numbers of patients—several thousand, at least—if the subtle differences in survival are going to be detectable, he says.

Even if more flexible protocols do help keep subjects in clinical trials, some experts believe that it will no longer be possible to run large trials on every drug combination in all stages of HIV disease for long enough to get data on changes in death rate or symptoms, the gold standards for clinical trial efficacy. And that is resurrecting the issue of surrogate markers for judging the efficacy of a treatment. Each camp's arguments mirror those used a few years ago when the use of CD4 counts, which assess the status of the principal immune cell destroyed in AIDS, as a surrogate marker came under scrutiny. That practice was curtailed after a barrage of criticism from statisticians and clinical trialists (*Science*, 10 June 1994, p. 1538), who argued that surrogate markers are deceptive, not least because they can miss the toxic side effects that outweigh any beneficial effects of a drug.

But in the current AIDS research environment, surrogate markers, especially viral load, are regaining popularity. Alabama's Saag is one of the proponents of the surrogate marker approach. He points out that changes in the amount of virus in a patient's blood are a far more direct measure of a drug's activity than CD4 counts. Considering the urgency of the situation, he says, "if a drug regimen persistently lowers the viral burden, it should be enough to convince us of a drug's efficacy without having to go to more grotesque clinical endpoints."

But others fear that AIDS researchers may be jumping the gun on the use of surrogate markers. They counter that even though viral load is a good prognostic tool—patients with a high virus count usually decline very quickly—so far there's been no definitive study showing that a drug that decreases viral load improves survival or any other clinical symptom of HIV disease. "We need five or six good clinical trials ... to be able to say that viral load is a viable surrogate marker," said biostatistician Laurence Freedman of the National Cancer Institute.

Some AIDS research experts at the meeting took an even firmer stance against surrogate markers. They argued that it's not possible to validate a surrogate marker for drug efficacy, because a marker that correlates with survival under one drug regimen may not with a second regimen because of different toxicities. "You can have a home-run surrogate marker drug that kills more people than the disease," said AIDS activist Peter Staley, founding director of the Treatment Action Group in New York City. To illustrate his point, Staley referred to the recent brouhaha over the calcium blocker nifedipine. On the basis of nifedipine's ability to lower high blood pressure—a surrogate marker for stroke and heart disease—it is prescribed to millions of Americans. But a meta-analysis of 16 clinical trials reported in the 1 September issue of *Circulation* suggests that patients with heart disease who take the highest recommended dose of the drug die at three times the rate of patients who do not.

"If you want to know the clinical benefits [of a drug], you have to look at clinical endpoints," said David Feigel, head of the FDA's anti-retroviral drug division. "There's no free lunch to this." And that's a sentiment with which Staley clearly agrees: "As AIDS activists, we've always realized that there is a crisis in [drug] access, but there is also increasingly a crisis in information." And without clinical endpoint studies, he said, "we will never know whether we are inadvertently doing more harm than good around anti-retroviral therapy."

–Rachel Nowak

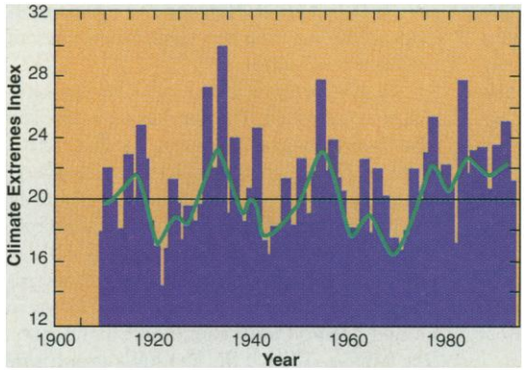
GLOBAL CHANGE

Scientists See Greenhouse, Semiofficially

The greenhouse warming is now official—at least that was the unofficial word last week. The global warming of this century "is unlikely to be entirely due to natural causes," in the words of a draft report from the United Nations–sponsored Intergovernmental Panel on Climate Change (IPCC), which represents the consensus view of the international scientific community. That judgment, however, came not in an official news release but via the Internet and the *New York Times*.

The IPCC report, the panel's first full report in 5 years, will not be officially approved until later this year. But in a well-intentioned effort by U.S. researchers to expedite review of the draft, part of it—a selective synthesis of the full report—was posted on the World Wide Web, where it was available to anybody who cared to read it. "We weren't the ones who published it," says Bruce Callander of the IPCC Working Group I technical support unit in Bracknell, England. "This is not an IPCC-approved statement. At the moment, the document could change." But the essence of the statement is likely to survive into the final report, say panel members, and it offers a window on the latest thinking on climate change—and on the meaning of publication in the electronic age.

The source of the leak was the home page of the U.S. Global Change Research Program (USGCRP), where the draft of the IPCC synthesis report had been placed, according to Michael MacCracken, executive director of USGCRP in Washington, D.C. The idea was to make the synthesis, which had been transmitted to the U.S. government for comment, more accessible to the U.S. scientists who would help supply that critique. The electronic document was festooned with warnings that it was for U.S. government review only and not for publication or distribution, but a *Times* reporter read the document. The *Times* considered its appearance on the Web to be tantamount to publication, says Richard Moss of the IPCC technical support unit in Washington, and went with the story.



Fever line. A composite index of weather extremes has been high since the mid-1970s.

Unofficial though it may be, the IPCC statement on detection of greenhouse warming marks a milestone in awareness that human activity is changing the climate. Since the last full IPCC report in 1990, researchers trying to model what greenhouse warming should look like have gained a better understanding of the climate system, including how pollutant aerosols have been cooling some regions (*Science*, 16 June, p. 1567). As a result, the models and the temperature record are now "much more similar than they are different," says Thomas Karl of the National Climatic Data Center in Asheville, North Carolina, who is an author of part of the Working Group I report. Karl and other researchers have also traced an increase in weather extremes since the mid-1970s that seems to bear the signature of the greenhouse effect (*Science*, 21 April, p. 363).

The evidence suggests that the observed warming "is unlikely to be caused by natural variability," says Karl, who cautions that he is speaking for himself, not the IPCC. "There's a 90 to 95% chance that we're not being fooled." For 99% confidence, he says, we'll have to wait at least another 5 years.

–Richard A. Kerr