Editorial & Letters

EDITORIAL

Challenges for European Biology

The historic achievement of European monetary union invites bold choices for the future. Our knowledge-based society needs to nurture and utilize science to remain true to our cultural legacy and to compete effectively on the world scene. A case in point is the biosciences which, flowing from fundamental molecular biology, are transforming medicine and hold immense promise for industry, agriculture, and the environment in the 21st century. Europe, which made critical contributions at the origin of molecular biology, retains considerable strength but is facing a triple challenge that must be recognized and candidly addressed.

The first challenge is the stunning pace of change in biology. Interdisciplinarity has become essential as the barriers between traditional disciplines crumble. Discoveries in model organisms highlight the fantastic unity of life, resulting from evolution by common descent, and are readily applicable to human biology. An informational science of the whole organism is in the making as molecular, cellular, and developmental biology merge and connect with physiology, and as genomics and bioinformatics shift the focus of analysis from individual components to biological systems. There is renewed emphasis on interfaces with chemistry, physics, and engineering. Biology is now a "bigger science," dependent on novel synchrotrons, microscopes, DNA chips, stock centers, and interconnected global databases. In parallel, the time frame of application of knowledge—the distance between laboratory and factory or hospital bed—is short, and the flow of information reciprocal; cooperation between academic or medical centers and biotechnology companies is at a premium.

The second challenge to European biology is structural inflexibility. This includes organizational and disciplinary conservatism in academia; excessive reliance on pyramidal power structures, when scientists need independence in their creative 20s and 30s; neglect of advanced postdoctoral training through overemphasis on lifetime employment; and top-down reflexes rather than trust in investigator initiative coupled with critical peer review. Despite the evident advantages of centers of excellence with critical mass, some countries succumb to the temptation to "spread the rain evenly." International schemes for postdoctoral mobility are successful but do not extend to independent investigators. The culture of collaboration is recognized as a European advantage, but internationalism is not yet as strong as the visionaries of the previous scientific generation would wish.

The third challenge is stagnant funding for both national and international institutions, contrasting sharply with world trends. We encounter an almost obsessive preoccupation with the sentiment "we have done enough science, now let's apply it." In the United States, public funding focuses on basic research, strongly advocated by the biotechnology industry as the source of novelty and trained personnel. The National Institutes of Health, already the world's largest funder of biomedical research, has experienced 7% annual increases recently and enjoys a remarkable bipartisan consensus that its budget should be doubled within 10 years, possibly 5. Similarly, China is quadrupling research funding from 1995 to 2000, and Japan is launching new initiatives in brain science and the human genome and plans a massive facility for large-scale protein structure analysis.

The contrast with Europe is dramatic. For example, last year lack of funds forced the European Molecular Biology Organization to cancel plans for third-year postdoctoral fellowships, despite strong consensus about the need for them. Germany's parliament, the Bundestag, rejected the promised 5% sustained annual increases for the Max Planck Society. Funding for the European Molecular Biology Laboratory will not permit any growth in real terms in 1998–2000. In February 1998, the Council of Science Ministers cut, in real terms, the European Union (EU) science and technology budget for 1998–2002, approving only 84% of the funds voted by the European Parliament. We are beginning to see some relative reorientation toward the life sciences, notably in Germany and the EU, but overall national science budgets remain flat (with a few exceptions, such as Finland).

Europe has excellent established scientists and talented, well-trained, and mobile young biologists. But structural reform and increased flexibility in the science system are overdue. And substantial investment in biology, across the continent, is necessary if Europe is to retain a position in the front rank of this major scientific and technological revolution.

Fotis C. Kafatos

The author is the Director-General of the European Molecular Biology Laboratory.

LETTERS

Stopping AIDS

Debate about AIDS vaccine trials in the United States and elsewhere continues (right, distribution of condoms in Thailand, where AIDS is widespread and vaccine trials are planned). Jonathan Mann answers his critics, and readers from Australia and the West Indies comment on the ethics of conducting trials in developing countries.

M. TRESSIN/GAMMA LIASON

The Ethics of AIDS Vaccine Trials

The letter "AIDS vaccine development" by Moises Agosto *et al.* (8 May, p. 803) was not altogether accurate and did not address substantive issues raised in my testimony before the President's Advisory Committee on HIV/AIDS.

The major problem is the urgent need for a coherent, milestone-driven process for AIDS vaccine development. A strategic approach leading from basic science through all stages of vaccine development would set realistic targets to guide progress, identify critical decision points, and mobilize available resources.

Second, the decision-making process that has been created within the U.S. National Institutes of Health (NIH), while rich in basic science, needs adequate representation and input from experts in clinical vaccine development and in public health. National and global public health would be better served by a restructuring of the federal program for AIDS vaccine development to achieve maximal synergy among basic scientists, clinical vaccine researchers, and public health experts.

Third, the estimated 40,000 new human immunodeficiency virus (HIV) infections in the United States in 1999 will occur predominantly in marginalized populations, including ethnic or racial minorities, inner-city poor, adolescents, and women. In this context, the federal government has a particular responsibility. Put bluntly, if 40,000 new HIV infections were occurring among middle- and upper-class college students, progress toward efficacy testing of AIDS vaccine candidates would likely be further advanced. This raises legitimate human

rights concerns regarding the societal accountability of federally financed science. The history of AIDS therapeutics indicates clearly that societal pressure and accountability can help accelerate, and create conditions to enhance, the pace of AIDS vaccine development.

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The Policy commentary "The highest attainable standard: Ethical issues in AIDS vaccines" by Barry R. Bloom (*Science*'s Compass, 9 Jan., p. 186) is thoughtful and provocative. Yet it does not fully discuss several issues pertinent to HIV and AIDS preventive vaccine trials in developing countries.

Bloom appears to accept the premise that the crises presented by HIV and AIDS in the developing world are so severe that we should relax standards that protect individuals in order to promote the common good. This premise, however, could lead researchers into exploiting the vulnerable. Several trials illustrate this problem: in China, researchers injected HIV-positive individuals with live malaria parasites (*1*) in an attempt to stimulate their immune systems; in trials in Thailand and several African countries, in studies of HIV vertical transmission (the passing of HIV from from mother to fetus), researchers gave some women a placebo instead of an effective (but expensive) treatment (the drug AZT) for their condition (*2*).

Bloom states (p. 188) that "guidelines enjoining developing countries from carrying out Phase II trials [initial clinical trials to determine vaccine or drug activity and efficacy as well as dosage levels] until they are completed in developed countries are indeed paternalistic or worse, and ought to be modified." Such a statement appears to assume optimistic outcomes for such trials, but this may not be the case. For example, a volunteer might receive a trial vaccine, mistakenly feel a false sense of security, and then engage in risky behaviors. The results of such a trial could reveal the vaccine to be ineffective, and this individual could die.

It can be difficult to know whether the words "informed consent" mean the same thing for a volunteer as they do for a highly educated researcher. In their discussion of proposed HIV preventive trials in Thailand, Boyd and Ratanakul state, "informed consent implies that those individuals who are recruited, educated and chosen for clinical trials with the putative HIV vaccine understand the risk and potential benefit of the vaccine. It is necessary to discern whether or not the average Thai citizen is acting autonomously...or on the belief that prior vaccine approval by doctors, professors, and government officials constitutes a substituted judgment upon which the individual acts" (*3*).

Such problems are also evident in recent trials of AZT to prevent vertical transmission. A follow-up study that took place in Côte d'Ivoire after such a trial found that many of the participants did not understand the implications of the trial, even though they gave their consent (*4*). Some women believed that they were being promised medical care, although they had been told that they could receiving only a placebo. Others believed that at least some of the pills that they were given would work against the transmission of HIV to their foetus, but this was the very point being tested. While it is questionable that efforts were made to ensure that consent was based on full comprehension of the trial—one woman was given information about the trial minutes after receiving a positive HIV diagnosis (*5*)—the confusion about the meaning of participa-

tion in such a trial has serious implications. One African researcher recently stated, "in an environment where the majority can neither read nor write and is wallowing in poverty and sickness, hunger, and homelessness, and where the educated, the powerful, the rich, or the expatriate is a semi-god, how can you talk of informed consent?" (6).

One possible solution to these ethical problems would be to carry out the most risky trials with volunteers who have the greatest recourse to treatment and the fullest possibility of understanding the risks involved. Buchanan and Brock argue that the standard of competence (with regard to the volunteer's understanding of the meaning of informed consent) ought to vary in part with the degree of risk involved in the procedure (7). Performing Phase II trials in industrialized, developed countries would minimize the health risk to volunteers (because of the availability of combination therapy) and allow a higher probability that the volunteers would have a satisfactory understanding of the dangers and benefits inherent in the trials.

Until HIV vaccine trials show real promise, volunteers should only participate in such research on the basis of a full understanding of the personal risks and benefits and out of their own sense of altruism (8). Every effort must be undertaken to address such concerns, even if the overall progress of vaccine research is slowed.

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References and Notes

1. H. J. Heimlich *et al.*, paper presented at the 11th International Conference on AIDS, Vancouver, Canada, 7–12 July 1996.
2. D. Zion, *Nature Med.* **4**, 11 (1998).
3. A. L. Boyd and P. Ratanakul, "AIDS Vaccine Trials and Ethics," UNESCO Bioethics Conference, Kobe, Japan, 4–8 November 1997, p. 3.
4. As described in a *New York Times* article (*5*).
5. H. French, *New York Times*, 9 October 1997, p. A1.
6. O. Tomoori, quoted by P. Lurie and S. Wolfe, in "Letter to [U.S. Secretary of Health and Human Services] Donna Shalala," 23 October 1997.
7. A. Buchanan and D. Brock, *Deciding for Others: the Ethics of Surrogate Decision Making* (Cambridge University Press, 1989), p. 51.
8. Robert Veatch suggests that in order for proper informed consent to be obtained, investigators must ensure full disclosure, understanding, "voluntariness" of the volunteers, and agreement to the procedure or trial [*Medical Ethics*, R. Veatch, Ed. (Jones & Bartlett, Boston, MA, 1989), p. 180].

It seems reasonable to seek international modifications of ethical guidelines to facilitate some Phase III trials (to test efficacy and dosage in comparison with other treatments). Bloom, however, implies that placebo trials and trials that do not treat HIV-positive volunteers are ethical in developing, but not developed, countries. The guidelines of the Council for International Organizations of Medical Sciences (CIOMS) is not silent on these issues; it urges sponsors to negotiate offers of treatment with host governments and states that ethical standards for research in developing countries should match those in the sponsor's own country (*1*). If sponsors are ethically obligated to provide treatment in the developed world, why not also in countries where health care resources are scarce and where the impact of treatment might be great?

The efficacy of new vaccines over existing ones can be determined without placebos, and placebo trials are not justifiable by the Declaration of Helsinki, as they offer no therapeutic value to volunteers (*2*). Preliminary data may affect the willingness of volunteers to participate in certain parts of a trial; many may prefer 20% efficacy to 15%, even if no "best proven method" exists. Phrases like "best proven method" and "reasonable availability" allow institutional review boards (IRBs) to debate the ethics of providing antiretroviral drugs in countries that can't afford them. What constitutes reasonable expectations of sponsors varies in different circumstances, and what is ethical in one situation may not be so in another. Independent ethical review of such trials might be offered at the CIOMS level, as Bloom suggests, and would compensate for weaknesses in the IRB system. Researchers involved in similar trials should be heard by reviewers, but conflict of interest would exclude their being reviewers.

There is no duty to treat HIV-positive partners if study design precludes identification of sexual partners, and it may sometimes be ethical to refer HIV-positive volunteers to their local health service, even when available treatment is "substandard." Substandard treatment is sometimes cost-effective, and low-budget prevalence or behavioral studies may serve public health interests.

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References

1. *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS in collaboration with the World Health Organization, Geneva, 1993), pp. 43–46.
2. Annex 2 in *ibid.*, pp. 51–52.

Response: I appreciate the lively and thoughtful contributions to the dialogue on ethical issues in AIDS vaccine trials and am grateful for the opportunity to respond.

Zion raises a fundamental issue, namely whether it is ever possible for people in developing countries, particularly people in poor countries with limited education, to provide truly informed consent comparable to that in developed countries. She urges retaining the existing guidelines stipulating that Phase II trials only be carried out in developed countries and, I presume, that Phase III trials be carried out simultaneously in developed and developing countries. I am troubled by her premise, namely, that people in developing countries are too limited in their knowledge and experience to give consent that is adequately informed for two reasons: it is, with the best of intentions, nevertheless condescending, and, if accepted, it would render unjustifiable not only carrying out Phase 11 trials, but also Phase III trials in developing countries. The anecdotal report in the *New York Times* indicating that women in Côte d'Ivoire had little understanding of what they had consented to, or their alternatives, is troubling. Knowing that great effort is invested at many trial sites in genuinely trying to provide volunteers with clear and intelligible information on risks and choices, it is unfortunate that social and behavioral studies designed systematically to evaluate the validity of the informed consent process, both in the United States and in developing countries, are apparently not available. That is a priority that merits support. The ethical guidelines are clear—consent must be freely given and informed, and volunteers in both developing and developed countries, I believe, can and should meet those criteria.

Macpherson argues that I imply "that placebo trials and trials that do not treat HIV-positive volunteers are ethical in developing, but not developed, countries" and asserts "[t]he efficacy of new vaccines over existing ones can be determined without placebos, and placebo trials are not justifiable by the Declaration of Helsinki, as they offer no therapeutic value to volunteers." Regrettably, the reality is that resources and standards of care differ between different countries. CIOMS guideline 15 commentary indicates that "although sponsors are not obliged to provide health care facilities or personnel beyond that which is necessary for the conduct of the research, to do so is morally praiseworthy. The sponsors have an obligation to ensure that volunteers who suffer injury as a consequence of the research interventions obtain medical treatment free of charge...sponsors and investigators should refer for health care services volunteers or prospective volunteers who are found to have diseases unrelated to the research." Can contracting HIV infection (by engaging in risky behaviors) be construed as an injury that is a consequence of a vaccine trial protocol (use of a placebo)? The Declaration of Helsinki makes no mention of placebos, and the commentary of

CIOMS Guideline 14 states, "if there is already an approved and accepted drug for the condition that a candidate drug is designed to treat, placebo for controls usually cannot be justified" (*1*). That is a conditional statement rather than a total restriction on placebo-controlled trials, and the debate centers around under what conditions placebo trials, after the first vaccine trial, if any, can ethically be conducted. Because no vaccine for HIV has yet been "approved and accepted," and because prophylactic vaccines do not fall into the category of "best proven diagnostic or therapeutic method," it could be argued that there is little specific guidance with regard to the appropriate controls for trials of a new vaccine, if an existing vaccine of low efficacy did exist. It is my view that many vaccines with low protective efficacy would not meet the current standards of "best proven prophylactic" or "approved and accepted," and in such a circumstance placebo controlled trials may well be ethically conducted. But the issue should be resolved in the context of available data on specific vaccines, their safety and possible efficacy, after full public discussion.

Finally, I would like to propose that consideration be given to a specific modification of the Declaration of Helsinki and CIOMS guidelines, in which "the best proven diagnostic and therapeutic method" would be replaced with, "In any medical study, every patient—including those of a control group, if any—should be assured of the highest attainable standard of care." It was recently brought to my attention that this change would be consistent not only, as I had indicated, with the Preamble to the Charter of The World Health Organization, but with Article 12 of the International Covenant on Economic, Social, and Cultural Rights, which recognizes "the right of everyone to the highest attainable standard of physical and mental health" (*2*).

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References

1. *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS in collaboration with the World Health Organization, Geneva, 1993), pp. 37–43.
2. H. J. Steiner and P. Alston, *International Human Rights in Context: Law, Politics, Morals* (Clarendon, Oxford, UK, 1996), pp. 1175–1181.

Corrections and Clarifications

■ The Random Samples item "New promise for silicon" (22 May, p. 1199) should have identified Patrik Schmuki at the Swiss Federal Institute of Technology as the principal author of the research described. Lynden Erickson at National Research Council of Canada also participated in the research.

■ In the report "Budding yeast Cdc20: A target of the spindle checkpoint" by L. H. Hwang *et al.* (13 Feb., p. 1041), the labels in figure 1A (p. 1042) for the DNA-binding domain fusion and activation domain fusion were transposed. They should have indicated that the Mad1, Mad2, Mad3, and Snf1 genes were fused to the DNA binding domain and that the Cdc20 and Snf3 genes were fused to the activation domain.

Letters to the Editor

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