

No Consensus on Rules for AIDS Vaccine Trials

GENEVA, SWITZERLAND—A meeting held here last week to try to set ethical ground rules for AIDS vaccine trials in poor countries almost reached boiling point when the participants grappled with a key question: If a vaccine is tested in a country that cannot afford anti-HIV drugs and volunteers become infected during the trial, should they be given state-of-the-art treatment? The answer could determine the ethical, financial, and scientific viability of AIDS vaccine tests. But for the 85 AIDS vaccine developers, ethicists, public health officials, lawyers, and activists from more than two dozen countries who tried to answer it, consensus proved elusive.

The meeting—an ad hoc advisory group to the United Nations' AIDS program, which will go on to recommend changes to international guidelines for all clinical trials—did reach agreement on some points. For example, the participants recommended ending the current requirement that a vaccine be tested first in the country where it is made, and they said trials should be more closely monitored to make sure that participants truly give their consent. These recommendations could lead to “major changes in the way trials are done,” said Barry Bloom, a researcher at Harvard University who heads the UNAIDS Vaccine Advisory Committee. But the central controversy over how to treat those who become infected—the question that led to the meeting being called in the first place—remains unresolved.

The problem it poses for researchers was highlighted at the meeting by Mary Lou Clements-Mann of Johns Hopkins University in Baltimore. She pointed out that vaccines rarely prevent infection; rather, they prevent or modify disease. Hence a critical measure of the success of an AIDS vaccine trial would be whether the vaccine lowers the “viral load”—the amount of HIV in the blood—in people who get infected. But if many of those who become infected soon begin taking potent anti-HIV drugs, says David Ho of the Aaron Diamond AIDS Research Center in New York City, “you’re not going to be able to see anything.” Thus the widespread use of anti-HIV drugs could make it “impossible to design a scientifically valid [vaccine] trial,” warned Clements-Mann.



Mired mess. Harvard's Barry Bloom foresaw ethical problems for vaccine trials.

But Don Francis, head of the San Francisco-based biotech company VaxGen, which just last week launched in the United States the first efficacy trials of an AIDS vaccine, argued that not everyone would start treatment immediately, and because researchers will take blood from participants every 24 weeks or so, they should be able to make at least one viral-load measurement in many untreated people who become infected. If the vaccine had an effect, said Francis, it should be relatively easy to determine. He remained skeptical. “I think it’s tough in a country like the United States,” he said. “Patients are going to be treated very quickly.”

This problem could, potentially, be avoided by carrying out trials in poor countries where the expensive cocktails of anti-HIV drugs are unavailable and unaffordable, but is that ethical? According to the two most influential guidelines today for clinical research—the Declaration of Helsinki and a subsequent document written by the Council for International Organizations of Medical Sciences—the answer appears to be no. Both state that “every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method.”

This principle was put to the test last year, when the Public Citizen's Health Research Group, an influential consumer-advocate organization based in Washington, D.C., slammed drug trials in developing countries that aimed to prevent mother-to-infant transmission of HIV. Public Citizen complained that the trials used placebos even though a U.S.–French study had already proved that an intensive regimen of the anti-HIV drug AZT would prevent transmission (*Science*, 16 May 1997, p. 1022). The researchers countered that they needed placebos in order to determine quickly whether a cheaper, simpler course of AZT—which would be more applicable in poor countries—might decrease transmission, too. (The dispute became moot when an interim analysis of one trial found that the shortened treatment worked.)

Public Citizen's attack set alarm bells ringing for AIDS vaccine researchers, because the same considerations should apply to people who become infected during vaccine trials. “I knew if we didn't deal with it in vaccines, we were going to get into the same mired mess,” said Bloom.

The majority of the participants at the Geneva meeting agreed with the practical argument that people who become infected

Wisconsin Medical School in Madison.

Still, the panel lifted EMFs off the canvas—however briefly—after a one-two punch had knocked the controversial topic off the list of credible health threats. In 1996, a National Academy of Sciences panel found “no conclusive and consistent evidence” for harm from residential exposure to EMFs generated by power lines, appliances, and other sources. Then last year, a major National Cancer Institute (NCI) epidemiological study found no evidence of childhood leukemia from EMF exposure (*Science*, 4 July 1997, p. 29).

Even before the academy and NCI weighed in, however, Congress in 1992 had created a research program called RAPID, run by the NIH's National Institute of Environmental Health Sciences (NIEHS) and the Energy Department, to examine EMFs. The law required NIEHS to form the advisory panel to review RAPID, which has spent \$66 million on studying the effects of EMFs on everything from gene expression to breast cancer on Long Island. Chaired by Michael Gallo, a toxicologist at the University of Medicine and Dentistry of New Jersey—Robert Wood Johnson Medical School in Piscataway, the 30-member panel used a more liberal standard than most U.S. bodies would in judging EMFs: It followed International Agency for Research on Cancer criteria, which allow a substance to be labeled a carcinogen based only on an association in a population, even in the absence of evidence linking a substance to tumors in lab animals.

The latest EMF indictment is not based on any hot new data. An NIEHS-commissioned analysis of pooled data from several population studies upheld earlier findings—namely, that children living near power lines appear to have a 56% increased risk of leukemia. And it considered other studies finding a similar leukemia risk in adults exposed to high levels of EMFs at utilities and other workplaces. The panel voted 19–9 to classify low-frequency EMFs as a “possible human carcinogen”; their 400-page report, set for release this month, calls the vote “a conservative, public health decision based on limited evidence.”

Experts are quick to point out that any cancer risk from EMFs is slight. After a 2-month public comment period on the report, NIEHS will calculate how many U.S. cancer cases might be due to EMFs, then send its final review on to Congress and other agencies. The panel did boldly come through with one recommendation: more research. If there is a link between EMFs and cancer, explains panelist Jerry Williams of Johns Hopkins University, “it's very small, very subtle, and very complex, and something we don't understand at any level.” —JOCELYN KAISER

DAN LUKEN

during an AIDS vaccine trial should be offered the "highest attainable" treatment in their locale that can be sustained after the trial ends. To offer more, said Dwip Kitayoporn of Thailand's Mahidol University, would be "like leaving a Cadillac or Rolls Royce in our country, but no one can afford to drive it or even repair it." Major Rubaramira Ruranga, an HIV-infected Ugandan who works at a research center in Kampala, warned that people may also sign up for vaccine trials just to get access to drugs. "We're going to create a safe haven for people who are going to be put on the trial," Ruranga said. This, others noted, would violate the ethical principle that researchers must not "unduly influence" people to join trials.

But an impassioned, ardent minority rejected the idea that trial volunteers should be treated any differently from those in developed countries. Dirceu Gerco, coordinator of an AIDS vaccine center in Brazil, worried that setting a lower standard for poor countries was a slippery slope. "When you put the level of ethics below the maximum, it's very easy to lower it more," said Gerco, whose sentiments were shared by several other Brazilians at the meeting.

Francis and several Thai scientists underscored how this debate is far from theoretical: They are now gearing up for a large trial of the company's vaccine in Thailand before the end of the year. Neither the company nor the cash-strapped Thai government plans to give cutting-edge treatments to people who become infected. When Public Citizen's Peter Lurie was asked at the meeting if the group would campaign against this trial, he said no comment—which is one more critical question that the meeting left unanswered.

—JON COHEN

WILDLIFE BIOLOGY

Fungus May Drive Frog Genocide

The case is so frustrating it would make even Hercule Poirot sigh. Amphibian populations have been plummeting in the past 2 decades, but the perpetrator has left precious few clues to its identity.

Time and again, scientists have visited woods filled with frog song just 3 or 4 years earlier, and "they're just gone," says David Wake of the University of California, Berkeley—the frog corpses already decayed or eaten. Now, researchers have finally caught a killer in the act.

The accused is a new fungus that has turned up in 120 frogs and toads of 12 species in Australia and seven species in Panama



Mug shot. Prime suspect in frog deaths in Australia and Panama, the chytrid fungus.

often during mass die-offs in relatively pristine areas. Fourteen scientists from Australia, the United States, the United Kingdom, and Canada will describe the fungus—from the phylum Chytridiomycota—in the 21 July *Proceedings of the National Academy of Sciences*. "I don't think this is the cause of amphibian declines," says Allan Pessier of the National Zoo in Washington, D.C., who is part of a second team that has seen the same fungus in zoo populations of amphibians in the United States. Researchers haven't found any fungi when they've looked for them in frogs in California, for instance, where pesticides are the leading suspect in amphibian die-offs, says Gary Fellers of the University of California, Davis. But, adds Pessier, "in my opinion, this is a significant finding."

After noticing spore casings on the skin of rainforest frogs that died in Queensland, Australia, in 1993, a team led by veterinary pathologist Lee Berger of James Cook University in Queensland homed in on a suspect: a new species of chytrid fungus, whose prior rap sheet had it infecting plants and insects, not vertebrates. Meanwhile, U.S. scientists had found a similar fungus in frog corpses after a die-off in western Panama in January 1997. "This is the only thing the dead and dying frogs shared in common," says veterinary pathologist D. Earl Green of the U.S. National Institutes of Health. The team has yet to isolate the fungus and prove it's the culprit, rather than something else on the skin. They are also unsure about the killer's modus operandi—whether it exudes a lethal toxin or suffocates frogs by clogging their skin pores, through which they breathe.

Also a mystery is just how the fungus turned up on two far-flung continents in such a short time. One unsettling theory is that researchers traveling between Australia and Central America carried it with them on their boots. Another is that the fungus had been lurking in both hemispheres but didn't start killing frogs until after they were weakened by something else—such as UV light coming through the thinning ozone layer, or pesticides. One way to sort this out is to ex-

amine the fungal DNA to establish the phylogenetic relationship among isolates.

The DNA studies will also help determine how fast the fungus might be country hopping. For example, chytrid may have spread to Panama from Costa Rica, where in 1988 half the 40 amphibian species on a Monteverde ridge vanished. Although the detective work is far from finished, says team member Peter Daszak of Kingston University in the U.K., "what we've got for the first time is real evidence—dead bodies."

—JOCELYN KAISER

ARCHAEOLOGY

Eight Millennia of Footwear Fashion

From the bear-fur shoes that once graced the feet of Japanese samurai to the sleek platform sandals that strut down runways today, people have long garbed the humblest part of the human body—our feet—in high fashion. Now ancient sandals and slip-ons from central Missouri reveal that attention to fashion in footwear goes back 8000 years or more. On page 72, archaeological textile expert Jenna Kuttruff of Louisiana State University in Baton Rouge and her colleagues



Fancy footwear. An undated fiber sandal from the cache at Arnold Research Cave.

analyze and date a rare collection of 35 perishable fiber and leather shoes excavated decades ago from a Missouri cave.

One shoe is dated at more than 8000 years old, making it among the oldest in North America. And the shoes' complex weave and design indicate that early North Americans were just as fashion conscious as we are. "The complexity in design means that we had artists and craftspeople even then," says Kathryn Jakes, a fiber specialist at Ohio State University in Columbus. Adds James Petersen, an archaeologist at the University of Vermont in Burlington: "In modern society we show our status and individuality through our clothing. But one would not have guessed this of prehistoric native North America 8300 years ago," as social distinctions in personal effects such as jewelry don't generally appear until 4000 to 5000 years ago.



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