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Wheat Domestication: Archaeobotanical Evidence

Genetic evidence of Manfred Heun *et al.* (Reports, 14 Nov, p. 1312) for einkorn wheat domestication in southeast Turkey has been countered by Martin K. Jones *et al.* (Letters, 16 Jan., p. 302). Jones *et al.* cite evidence that agriculture began earlier in the southern Levant and that einkorn was one of the original domesticates there. Recent archaeobotanical work does not support the picture presented by Jones *et al.*

Archaeological plant remains from four pre-pottery Neolithic A (*1*) sites are said by Jones *et al.* to indicate domestication of einkorn, emmer, and barley in the southern Levant at about 8000 to 7700 years B.C. (radiocarbon-dated). Einkorn is absent from all four sites and from the earlier site of Ohalo II (17,000 B.C.) in the same region (*2*). There is no evidence for domesticated plants in the PPNA levels of Jericho, Netiv Hagdud, and Gilgal (*3*). The earliest level (IA) of Aswad (7800 to 7600 B.C.) contains emmer and barley that may be domesticated (*4*). Domesticated einkorn does not appear in the region until the PPNB, at Jericho (7300 B.C.) and level II at Aswad (6900 B.C.).

In contrast, both wild and domesticated einkorn and emmer are present at early agricultural sites in the northern Fertile Crescent of southeast Turkey and northern Syria dating from 7700 to 7500 B.C. (*5*). Wild einkorn is also present in pre-agricultural levels of sites in this region, including Mureybit (8500 B.C.) (*6*), phase 1 of Abu Hureyra (9500 to 8000 B.C.) (*7*), Dja'de (9600 B.C.), and Jerf al Ahmar (9800 BC) (*8*). This fits well with the current-day distribution of wild einkorn, abundant in the northern Fertile Crescent, but virtually absent from the southern Levant (*9*). Study of seeds and charcoal from early Holocene sites in southwest Asia confirms that vegetation at this period was similar to current-day potential vegetation(*10*).

In view of the small number of excavated sites and the large error limits associated with Neolithic radiocarbon dates, current archaeobotanical evidence does not allow localization of agricultural origins to any one subregion within the fertile crescent. However, the genetic evidence for domestication of one crop, einkorn, in southeast Turkey agrees well with archaeobotanical evidence. Whether other crops were domesticated in the same part of the Fertile Crescent remains to be established.

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References and Notes

1. The earliest Neolithic of southwest Asia is divided into the PPNA (8300 to 7600 B.C.) and the PPNB (7600 to 6000 B.C.) periods.
2. M. E. Kislev, D. Nadel, I. Carmi, *Rev. Palaeobot. Palynol.* **73**, 161 (1992).
3. Plant remains from the PPNA levels at Jericho consist of fragmented grains of emmer and barley of undetermined wild or domesticated status, dating to about 7500 B.C. [M. Hopf, in *Jericho*, K. Kenyon and T. A. Holland, Eds. (British School of Archaeology in Jerusalem, London, 1983), vol. 5, pp. 576–621]. The only cereal remains at Netiv Hagdud (7700 to 7400 B.C.) are of wild barley [M. E. Kislev, in *An Early Neolithic Village in the Jordan Valley*, O. Bar-Yosef and A. Gopher, Eds. (Peabody Museum of Archaeology and Ethnology, Harvard Univ., Cambridge, MA, 1997), pp. 209–236]. Plant remains from the nearby site of Gilgal are unpublished and therefore of uncertain status.
4. W. van Zeist and J. A. H. Bakker-Heeres, *Palaeohistoria* **24**, 165 (1982).
5. Domesticated einkorn, emmer, and barley are reported from Cafer Höyük at 7500 BC [D. de Moulins, *Cah. Euphrate* **7**, 191 (1993)] and from Abu Hureyra at 7700 B.C. (phase 2A) [D. de Moulins, *Agricultural Changes at Euphrates and Steppe Sites in the Mid-8th to the 6th Millennium B.C.* (Britsh Archaeological Reports, Int. Ser. 683, Oxford, 1997)].
6 W. van Zeist and J. A. H. Bakker-Heeres, *Palaeohistoria* **26**, 171 (1984).
7. G. C. Hillman, S. M. Colledge, D. R. Harris, in *Foraging and Farming: The Evolution of Plant Exploitation*, D. R. Harris and G. C. Hillman, Eds. (Unwin Hyman, London, 1989), pp. 240–268.
8. G. Willcox, *Veg. Hist. Archaeobot.* **5**, 143 (1996).
9. D. Zohary and M. Hopf, *Domestication of Plants in the Old World* (Clarendon, Oxford, 1993).
10. G. C. Hillman, in *The Origins and Spread of Agriculture and Pastoralism in Eurasia*, D. R. Harris, Ed. (Univ. College London, London, 1996), pp. 159–203.

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HIV Vaccine Trials

Barry R. Bloom (*Science*'s Compass, 9 Jan., p. 186) provides an insightful analysis of ethical issues in human immunodeficiency virus (HIV) vaccine trials. The implicit ethical imperative to provide the "best proven preventive" methods to trial participants, however, should include social and behavioral interventions to reduce HIV risk behavior, a topic not covered in Bloom's discussion. The 1997 National Institutes of Health (NIH) Consensus Development Conference on "Interventions to Prevent HIV Risk Behavior" (*1*) can be used as a summary of current "best proven preventive" methods.

Effective HIV prevention programs usually include providing means for "safer" behaviors, such as condoms to prevent sexual transmission and sterile injection equipment to prevent transmission among injecting drug users. This can often be done at moderate financial cost, but intense political opposition to providing the means for safer behavior occurs in many countries, To cite only one example, in the United States, the federal government has yet to provide any funding for syringe exchange programs and, in almost all states, possession of sterile injection equipment for illicit drug use remains a criminal offense (*2*). The absence of the best proven preventive methods in a community is often an indication that persons at high risk for HIV infection do not have the political power they need to obtain those services.

The existence of effective risk reduction programs raises important ethical questions for HIV vaccine trials: Should trials be conducted in the absence of "best proven preventive" methods? Is it sufficient that trial participants simply receive more prevention services than they would have in the absence of a trial? Should any trials be located in areas where political leaders refuse to provide prevention services (as this would contribute to high HIV incidence and probably reduce the costs of a vaccine trial)? Failure to consider risk behavior reduction interventions in HIV vaccine trials could lead to exploitation of relatively powerless people at high risk for HIV infection.

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References

1. *Interventions to Prevent HIV Risk Behaviors* (National Institutes of Health, Bethesda, MD, 1997).
2. L. O. Gostin, Z. Lazzarini, T. S. Jones, K. Flaherty, *J. Am. Med. Assoc.* **277**, 53 (1997).

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To imply that those who criticize the ethical standards of the clinical trials performed on women infected with the human immunodeficiency virus (HIV) in Africa do not consider the socioeconomic heterogeneity of society (Edward Mbidde, Editorial, 9 Jan., p. 155) seems erroneous. In addition, to state that "a discussion of ethical principles in biomedical research that ignores the socioeconomic heterogeneity of society is not ethical and not worth holding" appears to miss the major points that stimulated the discussion about the study in question (the ACTG 076 trial of AZT's ability to prevent maternal transmission of HIV).

The key question is not whether economic circumstances may influence ethical norms, but whether the highest ethical standards should be applied to all clinical trials, regardless of whether they are performed in highly industrialized countries or in countries where basic human needs are jeopardized by poverty. Unquestionably, the controversial clinical trial, which included a group of HIV-infected, pregnant women receiving placebo, would not meet the ethical standards necessary for approval in the United States.

Supporters of absolute ethical rigor argue that "[i]n any medical study every patient—including those of a control group, if any—should be assured of the best proven diag-

nostic and therapeutic method" (*1*). On the basis of these principles, "Human beings in any part of the world should be protected by an irreducible set of ethical standards" (*2*). Indeed, joint guidelines for research in the Third World, issued by the World Health Organization and the Council for International Organizations of Medical Sciences (CIOMS), require that human subjects receive protection at least equivalent to that of the sponsoring country (*3*).

These high moral principles may appear as roadblocks on the path of medical progress, as Mbidde implies. He therefore suggests abandoning stringent ethical rules in order to facilitate the development of an anti-HIV therapy. I do not agree with him. Acceptance of a double standard, even with the most altruistic of motives, would create the risk of exploitation of those with the least access to health care. Clearly, the Third World population is the most vulnerable. Thus, the demand for the highest ethical principles in clinical trials at universal level is not ethical imperialism but ethical imperative.

It is not the application of ethical rigor that delays the cure for AIDS, but rather the extraordinary complexity of the disease and ever-insufficient funding.

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References

1. Declaration of Helsinki IV, 41st World Medical Assembly, Hong Kong, September 1989, in *The Nazi Doctors and the Nuremberg Code: Human Rights in Human Experimentation*, G. J. Annas and M. A. Grodin, Eds. (Oxford University Press, New York, 1992), pp.339–342.
2. M. Angell, *N. Engl. J. Med.* **319**,1081(1988).
3. *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (Council for International Organizations of Medical Sciences, Geneva, 1993).

Response: I thank Kalebic for commenting on an important and difficult subject: the ethics of biomedical research in resource-poor countries. If all the countries where these studies are conducted were as rich as the United States, which can afford the cost and logistics of giving ACTG 076 to its HIV-positive pregnant women, I do not think we would be having this debate. I agree with the principle that the highest ethical standards should apply to all clinical trials, irrespective of the site. But who determines those ethical standards for the different sovereign states? Should we do clinical trials for the sake of the trials or look ahead at the use of the results outside research settings?

I disagree with the notion that economic circumstances may not influence ethical norms. And the 1993 CIOMS guidelines (*1*) articulate this very clearly in the following quote: "the revised guidelines are 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...." Needless to say, the economy is among those circumstances.

Kalebic's suggestion that the Third World population is the most vulnerable appears paternalistic. There are well-trained researchers who are nationals of the countries who are part of these studies. There are scientific and ethical review committees of competent people charged with the responsibility of scrutinizing the science and ethics of a given study. Part of this responsibility is to protect the welfare and the rights of the study subjects.

It would be wrong to abandon the stringent ethical rules without cause. The HIV epidemic marches on in many developing countries where the resources to buy the highly active antiretroviral agents are not available. It is logical that we reexamine the current ethical guidelines with a view toward removing any impediments therein. This process is in motion.

I agree with the observation that the availability of adequate funds is a central issue in

stemming the HIV epidemic. With the limited resources in hand, we can do at least two things: stand back until enough funds become available (to afford ACTG 076) or do the best we can with what we have (trials of short-course AZT alone or in combination).

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Notes

1. *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (Council for International Organizations of Medical Sciences, Geneva, 1993).

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Helper CD4⁺ T Cells and HIV-1

The study "Vigorous HIV [human immunodeficiency virus]-1–specific $CD4^+$ T cell responses associated with control of viremia" by Eric S. Rosenberg *et al.* (Reports, 21 Nov., p. 1447) suggests a possible mode of immuno-intervention in AIDS patients. However, the frequencies (1/10,000 and 1/19,000, respectively) of the T cell precursors that reacted against p24 antigen detected in the two long-term, nonprogressor patients described in the study could be an underestimation of the real frequencies because, in the regular T cell proliferation assay (figure 3 in the report), Rosenberg *et al.* say they used 105 cells per well and detected a stimulation index of 100 on day 3. It is unlikely that only 10 cells at the start of culture (105 divided by the calculated frequency of 104) would give such strong proliferation; with a doubling time of 18 hours, those initial 10 cells would result, after four doublings, in 160 cells; such a small number of cells is not likely to reflect the brisk proliferation detected. This relatively low frequency could be a result of the assay conditions: Rosenberg *et al.* do not report adding interleukin-2, which is known to affect the detected frequency. In our experience, interleukin-2 can increase the detected frequency 10-fold (*2*), an effect also noted by others (*3*, *4*). In addition, Rosenberg *et al.* do not report examining the cell frequency below 103. Because limiting dilution assays may have multiple-hit patterns (*4*), the authors could have missed the detection of high-frequency cells.

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References

1. F. Mor and R. Cohen, *J. Clin. Invest.* **90**, 2447 (1992).
2. J. Rossert, L. Pelletier, R. Pasquier, P. Druet, *Eur. J. Immunol.* **18**, 1761 (1988).
3. A. W. Lohse, M. Dinkelmann, M. Kimmig, J. Herkel, K. H. Meyer zum Buschenfelde, *J. Autoimmun.* **9**, 667 (1996).
4. K. Fey, I. Melchers, K. Eichmann, *J. Exp. Med.* **158**, 40 (1983)

Response: We agree with Mor that the precursor frequency analysis likely is an underestimation of the true frequency of HIV-1–specific helper cells, for the reasons he outlines. We had initially not included these data in the manuscript, but were requested by the reviewers to add them. The type of functional assay used can be anticipated to underestimate the true frequency because the frequency calculation is based on the assumption that a single HIV-1–specific helper cell in a well will result in a positive readout (the single-hit hypothesis). We are in the process of trying to develop a more sensitive assay system.

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