Readers discuss declining human fertility in the world and how to address it. Two members of a team that inspected a Japanese laboratory in 1997 comment on their biosafety findings. They state that "[l]aboratory-acquired infections are well documented...including Japanese reports.... It is possible that such infections can be transmitted into the community." And two representatives of the DuPont Merck Pharmaceutical Company clarify their firm's Cre-loxP patent policies.

Declining Fertility

John Bongaarts displays broad knowledge of world demographic trends (Policy Forum, *Science*'s Compass, 16 Oct., p. 419), but when he slips from statistics into advocacy, the result is questionable.

Below-replacement fertility levels in the developed world do not herald an imperative for economic incentives to enhance fertility. If the richer nations perceive a need for offsetting the modest population declines that would otherwise ensue over the next century, they need only relax immigration rules, expanding opportunities for the best-educated and most industrious aspirants from the third world.

Joshua Mitteldorf
Department of Biology, University of Pennsylvania, Philadelphia, PA 19104, USA. E-mail: jmitteld@brynmawr.edu

As Bongaarts mentions, the United Nations (UN), in its just issued *1998 Revision: World Population Estimates and Projections* (*1*), has revised its population projections sharply downward. The 1998 revisions now estimate that population at the mid-century mark will reach only 8.9 billion, a net loss of nearly a billion souls from the earlier number.

Even this figure is probably an overestimate. The UN "low-fertility projection," historically more accurate than its "medium-fertility" one, sees only 7.3 billion people inhabiting the world in 2050. Given that world population now stands at 5.9 billion, this means we will only add about a quarter of our present number to the human family before beginning what could be a wrenching descent.

What accounts for these dramatic declines? The answer is falling fertility, rising rates of AIDS, and more accurate prognosticating by the United Nations. Nearly half the world's population—44%—has now decided, for various reasons, not to completely replace themselves, or they are dying of AIDS before they can. The remainder is having far fewer children than their grandparents. The UN Population Division reports that the global average fertility level now stands at 2.7 births per woman, a mere 0.6 above the replacement level. In the early 1950s, women averaged 5 births. Fertility is now declining in all parts of the world. Over the past 25 years, the number of children per couple has fallen from 5.1 to 2.6 in Asia, from 5.0 to 2.7 in Latin America, and from 6.6 to 5.1 in Africa.

Europe has fallen to a mere 1.42 children per couple, one-third less than the 2.1 required to maintain population stability. To call a projected loss of 100 million people in Europe by mid-century, combined with the senescence of a substantial percentage of the remaining population, a "small decline" minimizes the massive social and economic disruption this will cause.

Steven W. Mosher
President, Population Research Institute, Post Office Box 1539, Front Royal, VA 22630, USA. E-mail: steve@pop.org

References

1. *1998 Revision: World Population Estimates and Projections* (Population Division, Department of Economic and Social Affairs, United Nations, New York, 1998).

Laboratory Safety

We took part in the inspection on 18 June 1997 of the Japanese National Institute of Infectious Diseases (NIID) (D. Normile, "Court hears fight over safety of lab," News of the Week, 9 Oct., p. 213). We are reluctant to comment on a case that is still before the Tokyo district court, but feel that statements presented in Normile's article need a response.

CREDIT: D. NORMILE

Is Japanese laboratory (right) too close to apartment buildings (left)?

First, Shudo Yamazaki, Director-General of NIID, is quoted as saying, "We think that [our] safety precautions are equal to or exceed those at America's National Institutes of Health." There should be documented evidence to support this. Such evidence would have to be derived from comparative, contemporaneous independent inspections of both institutes.

Yamazaki is also quoted as saying "There has never been a single case of disease caused by an escaped organism in Japan." This should also be taken with a pinch of salt, because there is no suitable public health surveillance program to back it up. Laboratory-acquired infections are well documented (*1*), including Japanese reports (*2*). It is possible that such infections can be transmitted into the community. On the day of the inspection, NIID workers were not provided with medical contact cards. Without these, how would a physician reliably be alerted to the possibility of an occupational origin for an infectious disease under investigation?

It is suggested that the World Health Organization's (WHO's) recommendation about siting laboratories away from public areas is taken out of context. We cannot accept that WHO intends this (*3*) solely to apply to hospital laboratories. The possibility of escape of pathogens can never be ruled out, and if the laboratory is located away from public areas, there are fewer members of the public available to act as hosts, thus reducing overall the risk of transmission of infection.

The article cites the "essential message" of the Oviatt-Richmond report, which is currently before the court. Taken verbatim from our report, also currently before the court, our message is

> If NIID wishes to engender confidence in the minds of the local residents' group that it really is able to guarantee that its location and activities are not a risk to public health and safety, or—more realistically—that its location and activities are of such a low order of risk as to be acceptable to the local residents' group, it will have to be prepared to provide the necessary hard evidence.

Such evidence was not available in June 1997, the absence of a procedure for dealing with accidental leakage or breakage of vials of frozen pathogen cultures being just one shortcoming.

We think that these are very important issues and that much would be gained by a wider debate. In particular, there would be an opportunity to widen the scope of biosafety science to include quality assurance of safety claims.

Finally, in view of the differences in the reports, we suggest that there is an urgent need for a body like WHO to develop an official protocol for the inspection of laboratories. Not only would this help to ensure common standards of inspection, it would help to focus the minds of laboratory management on biosafety performance needs.

C. H. Collins

Microbiology Department, Imperial College School of Medicine, University of London SW3 6LY, UK

D. A. Kennedy
Cranfield Biomedical Centre, Cranfield University, Cranfield, Bedfordshire MK43 0AL, UK. E-mail: kennedy@btinternet.com

References

1. C. H. Collins, *Laboratory-Acquired Infections* (Butterworth Heinemann, London, ed. 3, 1993), pp. 1–27.
2. H. Shimojo, *Bibl. Haematol.* (no. 40) (1975), p. 771; A. Oya, *ibid.*, p. 775.
3. *Safety in Healthcare Laboratories* (World Health Organization, Geneva, 1997), p. 16.

Patenting Genomic Technologies

The review article "Can patents deter innovation? The anticommons in biomedical research" by Michael A. Heller and Rebecca S. Eisenberg (*Science*'s Compass, 1 May, p. 698) has errors of fact and some erroneous assumptions as it relates to Cre-loxP patents owned and administered by the DuPont Pharmaceuticals Company.

Heller and Eisenberg misstate a purported DuPont "right to participate in future negotiations to develop commercial products that fall outside the scope of their patent claims" and our purported ability and intent "to leverage its proprietary position in upstream research tools into a broad veto right over downstream research and product development." We reserve neither right in our license agreements with academic and other not-for-profit institutions.

Cre-loxP is a highly regarded recombinase system that has demonstrated ability to efficiently and selectively introduce or delete DNA segments into the genome, even in quiescent postmitotic cells. DuPont has put this valuable technology into the academic domain at no cost and with a few necessary and limited restrictions. It is our sincere desire to broadly disseminate this valuable technology. To date, hundreds of academic research licenses have been granted, enabling scientists to push ahead with critical research. In such academic agreements, DuPont reserves the right to "pay a reasonable royalty or other financial consideration" and "will negotiate in good faith" to obtain nonexclusive, grant-back rights to improvements in the technology, a de minimum recognition that DuPont provides the technology at no charge to academics. If academic institutions desire to transfer technology using Cre-loxP to other nonprofit institutions, DuPont allows such transfer, providing that the recipient institution has signed a free research license. In keeping with DuPont's mission to make Cre-loxP widely available to the research community, all such transfers are favorably considered.

Academic research licenses are intended to allow unfettered intellectual pursuit, but *not* to allow free transfer of valuable intellectual property from the not-for-profit sector to the commercial realm. If academic institutions develop novel uses for Cre-loxP that they wish to commercially license or transfer to a for-profit entity, DuPont reserves the right to negotiate, along with others, with the institution in question for possible use of that new commercial product. Any transfer of Cre-loxP–based technology from the nonprofit to the commercial setting involves a "good faith negotiation of an arrangement, in either cash or non-cash consideration, and consistent with the contribution made by the Licensed Patents." In essence, if an academic institution deviates from its free research license and uses Cre-loxP technology in pursuit of commercially applicable research, there is a "transfer tax" imposed to move this from the academic to the commercial universe. No reasonable person could expect DuPont to enable academic researchers to commercialize inventions using our patented processes, obtained at no cost, without recognizing the contribution of this enabling technology.

DuPont has paid, and continues to obligate itself to pay, millions of dollars to universities and government institutions for access to patented technologies. DuPont believes that it is appropriate to pay for enabling and proprietary technology, so long as there are no stacking downstream obligations for nonpivotal technologies. Hundreds of scientists with a primary interest in advancing scientific knowledge have benefited and continue to benefit from free access to Cre-loxP technology. DuPont is proud to have contributed such an exciting technology into common use and is pleased by its rapid adoption.

David S. Block
Daniel J. Curran
Product Planning and Acquisition, DuPont Merck Pharmaceutical Company, Post Office Box 80722, Wilmington, DE 19880–0722, USA

Response

In our review, we cited DuPont's Non-Commercial Research License Agreements for Cre-loxP as one example of a reach through license agreement (RTLA) that provides access to upstream biomedical research tools in exchange for rights in future discoveries. Our concern is that as RTLAs proliferate, upstream owners will stack competing, inconsistent claims on top of future commercial products. The greater the number of owners who need to reach agreement, the greater the risk that bargaining will fail. The result may be a "tragedy of the anticommons," in which more upstream patent rights paradoxically lead to fewer downstream products.

The letter by Block and Curran contains ambiguities that leave us uncertain as to their meaning. They concede that, at least for "Cre-loxP–based technology," the agreements reserve a place at the bargaining table for DuPont in future "good faith negotiation." Perhaps, then, the error in our characterization was that further negotiations with DuPont would not be necessary for the transfer of discoveries that fall outside the scope of DuPont's patents. But elsewhere their letter suggests that users of Cre-loxP might be expected to pay a "transfer tax" to DuPont before pursuing commercial development of discoveries that were "enabled" by the use of Cre-loxP.

The language of DuPont's Non-Commercial Research License Agreement echoes these ambiguities. We have seen different versions of this agreement, some signed and others negotiated to impasse over certain key provisions. The agreements confer a license to use Cre-loxP technology "for Research Purposes only" and require the licensee to apply to DuPont for an additional license before using the technology for "Commercial Purposes." Two specific examples of "research for Commercial Purposes" are set forth, neither of which seems likely to involve ongoing use of Cre-loxP technology: (i) "research and development of therapeutic products towards filing of an IND [investigational new drug]," or (ii) "research, development and clinical trials towards commercialization of products resulting from such efforts." DuPont retains a veto right over all activities falling within its definition of use for "Commercial Purposes" by specifying that "[s]uch license, if any, is to be granted at the sole discretion of DuPont."

If, contrary to our characterizations, these agreements do not give DuPont "the right to participate in future negotiations to develop commercial products that fall outside the scope of their patent claims" and do not permit DuPont "to leverage its proprietary position in upstream research tools into a broad veto right over downstream research and product development," then what exactly do these provisions mean?

Suppose that an academic scientist uses Cre-loxP to create research animals in order to study the function of a particular gene. In the course of these studies, the scientist observes that the gene appears to