The Shame of Medical Research

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Until the 1990s American medical researchers performed most of their experiments on other Americans—frequently choosing subjects who were poor and vulnerable.[1] Now, however, they are increasingly likely to conduct their investigations in third world countries on subjects who are even poorer and more vulnerable. Part of the reason is AIDS—the first modern infectious disease to strike the developed and developing world simultaneously and to give both a large stake in finding a cure. Part of the reason, too, is the mounting financial and regulatory burdens of research in the rich nations, which cause investigators, both from universities and drug companies, to go to the poorer countries to test new treatments.

Whatever the reason, practice has overwhelmed ethics. The major international codes on human experimentation, including the principles proclaimed at Nuremberg in 1947 and the World Medical Association's Declaration of Helsinki in 1964, all say that the well-being of the subject always should take precedence over the needs of science or the interests of society, and that doctors must obtain "the subject's freely informed consent." But neither these codes nor the Western groups concerned with medical ethics have had the developing countries in mind. Countries in which clinical trials are now conducted are often too poor to pay for the medicines that are successfully tested. And the people recruited for those trials very seldom get the kind of medical care the participants in trials in prosperous countries can expect. Whether Western principles covering the treatment of people who are the subjects of research can and should be applied in Africa and Asia has become a bitterly debated question.

1.

The question was first posed by the research that followed the 1994 finding that is known by its grant number—076—in the Pediatric AIDS Clinical Trials Group, a consortium of university-based investigators funded by the National Institutes of Health (NIH). The purpose of the research, everyone agrees, was admirable: to learn how to prevent the transmission of HIV from HIV-positive pregnant women to their children. The dispute that arose concerned whether the research was conducted ethically.

In 076, American investigators proved conclusively, through clinical trials in the US, that giving AZT to HIV-positive pregnant women during their pregnancy and immediately before labor, and then to their newborn infants for six weeks, significantly reduced the rate of transmission of HIV. Without AZT, roughly one third of the women transmitted the virus to their newborn babies. With AZT, mothers passed on the virus only 8 percent of the time, for a total reduction of 66 percent. Clearly, AZT provided extensive protection against the spread of AIDS from mother to child.[2]

Even the 076 trial stirred some argument. AZT is a highly toxic drug, with many serious side effects, and investigators were administering it to pregnant women of whom only one third would have passed on the disease. Was it ethical to subject the fetuses of the other two thirds to a toxic drug, when, if left alone, they would not have suffered any adverse consequences?

AFP/Corbis

Volunteers beginning a trial of a new AIDS vaccine, Bangkok, Thailand, March 24, 1999

This question had to be submitted to the institutional review boards (IRBs) at the researchers' home institutions. By federal regulations, all human experiments supported with federal funds must first be approved by an IRB, and practically every university, hospital, or company doing such research has established one. The regulations spell out how an IRB should be organized (e.g., with no fewer than five members, with at least one not affiliated with the institution) and what standards it should enforce (research benefits must outweigh risks and investigators must give potential subjects enough information to insure informed consent).

But the final decision on what is or is not ethical research is left to the individual IRBs. There is no regular review of their decisions, and, despite some requests to create one, there is no national IRB to supercede them. In the AZT research on pregnant women, all the IRBs took the position that since no one could identify in advance which newborn would be spared the disease and which would contract it, it was ethical to subject all of them to the risk of toxic effects.

Giving AZT to HIV-positive pregnant women and newborn infants immediately became the standard of care in American hospitals. (Some doctors and public health officials even advocated compulsory HIV testing of pregnant women to ensure that their offspring were protected.) But this treatment stood little chance of being adopted in developing countries with mounting cases of AIDS. A six-month course of AZT costs about $800, far beyond the budgetary means of countries whose average annual expenditure per citizen for health care was below $25. Some American investigators, strongly suspecting that the virus was most likely to be passed during late pregnancy or childbirth, suggested that a short course of AZT might be almost as protective as the long course. Were this true, the cost of treatment would be markedly reduced and the benefits almost as great.

The clinical trials to test the efficacy of a short course of AZT required two groups, or arms as they are called. The active arm would receive the short course. But what would the second arm, the control group, receive? Should it get the full course of AZT that American women were receiving, or should it get a placebo? Almost all the researchers in the field—most of them in southern Africa and Thailand—decided to give the control groups a placebo. In February 1998, the result of the first trial was announced: the short course of AZT was effective, not to the degree of the full course but substantially more effective than the placebo. A small amount of AZT (at a cost of $50, as against $800 for the long course) reduced transmission by 40 to 50 percent, which was excellent news for countries like Thailand, which was able to afford the treatment. It was good news to African countries, which would have more difficulty paying for it but could hope to supplement their medical budgets with humanitarian aid.

But the positive findings did nothing to reduce the intensity of the debate over whether the control groups should have received some medical treatment. The basic issue was one of the ethical obligations to a control group facing deadly disease when an effective therapy existed. Since the efficacy of AZT against mother-to-infant transmission was fully established, why not give the control groups the long course of AZT and use this as the base against which to measure outcomes for the short course?

This was precisely the position adopted by Marcia Angell in a now famous *New England Journal of Medicine* editorial.[3] Angell cited the Declaration of Helsinki provision that control groups should always receive the "best proven diagnostic and therapeutic method," which in this case meant the long course of AZT. When researchers in southern Africa and Thailand gave control groups placebo, Angell wrote, they violated the Helsinki standards and demonstrated "a callous disregard of their welfare." She then went on to compare the research to the Tuskegee study, the most notorious American research scandal, in which, from the 1930s through the 1960s, the US Public Health Service had purposely withheld known effective treatments from black men suffering from syphilis. Angell charged that investigators were now withholding effective treatments from black women and children in Africa suffering from AIDS. "It seems," concluded Angell, "as if we have not come very far from Tuskegee after all. Those of us in the research community need to redouble our commitment to the highest ethical standards, no matter where the research is conducted."

Her position was supported by Sidney Wolfe and Peter Lurie, the physicians who head the Health Research Group of Public Citizen, the organization founded by Ralph Nader.[4] They calculated that as of 1997, sixteen research projects were investigating the effectiveness of short course AZT, using as subjects some 17,000 pregnant women in developing countries. In fifteen of the sixteen projects, nine of which were funded by the NIH or the Centers for Disease Control (CDC), the control groups did not receive AZT. (The one exception was a Harvard School of Public Health project in Thailand.)

Wolfe and Lurie could find no justification for allowing investigators to adopt lower standards abroad than they used in the US. "Researchers working in developing countries," they wrote, "have an ethical responsibility to provide treatment that conforms to the standard of care in the sponsoring countries, when possible." They conceded that if achieving that standard required exorbitant expenses, like building an intensive care unit, the requirement could be waived. But if the test involved a drug that the manufacturer could, and sometimes did, provide free of charge, then a different standard was truly a double standard, and this, they concluded, "creates an incentive to use as research subjects those with the least access to health care."

The position of Angell, Wolfe, and Lurie provoked responses every bit as vigorous and uncompromising. The head of the NIH, Harold Varmus, and the head of the CDC, David Satcher,

[1] The mixed record of human experimentation in the US continues to be explored, with recent attention devoted to the government's secret radiation experiments during the cold war. See Eileen Welsom, *The Plutonium Files* (Dial Press, 1999), and Jonathan D. Marino, *Undue Risk* (Freeman, 1999; forthcoming in paperback).

[2] E.M. Connor et al., "Reduction of Maternal-Infant Transmission of Human Immunodeficiency Virus Type I with Zidovudine Treatment," *The New England Journal of Medicine*, Vol. 337 (1994), pp. 1173–1180.

[3] Marcia Angell, "The Ethics of Clinical Research in the Third World," *NEJM*, Vol. 337 (1997), pp. 847–849.

[4] Peter Lurie and Sidney Wolfe, "Unethical Trials of Interventions to Reduce Perinatal Transmission of the Human Immunodeficiency Virus in Developing Countries," *NEJM*, Vol. 337 (1997), pp. 853–856.

defended 076, as did Michael Merson, executive director of the WHO Global Program on AIDS.[5] The long course of AZT, they said, was not only very expensive but required frequent medical monitoring that was beyond the capacity of developing countries. So giving AZT could in fact be compared to building an intensive care unit. They also argued that it might not be safe to use AZT in a population that was seriously undernourished and suffering from anemia, and that placebo trials were also quicker than others in getting an answer.

Since critics contested each of these points, defenders of the post-076 trials went on to insist that research ethics in developing countries should not be dictated by the United States. Local ethics committees, they claimed, were competent to review research projects, and since Africans and Asians had approved these trials, outsiders should not second-guess them. Varmus and Satcher quoted from a letter written by the chairman of the Uganda Cancer Institute research committee: "These are Ugandan studies conducted by Ugandan investigators on Ugandans. . . . It is not NIH conducting the studies in Uganda but Ugandans conducting their study on their people for the good of their people."

One last contention was too political to be voiced openly but was often hinted at privately. No country wanted to spend significant amounts of money on second-class treatment. If a short course of AZT was openly compared to a long course, health officials would have to ask political leaders to fund a program that was less effective than the American one. But if results from the short course were compared to those from a placebo, they would be able to request funding to reduce by half the number of newborn babies infected by HIV.

Just how irreconcilable are the differences between the two camps becomes apparent in the provisions of the 1993 "International Ethical Guidelines for Biomedical Research involving Human Subjects." Drafted by the Council for International Organizations of Medical Sciences and the WHO, the document attempts to formulate research ethics in developing countries with particular attention to combating AIDS. However, the document is ambivalent about the issues raised by the post-076 trials. First, it declares, "investigators must respect the ethical standards of their own countries." They "risk harming their reputation by pursuing work that host countries find acceptable but their own countries find offensive." But it then adds that investigators must respect "the cultural expectations of the societies in which research is undertaken" and ought not to "transgress the cultural values of the host country by uncritically conforming to the expectations of their own." So should researchers conduct such placebo trials? The document does not say.

2.

More and more instances of AIDS research that follows the post-076 model are coming to light, and their defenders are attempting to amend the Helsinki Declaration so that it will agree with their views. At the same time, the efforts to develop an AIDS vaccine are raising new and troubling questions about ethics in research. And quite apart from AIDS, the sheer amount of research in developing countries both by academic and drug company investigators is expanding enormously.

AIDS investigations in developing countries often withhold effective treatments from research subjects. It is true that AZT or antiviral drugs are expensive and difficult to administer under conditions of poverty; but probably as crucial is the fact that providing treatment fatally undermines the research. For example, under an NIH grant, investigators from the University of Washington and the University of Nairobi examined genital shedding of HIV-1 DNA and RNA during pregnancy, in order to analyze HIV transmission from mothers to their unborn children.[6] (This research program, or "protocol," and the others discussed below were obtained through the Freedom of Information Act.) Using HIV-positive women as research subjects, investigators took swabs of mucus from around the cervix and genital tract and also drew a blood sample during and after their pregnancy. The consent form told prospective participants:

> We . . . want to know more about the virus in the birth canal. We want to know whether every infected woman has the virus in her birth canal, or whether only some women have the virus here. We want to know whether there are reasons why some women might have the virus in the birth canal.

The researchers took their swabs at the twenty-fourth, thirty-second, and thirty-sixth weeks of pregnancy and then again two weeks and six months after delivery. If they discovered evidence of a sexually transmitted disease other than AIDS, they treated it. But they did not treat HIV, and they did not themselves provide the pregnant women with the AZT that could prevent transmission to their offspring. Although they acknowledged the efficacy of short-course AZT, their progress report to NIH noted:

> It remains essential to understand the mechanism of vertical [mother to infant] HIV-1 transmission in order to design feasible intervention strategies to decrease transmission.

If they had administered AZT, they would have been unable to conduct their study.

Under another protocol, researchers from Johns Hopkins in collaboration with Mulago Hospital and Makerere University in Kampala, Uganda, investigated the efficacy of an intensified version of gamma globulin (HIV-IG) in preventing HIV transmission from mothers to infants. They gave three groups of HIV-infected mothers different doses of the HIV-IG, but none of them received AZT. "The expense of AZT, compliance, and toxicity considerations," the researchers claimed, "make widespread use of this approach in developing countries impractical."[7] But rather than try to learn whether Ugandan pregnant women might comply with the demanding AZT regimen and whether it was actually more toxic for them than for Americans, they experimented with their new agent. The research could not have been conducted in the US because it withheld from the women a drug of known efficacy. By adopting a different set of rules, it could be conducted in Uganda.

In the fall of 1997, several months before the efficacy of short-course AZT was demonstrated, a team from the Walter Reed Army Institute of Research, Johns Hopkins, and Lampang Hospital in northern Thailand, with NIH funding, investigated transmission of HIV from mothers to infants by collecting blood and vaginal fluids from pregnant women. The consent form alerted the subjects to the possibility of taking AZT:

> A drug, called AZT, has been proven effective in reducing the risk of HIV transmission from infected mothers to their babies in studies performed in the United States and Europe. At present, it is unknown whether AZT would reduce risk of HIV transmission from infected mothers to their babies in Thailand.

The Thai Ministry of Public Health, the form explained, was planning such studies and the subjects were given the name of a doctor to contact for information. The consent form said: "We would encourage you to consider joining this AZT study."

At least two problems arise with this approach. First, the team did not itself offer to provide the subjects with AZT; those who wanted it would have to enroll in the Thai trials. The IRB in the US Surgeon General's office reviewed the project and asked whether this arrangement satisfied its own regulation that "any study must meet the same standards of ethics and safety that apply to research conducted within the US involving US citizens." The IRB decided that it did, on the grounds that "ethical objections are alleviated by unequivocal consent form endorsement of the use of perinatal AZT." It did not acknowledge that IRBs would not have approved a project in the United States in which researchers' endorsed but failed to provide an effective treatment to their subjects.

Why did the researchers in Thailand not give women AZT? Because the project was enrolling pregnant women who, lacking the drug, were transmitting the disease to their children—which was precisely what the investigators needed to have happen in order to do their study. As they told the NIH reviewers of their project, "The advent of AZT use was a concern of the [NIH] study section . . . [because] our analysis plan was based on identifying approximately 25–30 transmissions in the population." But the concern, the investigators declared, was unnecessary. "We will have at least 100 deliveries without

[5] Harold Varmus and David Satcher, "Ethical Complexities of Conducting Research in Developing Countries," *NEJM*, Vol. 337 (1997), pp. 1003–1005; and Vol. 338 (1998), pp. 836–844.

[6] "Genital Shedding and Intrapartum Transmission of HIV-1," NIH grant KO8 HD01160, Progress Report Summary, August 1, 1997, through July 31, 1998.

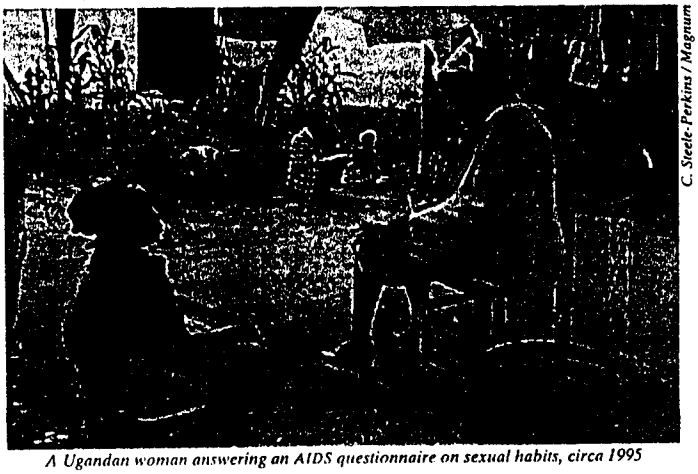
[7] "HIV-IG for Prevention of Vertical Transmission," NIH grant R01 AI34235-06, Progress Report Summary, February 1, 1997, through January 30, 1998, p. 27.

exposure to AZT in any form yielding about 20 transmissions." Only because the virus continued to be passed on was the study workable.[8]

Another NIH-supported project from the University of Washington explored the genital transmission of HIV. The subjects were four hundred HIV-positive prostitutes in Mombasa, Kenya, none of whom received AZT or antiviral therapy. Three hundred of the group who had, in addition to AIDS, other sexually transmitted diseases were treated for those diseases in order to learn how treatment affects the transmission of HIV. (The question being posed is whether antibiotics administered for syphilis reduce the rate of HIV transmission.) Another sixty women received oral contraceptives or injectable progesterone to learn whether methods of contraception affect the rate of HIV transmission. Finally, another ten women were examined daily for one month to learn if the quantity of cervical and vaginal HIV changes during the menstrual cycle. The investigators believed these studies would help to create new ways to prevent sexual transmission of HIV. Such a study could not be conducted in the United States, because it withholds a known effective treatment.

In Rwanda and Zambia, University of Alabama investigators are enrolling couples (rather than prostitutes) for their studies of HIV transmission. They follow the medical history of couples in which one partner is HIV-positive and the other HIV-negative—about 20 percent of all couples tested—to learn when, and under what conditions, the negative partner turns positive. These studies, they say, are "natural history studies," that is, they merely observe people. Since prescriptions for antiviral therapy are rare in both countries, the researchers are ostensibly following the "natural," that is, untreated, history of the disease. They do, they say, dispense "commonly available medications for infectious diseases" to the subjects, although not to local people generally; and while they provide "general health education on ways to avoid AIDS," they do not distribute contraceptives. The genocide in Rwanda crippled research there. ("Half of our pre-genocide staff," the team reported, "are known dead or remain missing and less than half of our study subjects have returned to Kigali.") But work goes forward in Zambia. Investigators were able to distinguish between subjects who were "rapid progressors" to death and those who were "long term survivors." They anticipate that understanding the viral and epidemiological differences between the two groups will produce effective public health and treatment strategies. Again the research depends on withholding effective treatment from subjects and not supplying contraceptives.[9]

One AIDS research project in Uganda recently made headlines mostly because its findings were published in *The New England Journal of Medicine* and were commented upon, negatively but now more cautiously, by Marcia Angell.[10] A team led by Thomas Quinn from Johns Hopkins, collaborating with investigators from the NIH, Columbia University, and Makerere University, Kampala, studied 15,000 persons in rural Uganda to see whether prophylactic use of antibiotics prevented the spread of sexually transmitted diseases. It turned out, two and a half years later, that the strategy did not work; but trying to salvage something from the research, which had included testing the subjects every ten months for HIV disease, the investigators went back to their records and, using family names and addresses, linked husband to wife in order to see what they could discover about HIV transmission. They identified 415 couples in which, when the project started, one partner had been HIV-positive and the other had not. Of the HIV-negative subjects, ninety had became positive during the study. The critical causal factor was the "viral load," that is, the degree of infection that the HIV-positive person was carrying. Higher loads led to higher rates of HIV transmission. It was this finding that the researchers submitted for publication in *The New England Journal of Medicine*.



C. Steele-Perkins / Magnum

A Ugandan woman answering an AIDS questionnaire on sexual habits, circa 1995

Since the policy of *The New England Journal of Medicine* is not to publish the results of unethical research, and since this particular protocol, like other post-076 ones, withheld effective treatment, Angell felt it necessary to explain why the report on it was accepted. She scrupulously identified all the considerations that would prevent such research from being done in the US, including, in most states, the need to inform the uninfected spouse that the partner was HIV-positive and to treat HIV disease when discovered. She did not believe that the later identification of the couples was a mitigating circumstance. Nor did she accept as a mitigating circumstance the fact that, according to the researchers, official Ugandan policy advises against partner notification. Faced with such a policy, she said, the researchers should have reconsidered the ethics of doing research in Uganda. In light of the frequent HIV testing, "seronegative partners of seropositive persons could easily have been identified and informed of their special risk." Angell also noted that the study's principal finding—that high viral loads are predictive of transmission—would not benefit Uganda since it could not afford the drug treatments that would reduce the viral load.

Why then did she publish the study? Two (unnamed) experts on ethics whom she consulted were divided on the question, she wrote, and she wanted to "focus attention on the vexing ethical issues." Angell still believed that "our ethical standards should not depend on where the research is performed." But this time, instead of invoking the precedent of the Tuskegee scandal, she concluded that "all these questions are debatable, and that there may be few answers that apply to every situation."

3.

In an effort to free researchers from the constraints of existing ethical codes, a number of investigators and bioethicists, led by Robert Levine, a Yale physician, have proposed to the World Medical Association several fundamental revisions to the Declaration of Helsinki.[11] The code currently reads: "In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method." Their amended version would read: "...should be assured that he or she will not be denied access to the best proven diagnostic, prophylactic or therapeutic method that *would otherwise be available to him or her*" (italics added). The Helsinki Declaration allows the use of placebos only "in studies where no proven diagnostic or therapeutic method exists." The Levine proposal states: "When the outcome measures are neither death nor disability, placebo or other no-treatment controls may be justified on the basis of their efficiency."

The two changes substantially reduce investigators' responsibilities. Under the Helsinki principles, they must supply their research subjects with the best therapies that have been developed; in the future, they would need only not interfere with subjects' receiving therapies. Subjects would no longer be "assured" of receiving the best proven therapy; instead, they would "not be denied access" to them. Moreover, the revision would allow investigators to provide subjects, including control groups, only with those therapies that were available to them in their own country; in effect, researchers would not be obligated to provide first world treatments in the third world. Finally, the revision opens the door more widely to placebo trials. Placebos may be used even when effective treatments are locally available if the injuries that would follow from not giving such treatments fall short of death or disability. In effect, the proposed changes to Helsinki would render ethical all the protocols I have described here.

Modifying the Helsinki standards would immediately affect the design of AIDS vaccine trials, which raise in particularly distressing fashion the question of what is owed human subjects in developing countries.

An AIDS vaccine is truly the best hope for stopping the ravages of the disease worldwide but nowhere more dramatically than in developing countries. Vaccines, it is true, are not easy to deliver in poor countries; ways have to be found to maintain the "cold chain," that is, to store the vaccines at an appropriately cool temperature, and to reach isolated populations. But the successes of smallpox and polio vaccines indicate that these difficulties can be surmounted. The very potential of an AIDS vaccine to save thousands of lives makes the ethics of testing it more complex. The NIH and several drug companies have begun testing HIV vaccines not only in the United States but in Thailand, and plans are underway to conduct vaccine trials in China, India, South Africa, Haiti, Peru, and Trinidad.

The first difficulty is that testing the vaccine requires using subjects who can be expected to be exposed to AIDS; otherwise no useful findings on its efficacy will be forthcoming. Of necessity, then, subjects will be drawn from vulnerable populations, including drug users, commercial sex workers, and sexually active, risk-prone gay men, all of whom may be easily coerced into joining the research. How to guard against such coercion is by no means obvious. Second, both American and Helsinki standards would require that subjects in such a trial initially receive educational counseling, clean needles, condoms, and perhaps even drug abuse treatment and vocational counseling. Thus, research ethics undercut research efficacy: if every subject heeded the advice and took the protective measures, the efficacy

[8]Department of the Army, Office of the Surgeon General, Memorandum for Director, Walter Reed Army Institute of Research, "Addendum to...'Evaluation of HIV-1 Viral Burden...,'" November 12, 1997, p. 30, with the "Informed Consent" revised September 10, 1997; NIH grant HD34343-03, Progress Report Summary, p. 20.

[9]"Heterosexual Transmission and Natural History of HIV Infection in Rwanda/Zambia," NIH grant R01 A140951-04, Progress Report Summary, October 1995, p. 25.

[10]T.C. Quinn et al., "Viral Load and Heterosexual Transmission of Human Immunodeficiency Virus Type I," *NEJM*, Vol. 342 (2000), pp. 921–929, 967–969; and Vol. 343 (2000), pp. 361–363.

[11]A disclosure may be in order. Levine and I were opposing expert witnesses in a recent case brought against Vanderbilt University for research it conducted between 1945 and 1947. In that study, pregnant women were fed radioactive iron (to study iron absorption), and told that they were receiving a "vitamin cocktail." Levine argued that such practices were in keeping with the ethical norms at the time. I insisted that such deception violated already recognized ethical principles governing human experimentation, and that the Nuremberg Code (issued a few months after the protocol ended) incorporated long-standing principles and did not invent them. Vanderbilt settled the case for $10 million and issued an apology, read in court, to the plaintiffs.

of the vaccine tests would be seriously impaired. Third, were subjects later to contract AIDS either as a result of a faulty vaccine or because of their own failure to take necessary precautions, a strong case could be made for their being given, at researchers' expense, AZT or the latest antiretroviral drugs. Judging by their past performance, researchers are not likely to expend the thousands of dollars necessary to meet this commitment.

By contrast, adopting local, not international standards would make the trials cheaper (because no treatment would have to be provided) and increase their efficacy (because by not supplying clean needles or condoms, subjects would be more frequently exposed to HIV). So too, if subjects who contracted AIDS were not given AZT or antiretrovirals, researchers would learn more about other properties of the vaccine, including whether it reduced the severity of the disease or the infectiousness of the virus.

With these advantages in mind, Barry Bloom, chair of the UNAIDS Vaccine Advisory Committee, recently observed: "Determination of the protective efficacy of HIV vaccine candidates may only be possible in trials in developing countries where the resources are not available to provide antiretroviral drugs."[12] Although aware of the ethical dilemmas of having science take advantage of a country's poverty, he and many colleagues say they cannot put aside the benefits of the knowledge to be gained. "If the best proven therapeutic standard of the industrialized countries were literally applied without qualification," Bloom argues, "could there ever be efficacy trials of AIDS vaccines or of many other interventions?" His conclusion is guarded but his preference clear: the Helsinki standards "require clarification and perhaps modification."

The attractions of conducting research in developing countries are not limited to AIDS or to academic investigators. Over the past ten years, American drug companies have been reducing their reliance upon universities to do their research, turning instead to for-profit contract-research organizations (CROs). (In 1991, according to one analysis, 80 percent of drug industry funding for clinical trials went to academic medical centers; by 1998, the figure had dropped by half.[13]) The CROs locate the research sites, recruit patients, and in some cases even draw up the study design and perform the analysis. And increasingly, the sites and patients they choose are abroad, particularly in developing countries.

In London last February, a two-day meeting, sponsored by a number of major pharmaceutical companies and addressed by CRO representatives, was devoted to "Unleashing the Untapped Potential of Clinical Trials in Southeast Asia," including China, South Korea, and Malaysia. The program announcement said: "Per patient trial costs are up to 25 percent lower than in the US & Europe. Lower per patient trial costs is just one of the benefits available to you by undertaking clinical trials in Southeast Asia." It also explained that the changing "disease profile" of Southeast Asians made them more like Americans and Europeans. For example, cardiovascular disorders, from which drug companies make huge profits, are fast replacing infectious diseases as the leading cause of death in these countries. Asians were also better subjects for clinical trials because they were "treatment naive," that is, previously unexposed to other medical interventions. Not explicitly stated but well known to all researchers is the additional fact that most Southeast Asian countries do not have effective review boards, or, for that matter, highly inquisitive and demanding patients. In this way, global economics goes hand in hand with global medicine.[14]

4.

The debates over the ethics of placebo trials spill over into the question of consent. Those who support the standards of the developed countries insist that all those who take part in a trial, whatever their culture, must personally agree to join it. But those who say they are ready to adapt to local custom would tailor consent requirements accordingly. In cultures where, in many important matters, tribal chiefs give consent for their tribesmen or husbands give consent for their wives, the same may be done for research.

What, in any case, do research subjects in Thailand or Uganda understand about the research projects in which they take part? What do the Nairobi prostitutes make of research on viruses in the birth canal? Very few studies in the developing world address this issue, but some findings there and elsewhere are suggestive. In the United States, where consent has been better investigated, anywhere from 25 to 50 percent of patients and subjects do not understand what it is that they have agreed to. Among two hundred patients being treated at the University of Pennsylvania Cancer Center, 40 percent did not know the purpose or

[12]Barry R. Bloom, "The Highest Attainable Standard: Ethical Issues in AIDS Vaccines," *Science*, Vol. 279 (1998), pp. 186–188.

[13]Thomas Bodenheimer, "Uneasy Alliance—Clinical Investigators and the Pharmaceutical Industry," *NEJM*, Vol. 342 (2000), p. 1540.

[14]Helen Epstein recently described in these pages how this process works in South Africa. See "The Mystery of AIDS in South Africa," *The New York Review*, July 20, 2000.

nature of the procedure they had undergone and 45 percent could not give even one major risk or cite a possible complication resulting from it. Such findings may possibly be explained by the age or education of the patients, poor communication by physicians, or blind trust by patients. But whatever the reason, consent is hardly informed.

The same must be true in developing countries. No one ought to justify placebo-based protocols simply because Ugandan or Thai subjects consented to join them. Not only would these subjects face all of the difficulties in getting information that their Western counterparts do, but they may well be encountering alien concepts. Take the idea of randomization. Subjects are informed (by doctors or white-coated assistants) that a toss of a coin will determine whether they receive treatment or placebo. The proposition is not self-evident, requiring as it does an understanding of rules of chance and an appreciation of the unusual fact that a doctor may not be giving treatment. Americans are often confused about this; when Johns Hopkins researchers questioned American drug users being recruited for a randomized HIV vaccine trial, 26 percent did not understand that some subjects would be receiving vaccine and others placebo. An investigator in Bangkok recently explained to me that there is no Thai word for placebo. The best the team could come up with is a term most accurately translated as "mimic." Accordingly, subjects in some of the Thai post-076 trials were told that they would either get medication or a substance that mimicked medication. Whether the term was understood as a stand-in for medicine or as a non-medicine is anybody's guess.

Finally, in some developing countries "consent" may be deceptive. In 1998 a team of South African doctors and public health workers questioned subjects who had enrolled in an HIV-transmission study about their knowledge of the disease. It turned out that they had an accurate understanding of HIV transmission. But in an unexpected finding, they also made it clear that they had had no choice about enrolling: 84 percent said they felt they had been compelled to participate. Just why they felt this wasn't clear, but they were evidently under pressure of some kind. A follow-up question asked whether the hospital would permit them to quit the study, and 98 percent said no. So much for the voluntary nature of informed consent.

5.

The immediate effort to relax international standards may not succeed. The WMA debated revisions to the Helsinki Declaration at its 1999 annual meeting in Tel Aviv and the participants, without exception, said that the proposed changes violated the fundamental ethics of research on human beings. At the WMA's October 2000 meeting held in Edinburgh, delegates resolved that any new treatment had to be tested against "the best current prophylactic, diagnostic, and therapeutic methods," thereby maintaining a commitment to a universal standard for research. And some organizations in the US are trying to strengthen the ability of developing countries to review research protocols. The Fogarty International Center of the NIH, for example, has begun a program that will provide representatives from developing countries with training in ethics, particularly American research ethics. Such training will not guarantee that local ethics committees will be more concerned with protecting fellow citizens than with cooperating with well-financed foreign investigators. But it might give them a clearer sense of ethical issues.

Nevertheless, the larger debate is unresolved. Whatever the moral force of the WMA, it has no power of enforcement, and a number of other organizations are putting forth guidelines that are far more equivocal. The UNAIDS Guidance Document, "Ethical Considerations in HIV Preventive Vaccine Research," released in February 2000, recommends that community representatives be included in the research approval process and that subjects be given counseling on reducing risks. But the document refuses to take a stand on the central questions. It distinguishes between ideal treatment ("the best proven therapy") and the minimum treatment (access to "the highest level of care attainable in the host country") but leaves it to the host country, the sponsor of the research, and the local community to work out the level of treatment. In so doing, it makes both ideal and minimum standards ethically acceptable. It also assumes, incorrectly, that the three constituents are equal in power and offers no suggestions about resolving conflicts among them.

With similar equivocation, a 1998 ad hoc meeting of selected investigators (including several whose protocols are discussed here) and some bioethicists issued a consensus statement, published in *The Lancet*, called "Science, Ethics, and the Future of Research into Maternal Infant Transmission of HIV." Its position was that "study participants should be assured the highest standard of care practically attainable in the country in which the trial is carried out." This standard would presumably be higher than the "available" level of care but below that of the "best proven therapy." But how is one to know what is or is not "attainable" in a country short of trying? And if a standard of care is attainable by importing resources or technology, does that matter? The efforts to whittle away at the Helsinki Declaration demonstrate the value of its clear and unambiguous standard.

After exhausting other arguments, proponents eager to modify the Helsinki Declaration insist, often passionately, that the tidal wave of AIDS sweeping the world, particularly in southern Africa, is so dreadful that researchers must be given a relatively free hand in order to find useful treatments. But the proposition has several weaknesses. As soon as research protections are weakened, profit-seeking companies will take advantage of them, not to cure AIDS but to increase their returns.

Even more important, to date the results of placebo-based AIDS trials have not brought medical benefits to Africa. Short-course AZT was supposed to be helpful, but it is infrequently used. (I am told by one investigator that in Lusaka, Zambia, some 2,000 pregnant women in research studies are the only ones receiving it, this in a city where over 30,000 women give birth each year.) At the moment, a new drug called Nevirapine is being hailed as the solution to maternal-infant transmission of HIV, mostly because it is very cheap and, to be effective, needs only be given at the onset of labor. But whether it will actually be used in developing countries is unclear. South Africa, for reasons that no one can understand, has already rejected it. And it is worth noting that when Nevirapine itself was tested, the control group was given AZT not in its proven short-course regimen, but only from the onset of labor through delivery. The investigators claimed that the short course was too complicated to be administered in a developing country.

6.

There are strong practical as well as principled reasons for Americans to follow American ethical standards when they do research abroad. IRBs have too little familiarity with developing countries to set different standards. They are ill-equipped to differentiate among the values and customs of Thailand, China, Uganda, or Zambia. They cannot possibly know whether the word "placebo" has been accurately translated. Moreover, making human rights relative to social and economic conditions in distant countries could come back to haunt us. Appalachia is not Westchester County and the mortality statistics in Harlem are worse than those in Bangladesh. Will American researchers be allowed to provide less treatment in our own impoverished regions than in prosperous ones? The question is not idle, for this is the position that the US Public Health Service adopted in conducting and rationalizing the Tuskegee research.

As Aryeh Neier, former head of the ACLU, has pointed out, American courts often must balance local values against national standards. When the stakes are not life-threatening, the courts have been respectful of local values, most notably in education. (The Amish get to educate their children by their own criteria, not those of the majority.) But in a matter of life or death, courts enforce national values. (A Jehovah's Witness parent may not decide for his child that death is preferable to receiving a transfusion.) A good case can be made that AIDS research in developing countries should follow this same principle.

Finally, abject poverty is harsh enough without people having to bear the additional burdens of serving as research subjects. When we take account of the misery and stunted hopes of people in Uganda, it is not enough for investigators to say that their research left them no worse off. That Ugandans did not have access to AZT before the research, during the research, or after the research does not resolve the ethical issue. As compensation to their subjects for enrolling in the research, investigators who come to Uganda should be required to leave their subjects better off. And the Ugandans should receive the benefits of treatment now, not in some distant future when pharmaceutical companies may, or may not, reduce the price of their drugs or vaccines so that citizens in poor countries can afford them. Do unto others as we do unto ourselves—a principle for researchers everywhere.