unpublished, preliminary data from a study of 572 AIDS patients treated with zidovudine (AZT). The study, she says, shows that patients' T4 counts during treatment are the most important predictors of whether they will survive. Fischl found that people with counts of fewer than 50 T4 lymphocytes per cubic millimeter of blood had poor survival outlooks compared to people with higher

T4 levels.

"Small changes in T4 cells can have significant biologic importance," even for patients who entered her study with fewer than 50 T4 cells, she says. As long as zidovudine boosted that level above 50, the patient's chance of survival brightened, Fischl notes.

Blood levels of T4 cells reflect the degree of damage done by HIV because the virus targets and destroys these key immune-system cells. "The T4 cell is the conductor of the immune orchestra, distinguishing self from nonself and calling into play a whole array of defense mechanisms," says AIDS researcher H. Clifford Lane of the National Institute of Allergy and Infectious Diseases (NIAID).

Asymptomatic people infected with HIV can have normal levels of T4 cells – about 800 to 1,200 per cubic millimeter of blood. But as the disease advances, the T4 count drops below 200 and microorganisms harmless to immunologically robust people start to take hold.

Work by John Phair of the Northwestern University Medical School in Chicago demonstrates a correlation between low T4 counts and infection with one such "opportunistic" infection. Phair has shown that HIV-infected individuals with T4 counts of less than 200 run a high risk of developing an otherwise rare pneumonia caused by the protozoan-like *Pneumocystis carinii*.

Phair studied 1,665 homosexual and bisexual men infected with HIV, finding that 400 had or developed T4 counts of 200 or less during the 42-month study. Out of that group, 100 contracted *P. carinii* pneumonia. Of the remaining 1,265 men with T4 cell counts above 200, only 68 developed the pneumonia during the study. But those 68 had their last T4 counts taken an average of 10 months prior to their pneumonia diagnosis, Phair says. He believes some of them had T4 counts of less than 200 by the time they developed pneumonia. Phair and his colleagues first presented these results at the Fifth International Conference on AIDS in Montreal last June.

While scientists generally concur that T4 counts are closely linked with the progression of AIDS and opportunistic infections, most have adopted a wait-and-see attitude toward other surrogate markers discussed at the September meeting. These markers include:

- HIV p24 core antigen, a protein component of the AIDS virus. Scientists may detect p24 in the blood soon after HIV infection; the protein sometimes appears again late in the disease. Researchers now use it as a measure of a drug's antiviral activity, but they agree that it fails as a reliable measure of how quickly an infected individual will progress to AIDS. It can't be used to judge a drug's efficacy when given to asymptomatic HIV-infected people because only 20 percent of such patients show evidence of the antigen in their blood, says Andrew R. Moss, an epidemiologist at University of California, San Francisco.
- β_2 microglobulin, a protein in the blood that reflects cell destruction. Like p24, this protein increases dramatically shortly after infection occurs, then declines, and finally rises again with full-blown AIDS. But unlike p24, it can be measured in the blood of any HIV-infected person, Moss says. His research shows β_2 can be used with T4 counts to foretell which HIV-positives face the greatest immediate risk of progressing to AIDS.
- Neopterin, a substance in the blood and urine of people with HIV infection. Scientists believe neopterin is released when immune cells called macrophages are activated. Moss says neopterin, like β_2, can be used alone or in combination with T4 counts for an early warning of AIDS development.

A so-called virologic marker, HIV p24 core antigen directly indicates the presence of the AIDS virus, whereas β_2 and neopterin reflect the decline of the immune system. Researchers don't have much experience yet with β_2 or neopterin, but Moss thinks both may prove valuable indicators of AIDS progression in the future.

Some scientists believe the evidence supports using T4 counts today to approve or grant wider distribution of promising AIDS drugs. "No one dies from elevated levels of β_2 microglobulin or neopterin. Nonetheless, these may have a place in our surrogate-marker armamentarium," says NIAID Director Anthony S. Fauci. "However, no one can make it without T4 cells; this almost certainly must stand out as the primary parameter of significance."

Adds NIAID's AIDS Division Director Daniel F. Hoth, "The logic is simple: We know that people without T4 cells die. We know that the less T4 cells you have, the more you are at risk of opportunistic infections. It makes sense to say that a drug which delays or prevents this decline is of benefit to a patient."

But other scientists say T4 counts are not the gold standard in AIDS research that some envision them to be. "Counts of [T4 cells], though widely used clinically, are variable and a crude predictor of progression when taken by themselves," argues Moss. "They are also expensive to perform and difficult to obtain in many countries."

Researchers need to conduct more studies linking the decline in T4 cells to a deterioration in the patient's health before asking FDA to rely on T4 counts alone to approve drugs, says Ellen C. Cooper, director of FDA's Division of Antiviral Drug Products. For now, FDA will continue to recognize T4 cells as one measure of drug efficacy, she says. But before granting marketing approval, the agency also wants evidence that an experimental treatment relieves symptoms or prevents the disease from causing death.

Although Fischl's preliminary results seem impressive, scientists must await her final report and confirmation of the findings by other researchers, say some scientists. Thomas C. Merigan Jr., who directs the Center for AIDS Research at Stanford University, would like to see studies linking a decline in T4 cells to the development of minor symptoms, such as weight loss, in a disease stage called AIDS-related complex. He suggests drug investigators continue using traditional endpoints until scientists confirm the T4 cells' power to predict HIV progression.

Other scientists note some pitfalls associated with using surrogate endpoints in drug evaluations. "If we test a drug with clinical utility that doesn't happen to affect the marker we've chosen to use, we stand the very frightening possibility of rejecting a useful drug," says AIDS researcher Paul Volberding of the University of California, San Francisco. On the other hand, he adds, a new drug might alter a marker without having any real impact on the progression of the disease.

For the research community, it seems clear that the search for a powerful tool to predict AIDS progression will continue. That search, however, may take a very long time.

In the meantime, people infected with the AIDS virus will continue their own desperate search for experimental treatment – through whatever channels available – and AIDS activists will continue the fight to get new AIDS therapies out of research trials and onto the drug market. That pressure recently contributed to FDA's decision to allow widespread distribution of dideoxyinosine (DDI), an unapproved AIDS drug (SN: 10/7/89, p.231). Manufacturer Bristol-Myers Co. of New York City is giving the drug free to patients who can't participate in ongoing clinical trials of DDI's efficacy.

Martin Delaney, executive director of Project Inform, a San Francisco group that provides treatment information to AIDS patients and others, thinks new drugs need to be tested and marketed as soon as possible. "The challenge before us," he says, "is to make the best reasonable, commonsense judgments we can with today's knowledge about the endpoints we've got here and now in the real world." □