

Cloning and Stem Cells — Handicapping the Political and Scientific Debates

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On August 9, 2001, President George W. Bush delivered an extraordinary prime-time television address to the nation that was devoted exclusively to an arcane topic of basic biomedical research: human embryonic stem cells. After months of fact-finding and rancorous debate, Bush announced that federal funding would indeed be provided for the study of these remarkable cells, though only for pre-existing stocks. Although disappointing to those who had hoped he would banish all such research, Bush's decision was at its core an endorsement of the promise of human embryonic stem cells and their importance to the fledgling field of regenerative medicine.

The debate over human embryonic stem cells is unfortunately embedded in the contentious issue of human reproductive cloning. The process of somatic-cell nuclear transfer, which was used to clone Dolly the sheep and could in principle be misappropriated to clone humans, has legitimate usefulness in research involving embryonic stem cells, as discussed expertly by Hochedlinger and Jaenisch in this issue of the *Journal* (pages 275–286). Nuclear transfer is a key method for exploring the earliest stages of embryonic development and for investigating the potency of embryonic and adult stem cells. By exposing the nucleus of an adult somatic cell to the milieu of the egg, nuclear transfer tricks the genome into reactivating embryonic genes and reinitiating embryonic development. From this reconstructed embryo, embryonic stem cells can be harvested. Nuclear transfer is thus a means to generate a customized embryonic stem cell that carries the genetic blueprint of a specific patient. Such a cell line would represent an important model for studying disease. In principle, cells with therapeutic usefulness could be derived and transplanted into a patient without the need for toxic immune suppression. By restricting federal support of research to the existing stocks of human embryonic stem cells, the President effectively discouraged research on this process, called “therapeutic cloning.”

This action set the stage for a host of legislative actions at both federal and state levels to define the permissible bounds of research. The justification

for more restrictive legislation hinges in part on scientific perceptions about the versatility and therefore the promise of adult as compared with embryonic stem cells — itself a topic of intense scientific disagreement. The debates in the halls of Congress and the scientific laboratories are inextricably intertwined, and the outcome will profoundly influence the future of regenerative medicine.

Essentially all laws currently wending their way through federal and state legislatures aim to criminalize human reproductive cloning but take different approaches to therapeutic cloning. Some expressly prohibit it, whereas others seek to protect or even foster it. The Human Cloning Prohibition Act of 2003 (H.R. 534), sponsored by Representative Dave Weldon (R-Fla.), passed the House on February 27 of this year by a vote of 241 to 155, and much the same bill has been introduced into the Senate sponsored by Senator Sam Brownback (R-Kans.) (S. 245). These bills criminalize the nuclear-transfer technology itself and, hence, outlaw both reproductive and therapeutic cloning. Still other bills (e.g., H.R. 916 and H.R. 938) seek to prohibit federal funding for research involving nuclear transfer of human somatic cells. But by specifying the method of cloning, these bills will require revision once a new reproductive-cloning technique surfaces.

Countering these proposals are several competing bills that aim to preserve the right to create customized human embryonic stem cells by means of nuclear transfer. The Human Cloning Ban and Stem Cell Research Protection Act of 2003 (S. 303), sponsored by Senator Orrin Hatch (R-Utah), aims not to outlaw nuclear-transfer methods but, rather, to outlaw the implantation of the products of nuclear transplantation “into a uterus or the functional equivalent of a uterus,” the last phrase being a chilling but prescient acknowledgment of the potential for the kind of *ex vivo* reproduction described in Aldous Huxley's *Brave New World*. Yet another effort to prohibit reproductive cloning alone, the Cloning Prohibition Act of 2003 (H.R. 801), amends the Federal Food, Drug, and Cosmetic Act to outlaw the use of nuclear transfer to “initiate a pregnancy.” Although expressly forbidding reproduc-

tive cloning, these bills aim to protect research and therapeutic applications of nuclear-transfer studies.

The map of state legislation resembles a patchwork quilt. Restrictions run the gamut from the prohibition of all forms of human cloning (in Arkansas, Iowa, Michigan, and North Dakota) to bans on reproductive cloning alone (in Louisiana, Missouri, and Rhode Island) to a bill passed in California last year expressly promoting stem-cell research, including nuclear-transfer studies. The California statute has since become a model for efforts in a number of other states (Massachusetts, Illinois, Maryland, New Jersey, New York, Pennsylvania, Texas, Vermont, and Washington).

These political debates are proceeding in concert with a lively scientific discussion of the nature of adult stem cells. Rosenthal's article in this issue of the *Journal* (pages 267–274) is an erudite review of the recent scientific sparring. Stem cells are defined by their capacity for self-renewal, differentiation into multiple lineages, and tissue regeneration, but all stem cells are not created equal. The most dramatic distinctions can be drawn between the stem cells of the early embryo, whose fate encompasses all cells of the organism (a property termed "pluripotency"), and stem cells from adult tissues, which function best to regenerate the tissue in which they reside.

This sharp contrast in plasticity between embryonic and adult cells has been documented in scores of classic experiments and, until recently, was unchallenged dogma in developmental biology. However, a recent wave of experiments has been interpreted by some scientists to mean that adult stem cells may indeed be more plastic than previously thought and may contribute to many tissues in a manner not unlike that of embryonic stem cells. The debate over the fundamental distinctions between embryonic and adult stem cells would be waged anonymously at otherwise stodgy scientific symposiums if not for its influence on legislation pertaining to cloning and stem cells. Were adult stem cells as versatile as embryonic stem cells, research on embryonic stem cells would not be needed, or so the argument goes.

The preliminary and highly controversial evi-

dence notwithstanding, notions of the plasticity of adult stem cells have been invoked to fuel the opposition to research involving human embryonic stem cells. Many, but not all, of the claims have been refuted and have been shown to be due to an artifact, misleading cell fusion, or exceedingly rare events that are exceptions to normal biologic function. On the basis of the data, no credible biologist would accept the idea that embryonic and adult stem cells have the same intrinsic or native developmental potency. It is incontrovertible that embryonic stem cells can generate all tissues, whereas it has never been shown that any form of unmanipulated adult stem cell has the same unbridled potential. Not all adult tissues (e.g., the myocardium and much of the brain) regenerate effectively from pools of stem cells, and thus at least some cell-replacement therapies might best rely on embryonic stem cells. Legislators should take heed: halting studies of embryonic stem cells because adult stem cells might be credible substitutes would be the wrong outcome.

Although the intrinsic plasticity of adult stem cells remains hotly contested, the latent pluripotency of virtually any cell can indeed be altered experimentally: nuclear transfer can cause adult cells to revert to their embryonic state. A worthy goal of biomedical research is to reprogram an adult cell directly, without having it pass through the intermediate stage of the preimplantation embryo. Reaching this objective would eliminate ethical challenges to such research. One day, direct reprogramming of an adult cell may prove feasible through a combination of chemical and genetic means. But this goal will be achieved more quickly if we are allowed to explore reprogramming with the use of currently available methods, which entail nuclear transfer and the creation of new lines of embryonic stem cells. Legislation that unduly restricts the pursuit of nuclear-transfer studies will cripple innovation in cellular engineering and may ultimately thwart our ability to exploit the full potential of therapies involving adult stem cells. It remains to be seen whether the Senate will act in the best interests of patients and the future of regenerative medicine.

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