REPORT OF THE COUNCIL ON ETHICAL AND JUDICIAL AFFAIRS*

CEJA Report 6-A-09

Subject: Human and Nonhuman Hybrids

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Referred to: Reference Committee on Amendments to Constitution and Bylaws (Daniel W. Van Heeckeren, MD, Chair)

Resolution 3 (A-08), "Studying the Ethical Implications of Creating Cytoplasmic Human-Animal Hybrids," submitted by the Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont delegations, asked that the American Medical Association (AMA) study the ethical implications of creating "cytoplasmic" human-animal hybrids. "Cytoplasmic" human-animal hybrids, more commonly known as "chimeric embryos" (other terms sometimes used are "cybrid" or "hybrid embryo"), are formed when human genetic material is introduced into a nonhuman embryo or transferred into an enucleated nonhuman egg by means of somatic cell nuclear transfer (SCNT).[1, 2] A chimeric embryo can also refer to a nonhuman embryo into which human stem cells have been transplanted.[1]

Chimeric embryos are being explored as alternatives to problematic research techniques that use human embryonic or adult stem cells. Supporters argue that using chimeric embryos overcomes the ethical challenges posed by using human embryos as sources of stem cells. It is argued that chimeric embryos permit in vivo stem cell research that would not be ethically responsible using human embryos because of safety concerns.[1] It is not yet fully understood what ill effects human stem cells may have when transplanted into human embryos or human patients. Chimeric embryos permit the study of stem cell potential without possible harm to a human or human embryo.[1] Further, the availability of embryonic stem cells currently depends largely on the number of unused embryos donated by prospective parents seeking fertility treatments.[3] The use of chimeric embryos responds to the shortage of stem cells for research purposes by creating an "assured source of stem cells for research" compared with the limited supply and challenges of obtaining human or creating human embryos for research purposes.[2, 4]

ETHICAL CONCERNS

There is wide, although not necessarily universal, agreement in the scientific community that stem cell research represents a very promising domain for the development of new therapies with significant potential to benefit patients.[5] The prospect of such benefit figures prominently in ethical justifications for such research.[5] At the same time, however, there has been considerable argument in both the professional literature and in public opinion that deriving stem cells from human

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embryos is ethically highly problematic and should be prohibited.[3, 5, 6] Hence the ethical appeal of alternative sources for stem cells.

However, creating human-nonhuman chimeric embryos raises ethical concerns of its own. Thus it has been argued that chimeric embryos violate deep-seated moral intuitions. For example, some contend that it is "unnatural" or a usurpation of "nature" to use molecular techniques to intentionally cross human-animal boundaries in this way. Or that chimeric embryos violate human dignity by imparting human characteristics to nonhuman animals. Or that introducing human DNA into nonhuman embryos or eggs violates the integrity of nonhuman species.[1] Opponents of chimeric embryos argue that science is running ahead of our capacity for careful moral deliberation and our practical ability to appropriately regulate and oversee research that touches on such fundamental issues as what it means to be "human" or to have "moral status."[3]

PUBLIC POLICY

Public policies internationally reflect these differing views about whether research with chimeric embryos is ethically appropriate. For example, in September 2007, the U.K. Human Fertilisation and Embryo Authority (HFEA) approved in principle research with chimeric embryos. According to the HFEA decision, hybrid cytoplasmic research may go forward provided that (1) the embryos are created by inserting human genetic material into an enucleated nonhuman egg, which results in an embryo that is 99.9% human; and (2) teams proposing to carry out research with such embryos demonstrate to HFEA that the planned project is both "desirable" and "necessary."[7]

The picture in Canada is somewhat more complex.[8] The Assisted Human Reproduction Act (2004) does not specifically prohibit transplantation of human embryonic stem cells into embryonic nonhuman animals (or into nonhuman fetuses or adult animals). However, guidelines from the Canadian Institutes of Health Research (CIHR) updated most recently in 2006 *do* forbid research that involves introducing human stem cells into nonhuman embryos or fetuses (and vice versa)—pending the establishment of an appropriately constituted body to oversee such research. CIHR effectively governs all research in this area in Canada.[8]

In the United States, there is no single, national policy that explicitly addresses human-nonhuman chimera embryos, either to permit such research or to forbid it. Key policy established by President George W. Bush restricted federal funding for such research to studies carried out with stem cell lines in existence before August 9, 2001, "where the life and death decision has already been made." In June 2007, Executive Order 13435 authorized the Secretary of Health and Human services to support and fund research on alternative sources of stem cells, so long as the stem cells "are derived without creating a human embryo for research purposes or destroying, discarding, or subjecting to harm a human embryo or fetus."[9] On March 9, 2009, President Barrack Obama revoked that order with a new Executive Order, *Removing Barriers to Responsible Scientific Research Involving Human Stem Cells.*[10] Neither addresses human-nonhuman chimeric embryos as such.

In 2005 the National Academies of Science (NAS) Committee on Guidelines for Human Embryonic Stem Cell Research noted that creation of a chimera would be governed under several different federal regulations, including human subjects protections, animal research protections, and, potentially, regulations of the Food and Drug Administration, and potentially involve a variety of oversight bodies, such as institutional review boards, institutional animal care and use committees, and institutional biosafety committees.[5] The NAS itself proposed that local oversight of all research involving embryonic stem cells be carried out by a single embryonic stem cell

research oversight (ESCRO) committee. But with the exception of urging a more stringent review of research involving transfer of human embryonic stem (hES) cells into nonhuman animals the committee's recommendations do not provide specific guidance with respect to chimeric embryos. Nor have they been implemented.[5]

AMA POLICY

There is no American Medical Association policy that deals specifically with chimeric embryos. H-460.915, "Cloning and Stem Cell Research AMA," (AMA Policy Database) adopted in 2003, states the AMA's general support for cloning for research that involves adult and umbilical cord blood stem cells and the use of SCNT in biomedical research, encourages federal funding for stem cell research, and calls on the AMA to continue to monitor developments in these areas (while prohibiting cloning for reproductive purposes). (Use of cord blood stem cells is addressed in ethics policy E-2.165, "Umbilical Cord Blood Banking.")

Ethics policies on cloning for research and xenotransplantation address issues relevant to chimeric embryos. Both permit individual physicians to decide for themselves whether they will be involved in research involving SCNT or xenotransplantation. However, both adopt an essentially "precautionary" stance toward both research with or therapeutic use of embryonic stem cells and the use of nonhuman tissues for transplantation.

Opinion E-2.146, "Cloning-for-Biomedical-Research," acknowledges that "controversy arises from the necessity to destroy embryos in order to extract their stem cells for use in biomedical research. The conflict centers on the moral status of embryos, a question that divides ethical opinion and that cannot be resolved by medical science." It enjoins physicians to remember their paramount obligation to patients in deciding about participating in stem cell research or using the products of such research with patients. E-2.146 also calls for appropriate oversight at the local level and monitoring of the field and development of guidelines at the national level to ensure that only stem cell research which is "uniquely promising" is carried out.

E-2.169, "The Ethical Implications of Xenotransplantation," speaks to the ethics of transplanting into a human anything from a non-human source. The opinion calls for a number of human subjects protections, such as special provisions for informed consent relating to the unique scientific challenges of xenotransplantation, including lifelong surveillance for zoonoses or other adverse consequences, focusing primarily on patient safety and public health. However, neither the opinion nor the background analysis on which it rests it explicitly discusses other ethical values at stake in mixing human and animal cells or tissues.[11]

CONCLUSION

Chimeric embryos raise profound questions about the meaning and nature of humanity as well as questions about the nature of species boundaries, how we may ethically treat embryos, and how we should understand our moral and ethical obligations to chimeras.[8] U.S. national policy is silent in this area, neither prohibiting nor endorsing the creation of embryos using SCNT to introduce human genetic materials into nonhuman embryos or ova, while policies in other countries reach significantly different conclusions about the appropriateness of research with chimeric embryos.

Given the difficulty of the questions raised, our seeming inability yet to understand well or ability to articulate compellingly the relevance of our moral intuitions as guides for policy or practice, the lack of consensus in the scientific and ethics communities, and the absence of persuasive evidence

for likely benefit to patients from research with chimeric embryos, the Council on Ethical and Judicial Affairs believes that at this time patients and the public are not well served by such research. The Council can say, at most, that physician-scientists who contemplate research involving chimeric embryos should proceed with extreme ethical caution.

We note that at the present time, this is an area that directly affects few physicians. Further, it is one that implicates other ethical concerns surrounding medical genetics and assisted reproduction that we find need to be better explored or defined in our *Code of Medical Ethics*. As we move forward in our project to critically review and modernize the *Code of Medical Ethics* we will revisit our analyses and opinions in related areas. We will re-examine the question of the ethics of research involving chimeric embryos as we develop more comprehensive ethical analysis and guidance on medical genetics in the revised *Code*.

RECOMMENDATION

In light of the foregoing review of existing policy relevant to human-nonhuman hybrids and the anticipated review and updating of AMA ethics policy overall on issues pertaining to genetics, the Council on Ethical and Judicial Affairs recommends that Resolution 3 (A-08) not be adopted and that the remainder of this report be filed.

REFERENCES

1. Karpowicz P, Cohen CB, van der Kooy D. It is ethical to transplant human stem cells into nonhuman embryos. *Nat Med.* Apr 2004;10(4):331-335.
2. Kmietowicz Z. Public support for hybrid embryos rises with knowledge, poll shows. *BMJ.* 2007;335(7618):466-467.
3. Robert JS. The science and ethics of making part-human animals in stem cell biology. *FASEB J.* 2006;(20):838-845.
4. Kolata G. Hybrid Embryo Mixture May Offer New Source of Stem Cells for Study *New York Times.* June 4, 2002, 2008;F.
5. Committee on Guidelines for Human Embryonic Stem Cell Research NRC. *Guidelines for Human Embryonic Stem Cell Research*. National Academies Press; 2005.
6. Committee HESCRA. *2008 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research*. The National Academies Press; 2008.
7. Human Fertilisation and Embryology Authority. *Hybrids and Chimeras: A Report on the Findings of the Consultation*. October 2007. http://www.hfea.gov.uk/docs/Hybrids_Report.pdf. Accessed April 13, 2009.
8. Robert JS, Baylis F. Crossing species boundaries. *Am J Bioethics*. 2003;(3)3: 1-13.
9. HHS/NIH Plan for Implementation of Executive Order 13435: Expanding Approved Stem Cell Lines in Ethically Responsible Ways. http://stemcells.nih.gov/policy/091907eo.htm.
10. Executive Order *Removing Barriers to Responsible Scientific Research Involving Human Stem Cells* issued March 9, 2009. http://www.whitehouse.gov/the_press_office/Removing-Barriers-to-Responsible-Scientific-Research-Involving-Human-Stem-Cells/. Accessed April 14, 2009.
11. American Medical Association. Opinion 2.169, The Ethical Implications of Xenotransplantation. *Code of Medical Ethics of the American Medical Association*. 2008-2009 ed. Chicago, IL: American Medical Association; 2008.