POLICY FORUM: GENETIC TECHNOLOGIES

Facing Inheritable Genetic Modifications

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The rapid pace of biomedical research has seriously challenged society's ability to make informed and reasoned choices about whether and how to proceed with its development and use. Typically, we proceed in a "reactionary mode," scrambling to match our values and policies to scientific advances. We are in danger of falling into that trap again with the announcement in March that intentionally modified mitochondrial DNA had been transmitted to human offspring, effectively altering the germ line (*1*). As Parens and Juengst remark in their editorial (*2*), this news "should trouble those committed to transparent public conversation about using 'reprogenetic' technologies to shape future children."

Efforts to modify genes transmitted to future generations have the potential to bring about not only a medical, but also a social revolution (*3*). The dilemma is that inheritable genetic modification (IGM) techniques developed for therapeutic purposes are also likely to be suitable for genetic alterations intended to improve what are already "normal" genes. IGM for such enhancement purposes could widen the gap between "haves" and "have-nots." A market economy, where techniques for IGM are available on the basis of ability to pay, would add inherited advantage to the benefits of nurture and education already enjoyed by the affluent.

If IGM were to take hold anywhere, it would likely be through infertility clinics. Web sites have already sprung up where couples can enter their preferences for height, weight, hair color, IQ, and even tanning ability of donors of egg or sperm in order to find just the right match (*4*). Yet this industry is virtually unregulated, it has been averse to public scrutiny, and its practices have been subject to severe criticism and law suits (*5*). In general, this is not an environment that should be counted on to foster the safest and most responsible uses of IGM techniques.

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Effectively regulating the multimillion dollar infertility industry, which has operated without public oversight since its beginnings, is likely to be difficult. The immediate task would be to collect accurate information on the number and locations of such clinics. An oversight structure would need to respond to concerns regarding intrusions into the practice of medicine, to provide for on-site inspections of the clinics, and to impose stiff penalties on those clinics found to violate a policy proscribing IGM.

The effect on future generations makes IGM a category of research deserving special consideration in developing public policy. This distinct feature of IGM is what prompted the NIH Recombinant Advisory Committee (RAC) to declare explicitly that it would not "entertain proposals for germ line alterations..." (*6*). More recently, the RAC indicated that more animal research is needed before if would even consider a preprotocol for in utero somatic gene transfer, because of the possibility of causing inadvertent changes in the fetus's germ line cells (*7*).

Outside the United States, laws, treaties and declarations, most of which originate in Europe, overwhelmingly proscribe "germ line" interventions in humans, or at least find them "ethically unacceptable." These positions rest on a concern for the risks involved with such a nascent technology and/or a need to consider the ethical, social, and human rights implications associated with these interventions. Among the exceptions are those where "the germ line alteration is not the aim, but only a side effect of medical treatment" (*8*) and "it may only be used if the risk entailed is outweighed by the anticipated benefits; and only on persons who are unable to have descendents." (*9*). It is rare to find a clear definition of what is encompassed under the rubric of "germ line" beyond the stipulation that interventions be capable of being inherited. Moreover, much of what has occurred internationally represents action taken several years ago (*10*).

We recommend that a system of oversight be put in place immediately in the United States, either through an expansion of the RAC's purview or by a new body. No research or clinical applications involving humans should proceed that have the direct or indirect potential to cause inheritable genetic modification in either the public or private sector until this body reviews and approves it. This means that no somatic genetic research where there is a reasonable foreseeable possibility of IGM should go forward until there is (i) sufficient data collection and scientific analysis to assess short- and long-term risks of inadvertent effects on the germ line; (ii) public discussion to determine the extent to which there is support for going forward with research that could result in secondary germ line changes; and (iii) establishment of an oversight body.

This oversight should be implemented at the national level with authority over human IGM in both the public and private sectors, a step that would require federal legislation. The oversight mechanism should be independent of the sources of funding for IGM research and applications (this would mean moving the RAC out of NIH) and must include as an essential component access for public participation at all levels of deliberation. It would be responsible for initiating and coordinating a national and international dialogue on the acceptability of IGM research and applications. If IGM research or applications were to proceed, oversight should include the scientific and ethical review of all protocols or procedures with IGM implications in the public and private sectors, and a process for monitoring the uses of IGM as they go forward.

For any system of public oversight, public safety must be paramount, especially where the genetic endowment of future persons will be affected. Currently, we have little experience and no evidence of the long-term safety of IGM, whether intended or inadvertent. There has not even been public consideration of how one would proceed in determining safety in humans across generations. We should begin establishing an oversight process now so that we can make informed and reasoned choices about the future.

References and Notes

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4. www.eggdonorfertilitybank.com/profiles/search.html.
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6. NIH Guidelines for Research Involving Recombinant DNA Molecules, Appendix M, *Fed. Reg.* **60** (27 April), 20737 (1995); see www4.od.nih.gov/oba/rac/guidelines/guidelines.html.
7. J. Couzin, *Science* **282**, 27 (1998).
8. Embryo Protection Act, enacted December 1990; effective 1 January 1991 (Federal Republic of Germany).
9. The Gene Technology Law, 12 July 1994 (Austria).
10. Supplementary material is available on *Science* Online at www.sciencemag.org/cgi/content/full/292/5520/1303/DC1