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Medical Morals: An Exchange

To the Editors:

Those in the scientific community who have sought to contribute to the struggle against AIDS and to reconcile the demands of the global AIDS problem with respect for the current ethical guidelines for biomedical research look to the broader scholarly community for understanding and guidance. It is disappointing, therefore, that there is so little insight or useful guidance forthcoming from historian David Rothman, who, in a provocatively entitled essay, "The Shame of Medical Research" [NYR, November 30, 2000], chose, rather, to impugn the motives of the AIDS research community. In his sweeping indictment of AIDS research, Professor Roth-

man, quoting highly selectively from institutional review filings and scientific papers, alleges that what motivates scientists to study AIDS in developing countries in Africa and elsewhere is really the ability to study scientific questions that cannot easily be studied in the US, where most HIV/AIDS-infected individuals have access to highly active antiretroviral therapy. It would have been generous—and surely pertinent—had he indicated that there is another much compelling reason—namely, that 95 percent of all HIV/AIDS victims live—and die—in developing countries.

HIV/AIDS is not, as Professor Rothman implies, a convenient vehicle for satisfying scientific curiosity. AIDS is the greatest epidemic in the history of humankind. It will be more devastating than the Black Death of 1346 or influenza of 1919. At present, we have no cure, no vaccine. The drugs that control the disease in the US are so expensive that they are unavailable to the overwhelming majority of the world's population that live in developing countries. This is the compelling reality that motivates the scientific community to carry out research on arguably the most challenging infectious disease problem biomedical science has ever faced.

What is an ethical study in a population of a developing country that is ravaged by an invariably fatal disease? The Declaration of Helsinki on the ethics of research involving human subjects was formulated in 1964 with only an industrialized world in mind. Both Helsinki and the CIOMS (Council of International Organizations of Medical Sciences and WHO) Guidelines, regarded by most as the standard ethical guidelines for research on human subjects, are silent on the technical or financial ability of poor developing countries to fulfill them. For example, the original guidelines require that individuals in a clinical study be entitled to "the best proven therapeutic and diagnostic method." In the case of the 076 protocol for AZT-prevention of maternal-child transmission of HIV, which stimulated public debate here and elsewhere, most developing countries could neither implement the best proven treatment—which included treatment of the mother starting at eleven to twelve weeks before birth (it is rare in many countries that women appear at medical clinics that early in pregnancy), with five doses a day of AZT, an intravenous injection of AZT during labor (not something readily done in villages in Africa), and six weeks' treatment of the newborn—nor afford the \$800 cost of the drug. That led to proposed clinical trials seeking to develop a more practical and affordable regimen that could be used to save lives. Some in the medical establishment believed that 076 was "the best proven therapeutic method" and that any modification to reduce cost and simplify technology to make it more applicable was unethical. Mercifully, trials with modified regimens did go on, and a far simpler and less expensive regimen than 076, using niverapine, was found. Professor Rothman sees that process as a slippery slope and recommends that we hold to the original guideline for ethical research—"the best proven therapeutic method." Does he recommend this even if it cannot be properly administered? And even if the drugs are not affordable or available in the developing country?

Leaving aside the sometimes emotional arguments made in the context of AIDS research, one might ask how relevant the current guidelines would be for trials testing the effectiveness of aspirin in a developing country, such as India, for prevention of death from heart attacks and strokes. Aspirin is a cheap drug, highly effective in industrialized countries at preventing about 30 percent of deaths from heart attacks, and 50 percent of deaths from strokes, yet it has not been appropriately tested or widely used in developing countries. Concerns about efficacy and adverse effects that might occur in Asian populations suggest that such trials would be justified. What would be the standard of care or "the best proven therapeutic method" for anyone in a large aspirin trial who suffered a heart attack? In the West it would be angioplasty or coronary artery bypass graft surgery. Would Professor Rothman insist that unless everyone in the populations could be assured access to those interventions, such a trial not be conducted? Would he make the judgment that a trial seeking to reduce death from heart attacks and strokes that failed to apply those treatments was unethical? Would it be better were the trials seeking understanding of how to intervene in AIDS in Africa not be done in any country that does not provide highly active antiretroviral therapy?

The preamble of the WHO Constitution states, "The highest attainable standard of health is a fundamental human right, without distinction of race, religion, political belief, economic or social conditions." Article 12 of the International Covenant of Economic, Social and Cultural Rights recognizes "the right of everyone to the enjoyment of the highest attainable standard of physical and mental health." Clearly reference to the highest attainable standard has had meaning beyond the minimum in the past. With these precedents in mind, UNAIDS suggested two-level guidance: "in the ideal, the best proven diagnostic and therapeutic method." Where that is not possible, it recommends "the highest level of care attainable in the host country." This is dismissed by Professor Rothman as "the minimum treatment." He asks, "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?" Does he really not know whether provision of drugs costing \$15,000 per person per year in a country with \$6 per capita health spending is attainable or sustainable? It is astonishing that he twice refers to the "highest attainable standard" put forward by UNAIDS, after open meetings around the world with scholars and activists from developing and industrialized countries, as a "minimum," when it is obvious that "minimum" means accepting current practice.

One doesn't have to be an academic to understand the difference, and that the highest standard attainable in the country must be better than current practice, unless it is, in fact, "the best proven therapeutic method." Failure to apply a standard higher than the current practice would be subject to challenge. Professor Rothman insists that "the efforts to whittle away at the Helsinki Declaration demonstrate the value of its clear and unambiguous standard." How ethical is this position if it means ceasing to do research for a preventive or treatment in developing countries? Why does Professor Rothman not consider the ethical issues in failing to carry out research? What is the real-world implication of his concluding statement "Do unto others as we do unto ourselves"? Who would pay and who would provide these therapies?

The medical research community has been searching for principles that would enable research to be conducted ethically to meet the needs of developing countries—not only AIDS research, but all clinical research. The fact that there are ongoing revisions of the Helsinki and CIOMS guidelines, and many new ethical guidelines being proposed around the world, suggests that these are hard questions upon which people of good will may differ. I would submit that, having engaged openly in debate of these complex ethical and equity issues, it is not the medical research community that should be ashamed.

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David Rothman replies:

Neither Dr. Bloom nor anyone else who has written to *The New York Review* or to me disputes a single fact about the many research protocols that I described. There is no disagreement that these investigations could not be conducted in the United States. Dr. Bloom's charge that I believe the researchers are driven only by scientific curiosity is both false and serves as a straw man to divert attention from the crucial issues. I did not intend to impugn the motives of individual investigators; indeed, I assume they are driven by a desire to help cure AIDS.

My belief, however, is that in trying to achieve this obviously important end, they made immediate and long-term judgments about means that are open to question. Perhaps the investigators were convinced, as Dr. Bloom is, that third world research should be conducted under different standards. But my argument is that one cannot rely on an analysis of motives when researchers decide that the best standard of care cannot be delivered and when the hypotheses they are testing depend on care not being delivered.

Should traditional research ethics be modified to combat this devastating epidemic? Not according to the World Medical Association. After a full discussion of AIDS in developing countries, it affirmed at its November 1999 meeting the universal rights of human subjects. It insisted that, in all countries, when new treatments are tested, "the best current prophylactic, diagnostic, and therapeutic methods" should be given to the control groups. Science should not take advantage of social misery to advance knowledge, no matter how vital that knowledge might be.

Dr. Bloom rejects this principle, taking issue with a human rights-based approach to medical research. His claim is that if investigators cannot follow different rules in different countries, the fight against AIDS will be impaired and more deaths from the disease will follow. But why should so uncompromising a utilitarian standard be limited to the third world, or to AIDS? If the threat of a disease is dire, why not allow investigators more latitude wherever they are? Why not experiment more vigorously with dying patients or with people living in pockets of poverty in the

United States? By the 1970s, Americans had rejected such an approach. Syphilis and hepatitis are terrible diseases. Nevertheless, we resolved that it was unethical for investigators to observe but not to treat black men with syphilis who lacked access to health care. We also decided that it was wrong to purposely infect with hepatitis the residents of a filthy and overcrowded institution for the mentally retarded because they would probably get it anyway.

Moreover, a human rights approach to research is not so impractical a standard for American researchers in third world countries. However rudimentary the indigenous health care system, American investigators generally set up their own facilities in order to methodically administer new drugs to their subjects; if required, they might be able to obtain, from one or another source, the funds necessary to give people who serve as controls the same standard of treatment that they would get in the US. Indeed, one of Dr. Bloom's Harvard colleagues did just that in Thailand.

The question is not, as Dr. Bloom contends, whether AIDS research can be done in countries that do not provide all their citizens with antiretroviral therapy but rather what researchers are obliged to provide their subjects. Dr. Bloom consistently links the ethical standard for American researchers with the existing standard of care within a particular third world country; so does the UNAIDS guideline. Indeed, his letter goes further than the guideline, arguing that the standard of care that is "attainable" must also be "sustainable." But research can be and should be held to a different standard, and for these very reasons I consider Dr. Bloom's position inadequate.

Are there limits on researchers' obligations? Yes. As I carefully noted, repeating the observations of Lurie and Wolfe, researchers are not obliged to build and operate an intensive care unit in a developing country. Hence, Dr. Bloom's hypothetical example about aspirin studies is irrelevant. Because investigators cannot do everything does not mean that they are exonerated from doing something.

Rather than invent imaginary situations, Dr. Bloom would have done better to have specifically addressed the ethics of the investigations that I described. On what grounds does he find it ethical for investigators not to give short-course AZT to the HIV-positive women they are observing so as to prevent transmission of the virus from mother to infant? Does Dr. Bloom believe that the surgeon general's Institutional Review Board was correct in finding that investigators had satisfied ethical requirements when they endorsed the use of AZT but did not supply it to their HIV-positive and pregnant Thai subjects in order to prevent transmission?

I cited in my article a research project in Zambia that, while withholding effective treatment, followed the medical history of couples in which one partner had been HIV-positive and the other had not. How could Dr. Bloom distinguish such a research project from the so-called natural experiments of Tuskegee and Willowbrook? Would he, like the researchers, have withheld from Ugandan couples information on the HIV status of the partner, and if so, on what ethical grounds? Dr. Bloom celebrates, as most everyone does, the breakthrough in AIDS treatment made possible by the successful testing of niverapine. (Even South Africa is now "considering" its use.) But he is silent on whether the niverapine researchers were ethically justified in not giving the control group the AZT short-course regimen that was specifically designed for developing countries.

In the one specific case that he does discuss, Dr. Bloom misconstrues the debate over the research that established the efficacy of short-course AZT. The concern was not whether short-course AZT should be tested; there was sufficient evidence that it would work to justify the trial itself. No one that I know was against reducing cost and simplifying technology. What was at issue, as my article explained, was that the control group was given a placebo, not long-course AZT, and thus instead of receiving treatment by the best proven methods, got no treatment at all.

As for my article's title, editors, not authors, choose titles; but I accepted "The Shame of Medical Research." Why? Because, first, it linked ethics to the structure of medical research, not to individual researchers. As we came to understand in the 1960s and 1970s, the source of ethical dilemmas in human experimentation was not "bad" researchers but a system that was thoroughly utilitarian in its ethic.

Second, the title suggests that the situation in which some medical research takes place gives cause for shame. The gross disparities in life chances among rich and poor countries and the readiness to take advantage of these disparities are shameful and need to be brought to light. Justifying that readiness by the urgency of the war on AIDS is inadequate not only for reasons of principle but because no one can demonstrate that, in the third world, either the subjects of the research or their countrymen have benefited, or will necessarily benefit, from the research.

Some thirty years ago, the philosopher Hans Jonas persuasively argued that there is inevitably something ethically questionable about human experimentation, for it uses people as a means to an end (greater collective knowledge), not as ends in themselves. In the first world, the requirements of informed consent and equal access to benefits, although they may not be consistently observed, allow us to continue experiments with human beings. But when human experimentation is transported to the third world and even these requirements are absent, then shame seems an apt description.