Editorial & Letters

EDITORIAL

Bioethics and Biological Weapons

Biological weapons, whether wielded by the military forces of nations or by terrorists, will continue to pose a serious threat to international security for the foreseeable future. Although access to toxic material and pathogenic strains of microorganisms is restricted, covert traffic in such agents is as difficult to control as that of illegal drugs. Since international travel of microbiologists qualified to perform applied biological weapons–related research is not restricted, the international bioscientific community must do its part to prevent the proliferation of biological weaponry to nations that now do not possess them and to eliminate these weapons where they presently exist.

To prevent acquisition of weapons of mass destruction, including biological weapons, the United Nations Special Commission and the International Atomic Energy Agency must continue their activities in Iraq as called for by United Nations Security Council Resolution 697 (1991), including investigating past weapons programs, inspecting and monitoring suspect facilities, and controlling import of dual-use equipment and supplies. However, to secure peace for the long term, these activities need to be augmented by initiatives taken by nongovernmental scientific organizations. Most important, once sanctions have been lifted by the United Nations, Iraqi scientists must be brought back into the fold of the international scientific community. Communication and collaboration among scientists from all countries encourage shared values, mutual respect, and friendships. Interpersonal scientific contact with Eastern bloc scientists during the Cold War had beneficial effects and offers a model for the reintegration of scientists from countries such as Iraq.

The international bioscientific community can take immediate steps to support colleagues in every country, including Iraq and the republics that once constituted the former Soviet Union (FSU), thereby countering the international proliferation of biological weaponry. Of special concern is the risk that scientific and technical workers who once were employed in a national biological weapons program, but now are unemployed or underemployed, might be induced by proliferant countries and terrorist groups to perform illicit biological weapons–related research and development. The best way to prevent this from happening is to provide those scientists with challenging and adequately remunerated work in their home nations. Recognizing this fact, the European Union, Japan, the United States, and other nations have established international programs designed to help weapons laboratories convert to peaceful uses. These programs, including the International Science and Technology Center, the Initiatives for Proliferation Prevention, the International Association for the Promotion of Cooperation with Scientists from the New Independent States of the FSU, and the Civilian R&D Foundation for the Independent States of the FSU, should be supported and promoted by bioscientists worldwide.

Scientists of countries alleged to be sponsoring or supporting biological weapons programs should be encouraged to participate in international scientific meetings, and electronic communication links should be established. In particular, the International Council of Scientific Unions (ICSU) and professional societies should help provide the equipment and funding necessary to set up electronic mail and Internet access for scientists from developing countries. Under Article X of the Biological and Toxins Weapons Convention (BWC), which enjoins member countries to cooperate in applied microbiology, BWC members could encourage reciprocal visits between scientists and fund joint research projects involving laboratories of all countries. Through these approaches, scientists of every country would become full partners in international collaborations.

In addition, science students from nations suspected of pursuing the acquisition of biological weapons should be invited to international forums that include discussions of ethics in science. The International Centre for Genetic Engineering and Biotechnology, headquartered in Trieste and New Delhi, might lead such an effort. Scientists imbued with a strong sense of ethics will be more inclined to slow the progress of biological weapons–related research or alert outsiders to activities that violate international law. The codes of ethics promulgated by professional societies such as ICSU and the American Society for Microbiology can provide useful guidance for action.

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LETTERS

Counting sheep

Questions are raised about whether the cloning of the sheep Dolly, an exceptional "single observation," has been adequately confirmed. Dolly's cloners respond. The schedule for the startup of a reactor at Brookhaven National Laboratory is explained. And more discussion of how to regulate mercury in fish is offered.

Dolly Confirmation

It has now been almost a year since the cloning of the sheep Dolly from an adult ovine cell was announced (*1*). The year has brought much agonizing discussion, potential legislation, and some laurels, but no more Dollies. The principal scientist, Ian Wilmut, has announced (*2*) that he and his group have no intention of trying again (to clone using mammary DNA and a host denucleated ovine cell). Some "very soon" to be delivered (*3*) cows that were to be cloned from adult cells have yet to appear. Other rumored events seem also to have dissipated. It is a well-known tenet of science that a single observation is not to be codified until confirmed by someone in some way. The single observation gains some credence when well controlled or of a unique nature, or both. It is the lack of any confirmation that provokes our skepticism; here are some of the detailed reasons.

1) The cloning was done once out of some some 400 tries. Only one successful attempt out of some 400 is an anecdote, not a result. All kinds of imagined and unimagined experimental error can occur.

2) The characterization of the mammary gland cells used as nucleus donors was poor; it could have been one of the donor's rare stem cells that was involved, as acknowledged in the paper (*2*).

3) The reason why the donor ewe was pregnant was not explained (*1*). This is important, because the cell which led to Dolly could have been of fetal origin. Why was no analysis of the fetus and its father's genotype performed? Given these DNA fingerprints, or even the sex of the fetus, one could have excluded a fetal cell as donor.

4) The demonstration that the four

microsatellite marker DNAs seem the same in Dolly and in the donor mammary cells is good, but not sufficient; it would probably be rejected by a jury called to deliberate on Dolly's origin, not an unlikely event given Dolly's commercial potential. Sheep are highly inbred and there are, to our knowledge, no data on gene frequencies in sheep populations; differences in DNA fingerprints can provide exclusion, but similarities are only a statistic.

5) An analysis of Dolly's mitochondrial DNA has not been given, although it could provide important clues to her origin; the genotype of the recipient oocyte and the mitochondrial genotype of the donor cell or that of any of the other players was also not given.

6) Last summer (*4*), and again recently (A. E. Schnieke *et al.*, Reports, 19 Dec., p. 2130), the same group announced the cloning of transgenic sheep, but from a fetal cell not an adult cell; Polly is not a Dolly. Remember, Dolly should be "aged" relative to her peer group. Barring new science, she must have retained any imprinted genes from the previous generation, she should have short telomeres, and her DNA should have an adults worth of mutations; a special creature in more ways than one.

7) No hint is given in the paper (*1*) that the donor ewe had apparently died a few years ago, thereby precluding pertinent immunological testing of genetic relationships.

If we are to try to seriously analyze the mammalian cloning issue and its human implications, we should ask for details on points such as these, and for stronger statistics plus independent confirmation, before considering cloning of adult cells by means of nuclear transfer as a fait accompli.

Discussing such issues before they are immediately upon us is correct. However, indulging in endless debates is less so, when one considers both the scientific weaknesses of the experiment and the possible impact on the societal credibility of science itself of the "facts" on which they are purportedly based.

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1. I. Wilmut, A. E. Schnieke, J. McWhir, W. A. J. Kind, K. H. S. Campbell, *Nature* **385**, 810 (1997).
2. G. Kolata, *New York Times*, 29 July 1997, p. C3.
3. ___ *ibid.*, 8 August 1997, p. A10.
4. ___ *ibid.*, 25 July 1997, p. A18.

Response: With reference to the skepticism of Sgaramella and Zinder about the origins of Dolly the sheep, we would like to provide clarification about some of the points they raise. Dolly is the only live birth that resulted from the transfer of nuclei from the adult-derived mammary cell cultures. Admittedly, a single birth from 400 attempted fusions is not an efficient system. However, the suggestion that "experimental error does occur" can be answered in a number of ways. First, Dolly is a Finn Dorset ewe. At the time of these experiments there were no other Finn Dorset cells being cultured in the laboratory and no Finn Dorset embryos being used in any other experimental system. Thus, in terms of breed, Dolly can only have been derived from the cell culture established from the mammary gland. These cell cultures were not established for the purposes of nuclear transfer, but had been previously isolated for other studies. The reason that a pregnant donor ewe was prepared was to establish, in culture, a cell line that exhibited mammary epithelial-specific characteristics for long-term culture. This was part of a collaboration between PPL Therapeutics and the Hannah Research Institute. For this reason, the genotypes of the fetus and the ram used for insemination were not analyzed, and no fetal material was retained for analysis.

Microsatellite analysis of Dolly mirrored exactly the pattern observed at both early (pre-nuclear donor) and late (post-nuclear donor) passages of the cell population. In addition, the cell population was predominately epithelial in nature. It is inconceivable that during the very short period of cell expansion, a rare fetal cell, if present, could have overgrown the mammary culture.

With regard to the mitochondrial DNA, samples from Dolly, all of the other lambs produced by nuclear transfer, the cell cultures, and representative samples from a number of randomly selected Blackface ewes (the breed used as oocyte donors) have been provided for analysis by independent third parties. When the results of these studies are available, they will be announced to the scientific community. Similarly, studies of the telomere length of the donor cells used for the production of Dolly, of Dolly herself, and of Finn Dorset sheep of representative ages are being analyzed at two centers. These studies are being coordinated with studies of all of the nuclear transfer offspring produced from embryo- and fetal-derived cell populations, of the cell populations themselves, and of the naturally produced offspring of those animals that have reached sexual maturity and have been bred.

We would like to point out that the methods described (*1*, *2*) have been duplicated successfully by using cell populations derived from embryonic material (*3*). Other groups are attempting to repeat the technology using fetal and adult cell populations. It

should be realized that only 11 months have elapsed since publication of our results (2); if one takes into account the time period required for gestation in sheep (5 months), one sees that it is unlikely that other authors would yet have had time to complete similar experiments and publish data.

Retrospectively, we and our co-authors realize that if the use of these cells for nuclear transfer had been anticipated, the skepticism of Sgaramella and Zinder could have been allayed by reference to an original donor tissue sample deposited with a respected neutral third party.

We were always aware that there would be some skepticism about our results and have been greatly encouraged by the positive reaction of the scientific community. We would like to think that this reflects the integrity with which we are accredited by our scientific peers. To us, as practicing scientists, this accolade is of paramount importance.

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1. K. H. S. Campbell, J. McWhir, W. A. Ritchie, I. Wilmut, *Nature* **380**, 64 (1996).
2. I. Wilmut, A. E. Schnieke, J. McWhir, W. A. J. Kind, K. H. S. Campbell, *ibid.* **385**, 810 (1997).
3. D. N. Wells, P. M. Misica, A. M. Day, H. R. Tervit, *Biol. Reproduct.* **57**, 385 (1997).

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Reactor Startup

In ScienceScope of 19 December (p. 2045), an item under the heading "No votes from research reactor?" relates to problems at the High-Flux Beam Reactor at Brookhaven National Laboratory and refers to a 22 November letter from the Basic Energy Sciences Advisory Committee (BESAC) to Martha Krebs summarizing recommendations from our public meeting on 30 July to 1 August that reviewed the issues.

The BESAC recommended that a full Environmental Impact Statement (EIS) should be undertaken before restarting the reactor; we had been advised that this could be completed in 15 months after a decision to undertake it. The EIS was recommended to help in reassuring the local community that all care is being taken; the implication that it is a delaying tactic for political reasons could not be farther from the truth. We recommended that actions should be planned to achieve a prompt restart after an acceptable outcome of the EIS, but we expressly did not recommend undertaking a $150-million upgrade. This upgrade was proposed in an earlier study undertaken at the request of the Office of Basic Energy Sciences, which reported in January 1996, as part of a study to explore alternatives to expanding the neutron research capabilities after the cancellation of the Advanced Neutron Source project. In our discussions, we drew from that earlier report, produced by a subcommittee chaired by Robert Birgeneau, to illustrate the scientific importance of neutron scattering studies, but we were careful in our recommendations to make it clear that the upgrade proposed in the Birgeneau study was not being recommended as part of the restart we advocated.

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Response: Stringer is correct that a previous panel, and not his, recommended the $150-million upgrade. Stringer's group did call for the reactor's power to be boosted from 30