African AIDS: Whose Research Rules?

The World Health Organization and the U.S. government are trying to set guidelines to guard against "safari research" and exploitation by foreign scientists

A FEW YEARS AGO, MICHELE BARRY, A CLINICAL researcher with Yale University's international health program, set out to help address the nightmare of AIDS in Africa. She was to participate in a study of the prevalence of HIV infection among pregnant women in Tanzania. The plan was to take maternal and infant cord blood and look for antibodies to the AIDS virus, a seemingly straightforward study. But there was a hitch.

Tanzanian officials insisted that the researchers not tell the women in the study either why the blood was being drawn or what the results of the blood tests were. The Tanzanians were worried that the results could cause hysteria among the women because there is no cure for AIDS, and the country's medical system can do little to provide even palliative therapy. And that presented the researchers with a dilemma: Yale's institutional review board, which had approved the study, required that subjects give informed consent before participating and that they be told the results of the blood test. Faced with these impossibly conflicting requirements, the researchers abandoned the study.

Giving up one study may be no tragedy, considering the scale of the AIDS disaster across the African continent. But this incident points up a quandary facing a growing band of researchers looking to Africa for clues about the course of the epidemic and how to combat it: Are ethical guidelines that have been developed to protect subjects of biomedical research in industrial countries appropriate for research in the Third World? And if this question is bedeviling epidemiological studies like Barry's, which entail little or no risk to those participating in them, it will be posed even more starkly by higher risk ventures such as the testing of experimental AIDS drugs and vaccines in Africa.

Already, according to one recent survey, close to 600 AIDS-related studies are under way in Africa, just over half of them involving collaboration with researchers from outside the continent. And, as experimental therapies and vaccines become available, there will be growing pressure to test them in Africa, with its huge patient population and high rates of transmission. More than 5 million people are infected by HIV in sub-Saharan Africa and half a million have come down with the disease since the epidemic began, the World Health Organization (WHO) estimates. And in some Central African cities, 20 to 40% of adults of childbearing age are infected with the virus. All this makes sub-Saharan Africa "a unique area to test a vaccine," says Thomas C. Quinn, an epidemiologist at the National Institute of Allergy and Infectious Diseases who has worked extensively in Africa.

Testing ground? *High HIV infection rates in African cities pose scientific and ethical challenges.*

This growing international research interest in Africa has prompted WHO and the U.S. Public Health Service (PHS) to try to set new ground rules that will avoid the kind of ethical impasse that halted Barry's study and also guard against exploitation of African AIDS victims. WHO convened a group of researchers and officials from health funding agencies earlier this year to help it sort through the issues. The PHS followed suit last month, gathering a group of clinical researchers, ethicists, and federal health officials together in Annapolis, Maryland, in a first step toward drafting rules that will apply to all PHS-funded research in Africa and other regions of the Third World. "What we're trying to do is prepare," says Ron St. John, deputy director of the National AIDS Program Office and organizer of the Annapolis meeting.

Among the issues they are grappling with: How should Western approaches to issues such as privacy, informed consent, and protection of research subjects be applied in such studies? How can research be geared toward the needs of the host country rather than the country sponsoring the work? Is it ethical to test experimental therapies or vaccines in countries that cannot afford to buy them when they reach the market?

Though neither group has issued formal recommendations, a draft report of the WHO meetings and a draft consensus statement from the PHS gathering, both of which have been obtained by *Science*, place great emphasis on ensuring that any research project in Africa involving foreign scientists be undertaken in close collaboration with indigenous researchers. This has not always been the case, according to the report of the WHO group. Though "many AIDS-related research activities have been collaborative in the true sense," the draft report says, "others have been directed solely by the sponsoring country, with little or no input from local investigators." Indeed, the report says that only about half the AIDS studies now being undertaken in Africa were even known to national AIDS control bodies when they were begun, "making it highly unlikely that the results would be rapidly utilized in local prevention or control programs."

The draft report goes on to complain about "the all-too-frequent example of so-called safari or helicopter research, whereby foreign scientists have used local contacts to gain access to a population group and obtain samples that are analyzed in their home laboratories, never making the results available to the so-called host investigator. These episodes have been very discouraging to local investigators, who have felt exploited."

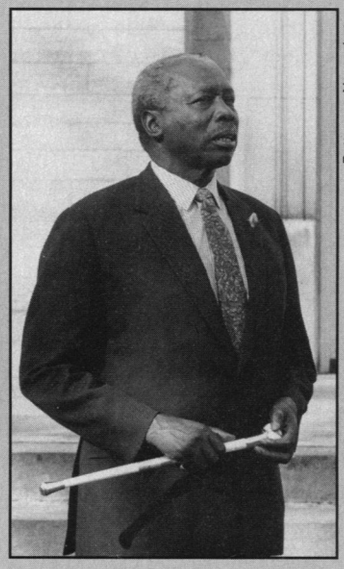
African researchers would obviously feel less exploited if they were involved in every stage of a research project, from its concept through the design and implementation, both groups pointed out. But what of a different kind of exploitation: Testing drugs or vaccines in developing countries that would primarily be used in the industrial world?

According to St. John, the participants at

International Doubts About a Kenyan Cure

News of miraculous cures for AIDS typically get a cool reception from the Western biomedical establishment, and dramatic claims by Kenyan researchers early this year were no exception. But they have proved hard to ignore. Tiny doses of alpha interferon taken orally, the Kenyan researchers said, not only depressed symptoms in virtually every patient they treated, but the drug actually removed all signs of infection in about 10% of the patients.

The claims, which have been heavily promoted in public pronouncements by Kenyan officials, including President Daniel arap Moi, have drawn headlines around the world. One result: Desperate AIDS patients from many African countries and even the United States have flocked to Kenya in hopes of being cured. And that, in turn, prompted AIDS researchers in other countries to try to repeat the studies. The World Health Organization (WHO) sponsored a series of quick tests of oral alpha interferon in Zaire, Zimbabwe, Cameroon, and the Ivory Coast. The verdict so far, according to experts who met at the WHO headquarters in Geneva last month to go over the results from Kenya and elsewhere: unproven but worth further study.



Bettmann Newsphotos

Kemron fan. *President arap Moi praises Kenyan ingenuity.*

The original Kenyan study, which was reported in the July issue of the *East African Medical Journal*, was conducted by physicians from the Kenya Medical Research Institute led by Davy Koech. It was conducted without any controls. Some 200 patients were given oral doses of 100 units a day of alpha interferon for 10 weeks. The drug, which the Kenyans dubbed Kemron, dramatically increased the patients' capacity to withstand secondary infections, Koech reported, and in 18 cases blood tests following treatment failed to detect HIV antibodies.

The WHO-sponsored trials in other African countries were also uncontrolled. According to a statement released by WHO after last month's meeting, they were launched in the hope that the Kenyan findings "could be readily and immediately confirmed." But "in comparison [with the Kenya study] the results obtained have been inconclusive." Though some patients appeared to improve, the statement said, it's impossible to say whether this was due to the treatment or to the patients' own raised expectations. Moreover, the alpha interferon used in the studies was not prepared in a consistent form; different formulations might produce different results. What's needed now, the WHO panel said, are properly controlled clinical trials "undertaken in accordance with an appropriate experimental design in which all relevant variables are monitored." David Heymann, acting chief of the WHO Office of Research, says he expects such studies will be starting before the end of this year.

Two small trials looking at low-dose oral interferon—one in New York at Mount Sinai Medical Center and the other at the Veterans Administration Medical Center in Amarillo, Texas—are in fact already under way in the United States. Kathryn Zoon, head of the Food and Drug Administration's laboratory of cytokine biology, says that, although both trials are still blinded, no striking changes in T cell counts have been observed in the preliminary data, which suggests that the drug has produced no dramatic improvement in immune status.

Alpha interferon has produced some promising results when injected into AIDS patients in very large doses, however. Earlier this year, for example, Anthony S. Fauci and H. Clifford Lane of the National Institute of Allergy and Infectious Diseases reported that treating asymptomatic, HIV-infected subjects with a recombinant form of alpha interferon slowed viral production and reduced the risk of developing AIDS-related opportunistic infections. A phase III trial of injectable alpha interferon alone and in combination with the nucleoside analogs AZT and ddI is now being conducted. An injectable form of alpha interferon has already been approved for treating Kaposi's sarcoma and genital warts, but again, the dosage is measured in millions of units, compared with the mere 100 units used in Kenya.

In fact, it was the puny dose as much as the uncontrolled nature of the Kenyan trials that raised skepticism among U.S. AIDS researchers. Zoon, for example, says she believes that the levels administered could produce no systemic effect.

Koech is undaunted by the skepticism, however. "I think this is an innovative approach to drug therapy," he said in a telephone interview with *Science*. "I am not trying even to convince my fellow scientists. What I am trying to do is treat the virus." Nor is the Kenyan government put off by the adverse assessments. In July, according to press accounts, President arap Moi hailed Kemron as a glittering example of Kenyan ingenuity and announced plans to mass produce the drug in Kenya and patent the formulation.

But even this has caused controversy. The main developer of low-dose oral alpha interferon, Joseph M. Cummins, president of Amarillo Cell Culture in Amarillo, Texas, has said he already holds several patents on the use of the drug. The drug itself is manufactured by Hayashibara Biochemical Laboratories in Okayama, Japan, and Cummins says it was he who first introduced Koech to the concept of low-dose oral alpha interferon as a possible treatment for AIDS.

Cummins, a veterinarian, has for years been promoting the idea of using oral interferon as a treatment for animal viral infections such as feline leukemia virus and a viral respiratory infection in cattle. He says he began to view the drug as a potential AIDS therapy in the mid-1980s, when a friend developed AIDS and began treating himself with interferon. The friend got better, and Cummins began trying to interest the U.S. research establishment, including the National Institutes of Health, without success in trials of oral interferon in human disease. After providing the drug to Alan Young of the Kenyan Agricultural Research Center, who used it to treat East Coast Fever in calves, Cummins went to Nairobi where he showed his results in animals to Koech who began using it to treat AIDS patients.

But even Cummins, one of the biggest promoters of the drug, has problems with Koech's results. Cummins, who attended the WHO meeting, says: "I have just reviewed all of that data, and I find it quite startling that they could draw any conclusions from such a messy study." ■ **J.P.**

the PHS meeting had no trouble agreeing that it is unethical to test drugs and vaccines in the Third World simply because it's cheaper and people are less liable to object. And the PHS panel's draft report states explicitly that "study participants and their community should have access to drugs, vaccines, and intervention/prevention strategies resulting from the study."

But even though such principles are easy to state, participants at the PHS meeting emphasize that, in practice, they can be difficult to implement because very different considerations often apply in determining the risks and benefits of research in poor countries. "The normal standard is you can only do research on somebody when the risks are justified in comparison to the benefits," says Robert M. Veatch, director of the Kennedy Institute of Ethics at Georgetown University in Washington, D.C., who spoke at the PHS meeting. In the developed world there is usually at least a minimal standard of health care that can be provided as an alternative to some risky, unproven therapy, he notes. But in the developing world, there may be no alternative and offering even a risky experimental one may be better than nothing, he said.

The promise of an experimental therapy may be sufficient inducement to persuade sick people to enroll in clinical trials, but is it ethical to offer incentives for people to enroll in epidemiological studies that will provide them no direct benefit? Quinn, who has run up against this problem in his work in Africa, says that even token compensation for subjects who agree to participate in research projects can cross a fine line between reasonable inducement and undue coercion. For that reason, he and his colleagues decided that any cash compensation would prove too tempting. Instead, in one study of maternal HIV infection they offered a photograph of a child to people who participated in their study, and in another it was a bottle of milk. But Barry says that even if no compensation is offered at all, Africans may still feel coerced: "Often [they] will not say 'no' to a white face because there is a colonialist legacy."

As for obtaining truly informed consent from would-be subjects of research projects, several participants in the PHS meeting said this is an area in which Western standards may collide most strongly with the reality in Third World countries. "It makes no cultural sense to have somebody give informed consent the way we often go about informed consent," says Barry. Warren Johnson, a tropical disease researcher at Cornell Medical Center, agrees: "I think its a little naïve for us to expect the same procedures we utilize in Manhattan in an urban, educated population to be meaningful and relevant to a rural, largely illiterate population," he says. "It's not very meaningful to have a thousand sheets of paper with an 'X' on them."

"People confuse illiteracy with lack of intelligence and even education," shoots back Peter Lamptey, director of Family Health International, an organization that conducts AIDS prevention work throughout Africa. "You can always translate [technical terms] to the level that people will understand and make an informed choice," he says. But even so, Lamptey concedes that there can be cultural barriers that make it difficult to gain informed consent. In some societies, for example, married women may not be able to give informed consent, instead deferring to their husbands.

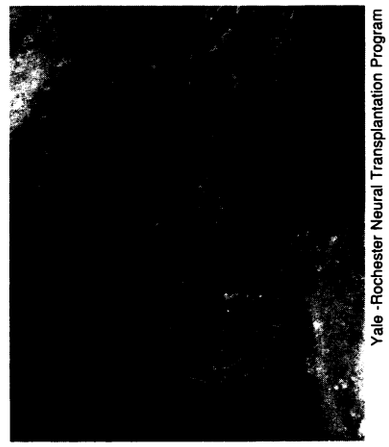
But, regardless of societal differences, St. John insists that no researcher is "excused from the ethical obligation of informed consent." The draft consensus document from the PHS meeting spells out some specific steps, including oversight by local communities, education of participants, and having a local person "familiar with the language, culture, ethics, and conditions of the participating subjects" obtain the consent.

One thing is clear: "Mounting an international research study may be much more complicated and require more effort to set it up than a domestic study," says St. John. But, he adds, overcoming these complications will be essential because more international collaboration will be needed to find effective ways of stopping the worldwide spread of AIDS.

■ JOSEPH PALCA

OTA Quietly Backs Fetal Tissue Work

So charged is the debate over the use of fetal tissue in research that few federal agencies choose to confront it directly. Last week, the Office of Technology Assessment proved itself no exception. Its latest report* focuses on "neural grafting," a process in which researchers transplant tissue into the central nervous system (CNS) with the aim of treating degenerative neurological conditions such as Parkinson's and Alzheimer's disease. But the most effective material for neural grafting—at least for now—is tissue from the fetal CNS, which is currently unavailable to federally supported researchers because of a moratorium imposed by Health and Human Services Secretary Louis Sullivan.



Yale - Rochester Neural Transplantation Program

Bridging the gap. *A monkey fetal tissue graft in the brain of an adult monkey. [Courtesy of John Sladek]*

Though OTA doesn't come right out and recommend overturning the moratorium, it presents a subtle case for doing so. First, the report estimates that neurological conditions for which neural grafting treatment looks promising—primarily stroke- or injury-related neural damage and Alzheimer's disease—cost society nearly $70 billion a year in medical costs and lost productivity. Then OTA points out that although neural grafting is entirely experimental at this stage, animal models and a limited number of clinical trials in parkinsonian patients suggest that the treatment may be quite effective in countering otherwise irreversible nerve damage. And finally, OTA says more research is needed into the efficacy of neural grafts. But such research virtually requires access to fetal tissue, OTA acknowledges.

OTA outlines three different options for Congress to consider: leave the HHS moratorium intact and delay important advances in neural grafting research; form a commission to assess the implications of the moratorium for society as a whole; or legislatively override the HHS moratorium and reconstitute the HHS Ethics Advisory Board to propose guidelines for fetal tissue research. Though OTA doesn't specifically tell Congress which option to choose, it does note that the federal moratorium "could retard the development of [neural grafting] techniques in the United States, leaving progress to be made by other countries," and adds that it may have discouraged basic research into neural grafting.

Some members of Congress, in fact, are already pushing the third option. Earlier this fall, Representative Henry Waxman (D–CA) proposed legislation to end the moratorium (*Science*, 31 August, p. 964).

■ DAVID P. HAMILTON

**Neural Grafting: Repairing the Brain and Spinal Cord* (Office of Technology Assessment, U.S. Congress, OTA-BA-462, September 1990).