Editorial & Letters

EDITORIAL

Bioethics and Local Circumstances

The ethics of the design of clinical trials to prevent transmission of HIV-1 from mother to child in developing countries have been criticized.* However, a discussion of ethical principles in biomedical research that ignores the socioeconomic heterogeneity of society is not ethical and not worth holding. Policies regarding health management differ within and between industrialized and developing countries because of their different economic capabilities. Whereas it is established policy that all HIV-positive pregnant women in the United States and other developed countries are offered azidothymidine (AZT), this is not achievable in many developing countries because the costs of the drug and logistical support are prohibitive. For example, Uganda (with 156,600 pregnancies per year) spends $6 annually in health care per person.

In the ACTG 076 trial of AZT's ability to prevent maternal transmission of HIV—frequently used as the "gold standard" against which other trials are measured—AZT treatment was started in a hospital setting between 14 and 34 weeks of gestation and continued (through delivery) until the newborn infant was 6 weeks of age. Yet in Uganda, fewer than 10% of all pregnant women have prenatal care for the first time during the first trimester, 30% during the second trimester, and 60% during the third trimester; only 40% deliver in a health facility.† So to conduct research in Uganda based on such a regimen would produce results applicable only in a research setting.

The future of clinical trials in Africa could depend on two factors. First, sponsoring agencies might slow down or stop the trials because of the ongoing debate about how best to conduct them. This would leave Africa in a terrible position because resources are not available there to do the trials. For maternal transmission studies, the results of testing alternative treatment regimens could lower the cost of therapy dramatically, to a point where it would be feasible for the governments to subsidize treatment. Evaluation of HIV vaccines is essential for Africa because the resources required for highly active antiretroviral treatment (HAART) are not available and other preventive interventions have their own limitations.‡ The second factor is the extent to which the people in developing countries will be influenced by the debate. Discussions that ignore the magnitude of the problem, gloss over the socioeconomic circumstances of poor nations, and apply previously developed ethical guidelines too literally may lead individuals to reduce their participation in future trials. So far, policy-makers and politicians have not interfered with ongoing trials because of the current debate.

Following the atrocities committed by Nazi research physicians, ethical guidelines to protect research subjects were laid down in the Nuremberg Code, the Declaration of Helsinki, and the "International Ethical Guidelines for Biomedical Research Involving Human Subjects" (issued in 1982 and revised in 1993).§ The 1993 guidelines were designed to be of use, particularly to developing countries, in defining national policies on the ethics of biomedical research, applying ethical standards in local circumstances, and establishing or redefining adequate mechanisms for ethical review of research involving humans. In their present form these guidelines will delay development of badly needed vaccines and treatment regimens. For example, they state that phase I drug studies and phase I and II vaccine studies should only be conducted in "developed communities of the country of the sponsor." Likewise, the guidelines say that phase III vaccine trials and phase II and III drug trials should be conducted simultaneously in the host and sponsoring countries. Barry R. Bloom discusses other ethical issues in this issue.‖ Regional meetings are being convened in Africa, Asia, Latin America, North America, and Europe early in the year to address the obstacles posed by the guidelines in their current form. Resulting improvements are expected to make the guidelines more specific so that there will be no roadblocks in the way of conducting ethical clinical trials.

Edward Mbidde

*M. Angell, *N. Engl. J. Med.* **337** (no. 12), 847 (1997); P. Lurie and S.M. Wolfe, *ibid.*, p. 853. †F. X. Miiro, personal communication. ‡E. K. Mbidde, *J. Intl. Assoc. Physicians AIDS Care* **3** (no. 11), 26 (1997). §CIOMS in collaboration with WHO, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS, Geneva, Switzerland, 1982; revised in 1993). ‖B. R. Bloom, *Science* **278**, 186 (1998).

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LETTERS

Frontiers and reforms

The European Molecular Biology Laboratory is said to have performed excellently despite budgetary constraints (right, EMBL's Heidelberg headquarters). "Gene manipulation" is said to be a "profound cultural issue" for the Swiss. Reform of the U.S. Food and Drug Administration is evaluated. Acupuncture is said to be "virtually useless." And is there "reason for optimism" that therapeutic drugs for treating addiction will be used?

EMBL's Outward Expansion

The News & Comment article "EMBL's outward expansion strains its core facility" by Nigel Williams (12 Dec., p. 1875) is thorough, but incorrectly implies that the headquarters of the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany, has been squeezed financially in favor of the outstations. The financial pressures that exist are felt both in the outstations and in Heidelberg (and also in national laboratories). The difficulty is that the budgetary growth that the member countries have been able to offer in this decade has not been commensurate with the agreed increase in EMBL activities, or with the growth of opportunities in the life sciences, pure and applied.

It is hoped that the increasing emphasis on biotechnology in Europe will highlight the importance and needs of this outstanding European center of research and advanced training. The EMBL council appreciates the excellent performance of the laboratory's scientists even under tight budgets and has full confidence in Director-General Fotis Kafatos and the priorities he has set, in which the Heidelberg laboratory ranks high.

Williams also states that the EMBL's governing council, made up of representatives of the governments of each member state, must make all decisions unanimously, making it easy for any government to stifle budget increases. Despite the fact that the scientific program and financial framework in which the EMBL has to work must be approved unanimously, nearly all other decisions require majority rule only.

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Gene Technology and Democracy

I disagree with Rolf M. Zinkernagel about the issues involved in the current debate before next year's Swiss referendum on a constitutional prohibition of gene manipulation (Editorial, 14 Nov., p. 1207). Discussions of this topic are not confined to Switzerland; in fact, the rest of the German-speaking regions of Europe are intensely interested in the issue. Apprehension about gene manipulation is related not only to the particular mentality of the culture ("nature is good," and so forth), but also—arising from the pervasive awareness of the Nazi abuses of science and medicine—to a general perception of "pure biologic thinking" as tantamount to extreme right-wing ideology (*1*). The problem is not one of "not understanding molecular biology," as Zinkernagel seems to imply, but is a profound cultural issue that needs to be dealt with in that context.

Zinkernagel also does not acknowledge that in the debate in the Swiss Parliament, I, along with other members of the Labour Party, introduced a counterproposal that could have averted the referendum now threatening our biological research. This proposal would have eliminated major problems while retaining the prohibition on the patenting of genetically generated organisms. It was, however, defeated by the pharmaceutical industry and their political representatives.

There is distrust throughout Europe—not only in Switzerland—of giant companies whose solicitude for their shareholders appears to outweigh their concern for their thousands of workers. This is exemplified by the merger of Ciba and Sandoz into the mega-Novartis, notwithstanding the eminently sound financial states of both companies before the merger.

If it is felt that researchers are too heavily influenced by the economic interests of pharmaceutical giants, they tend to lose authority as opinion shapers in political and societal debates such as the one at issue. I am afraid that Zinkernagel (and many other researchers) incur that risk by their erroneous assessment of this situation.

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References

1. E. Schuster, *N. Engl. J. Med.* **337**, 1436 (1997).

The Swiss vote on the "gene protection initiative" is a blatant example of the failure of scientists to communicate the urgency of research in biotechnology and genetics to the public. The development of vaccines and fundamental knowledge is vital in medical research and must not be sacrificed to veto by technophobic and opportunistic politics. Bioethicists, biologists, and science educators in general must publicly challenge the conventional wisdom of "statists" who are jeopardizing the future and even human survival with pseudoscientific and reactionary misinformation about biotechnology. Society can ill afford to suppress the development of new treatments and approaches to research in molecular genetics. Suppression of new technology cannot guarantee prevention of abuse in biotechnology, because such work will proceed in secret even if it is banned.

Openness is the only choice for scientific advancement in biotechnology and for human survival.

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FDA "Reform"?

The Food and Drug Administration (FDA) reform bill (ScienceScope, 14 Nov., p. 1215) passed by the U.S. Congress includes requirements to speed the review of new vaccines and drugs and to reauthorize the Prescription Drug User Fee Act (PDUFA). But to say that the bill "leaves FDA's research structure untouched " is incorrect.

To enhance the review process and expand FDA's capacity to responsibly manage new types of biologics, some of the "user fees" (charges to companies that submit products for FDA review and approval) supported relevant research by scientists who perform much of the regulatory review. During the negotiations for the new PDUFA, an ancillary agreement (which was not included in the text of the act, but was made between FDA negotiators and the Pharmaceutical Manufacturers Association) was written that specifically prohibits the use of PDUFA funds to support such research.

Also, research at FDA must now compete with new initiatives in tobacco and food safety, as these will require funding from an FDA budget that has remained flat since fiscal year 1996. These and other factors will result in an estimated reduction of