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Opinion

Why the moratorium on human-animal chimera research should not be lifted

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The National Institutes of Health (NIH) announced its plans to lift its moratorium on funding research that involves injecting human embryonic stem cells into animal embryos, which would allow for the creation of part-human and part-animal organisms known as chimeras. The NIH allowed only one month to receive public comments in the midst of a presidential election campaign. Lifting the moratorium means that, for the first time, the federal government will begin spending taxpayer dollars on the creation and manipulation of new organisms that would blur the line between humans and animals. Interestingly, this government effort is creating an uncommon coalition between pro-life groups and animal rights activists that oppose this medical research on ethical grounds; the former seeking to ensure the welfare of human embryos and the latter seeking to protect the well-being of animals. Unlike the issue of abortion, this research is complex. Yet, it is important that the pro-life laity and clergy be adequately informed on some of the basic science and ethics that surround this research. To fully understand why this research is unethical and why the NIH is pursuing this particular research, it is important to understand the ethical tenets governing human-subject research and why secular scientists are pursuing this scientific field.

Background

In 1974 the National Research Act (NRA) was passed (National Research Act 1974). This act created the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research in response to a history of unethical medical research that was conducted in the United States. The commission created a set of required rules that govern human-subject research (NCPHS 1979). First, the commission created the rules that there must be a respect for subjects as "autonomous agents, and second, that persons with diminished autonomy are entitled to protection" (5-12). Research subjects must be offered and provided informed consent. If a subject has diminished autonomy, then his or her surrogate, typically a family member, and along with the researcher, are required to make decisions that are in the best interest of the subject. Second, there must be a minimization of harm to the subject. There should be no deliberate risk of injury or death. Third, there must be an observance of justice to the extent that the research subject should not bear the risks of the research while others benefit from risks that the subject may endure. Fourth, the law states that individuals with lower capacity for making decisions such as children, the elderly, and the developmentally disabled require special protection. Obviously, the creation of human

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embryonic stem cells requires the destruction of a human embryo. For Catholics, who understand that life begins at conception, this research is immoral. Furthermore, if human embryos are regarded as human subjects with diminished autonomy and vulnerability, then human embryonic stem-cell research is illegal from the standpoint that it violates the NRA. Yet, the fact that the government and secular institutions permit this research indicates either (a) that they are ignorant of the law or (b) that they choose to believe that the NRA does not apply to the ethics of human embryonic research because they believe that embryos do not have the status of human persons.

During the Reagan and Bush administrations between 1980 and 1992, no nontherapeutic research using in vitro fertilization (IVF)-bred human embryos and no IVF research were governmentally subsidized. An ethics advisory board was required by law to approve any such grant, and no such permission was given. However, during this same time period, there was a concerted effort among the American Fertility Society and the American College of Obstetrics and Gynecology to create the concept of the preembryo, which gave the embryo less status at the developmental stage before full uterine implantation. Led by Dr. Clifford Grobstein, a developmental biologist, and Father Richard McCormick, S.J., of the University of Notre Dame, a movement began to redefine the embryo and the beginning of life. In 1986, Dr. Grobstein and Father McCormick formed an ethics committee that reaffirmed statements removing the moral status and protection of the conceptus up to fourteen days post-fertilization.

Subsequently, Senator Edward Kennedy of Massachusetts and Representative Henry Waxman of California pushed forward and helped enact the NIH Revitalization Act of 1993. The law overturned the existing ethics advisory board created by the Reagan Administration. The new law allowed the NIH to appoint a human embryo research panel to provide advice and identify areas of acceptable embryonic research that should receive federal funding. The panel outlined the following cases in which research involving human embryos would be deemed acceptable (National Institutes of Health 1994; Irving 2000):

- The creation of human embryos as research objects
- The removal of ovaries from brain-dead women and aborted fetuses so eggs (ova) can be recovered for laboratory fertilization and manipulation
- The testing of a panoply of drugs on the developing human embryo
- The use of human embryos to create specific cell lines
- The freezing and saving of spare embryos for medical research
- The testing of new cell lines for contraception
- The fusion of animal species cells or DNA fragments with human embryos.

To date, several of these forms of research have been allowed and are currently funded by the NIH. Thus, the current pursuit of animal-human chimeras is no surprise since the NIH conceived the notion over twenty years ago. It was only a matter of time before this research would surface as new technologies emerged.

Why Are Scientists Pursuing Human-Animal Chimera Research?

Recent advances in stem-cell biology and genetic engineering, through techniques such as the recent introduction of CRISPR, now make it easy to introduce permanent genetic alterations in a cell or whole organism. There are an increasing number of researchers who are interested in growing human tissues in organs of

animals by inserting human pluripotent stem cells, such as embryonic stem cells, into animal embryos. They would subsequently monitor the development of these tissues in a developing embryo. Proponents of this research claim that it will give new insight into human development and models of human disease, which would lead to new drugs and cures for treating several disorders. Furthermore, advocates of this research claim that chimera research could lead to the production of human organs designed for patients waiting for organ transplantation. The shortage of organ donors has led proponents of this research to rationalize the need for this scientific endeavor.

However, the current NIH Guidelines on Human Stem Cell Research prohibit the introduction of human pluripotent cells into early-stage embryos of non-human primates (National Institutes of Health 2009). Also, breeding of animals containing human cells is prohibited in which such cells contribute to the development of reproductive cells such as sperm or eggs. Chimeric research not only raises ethical and moral issues but also raises concerns for the treatment and welfare of animals. For example, pigs would most likely need to serve as hosts for human-animal chimeric organs because their organ size and metabolism is the most compatible with humans. A lift on this moratorium would now allow federal funding for such research.

Does Scientific Evidence Support the Hype of Human-Animal Chimera Research?

There have been several examples to date of over-hyped research and promises offered by scientists. These include the Human Genome Project (Hall 2010), gene therapy (Harris 2005), cancer vaccines (Walker 2004), fetal tissue transplantation (Green and Fahn 2002), and embryonic stem-cell research (Brown 2011). The fundamental question is whether chimeric research will achieve all the hype that is currently being claimed by a group of scientists. I believe that there is sufficient scientific experience to predict that human-animal chimera research will not meet the hype touted by advocates of this research. First, genetic mice models, called transgenic mice, have been used in research for decades. These mice have been bred with genetic alterations in several human genes thereby manipulating them to model human disease. However, there is ample experience that genetic mice models have failed to predict drug efficacy and safety in clinical trials (Bales 2012). It is well recognized that mouse physiology is quite different than that of a human. Second, it is scientifically naïve to believe that human fetal development could be rigorously understood by monitoring fetal development in an aberrant hybrid of human and mouse. This would be no different in the knowledge gained from monitoring fetal development from a chimera between a large mammal and a small mammal. Third, there is no evidence that genetic manipulation in fetal development predicts human disease in adults. The proteins and metabolism expressed in fetal development are quite different than those expressed in adults. Human disease is the result of years of interaction between a patient's genetic profile and dietary, environmental, and behavioral modifying factors in adults. These factors cannot be controlled for in fetal development, nor can they be reproduced in a fetus. Lastly, animal-human chimera organs for transplantation would pose serious risks because of the expression of animal proteins that could elicit serious immunological reactions. Advocates claim that personalized organs could be made to order for a patient (Vogel 2015). However, the creation of an artificial organ of

sufficient size would take too long, and the cost would be prohibitive and not reimbursed under our current fragile healthcare system. Also, these organs would not escape the requirement of immunosuppressive agents, which thereby increase the risk for opportunistic infections.

What Are the Current Policies for Chimera Research in Other Countries?

French law stipulates that chimeric human embryos are forbidden (Bourret et al. 2016). However, French laws are unclear about whether human cells introduced into animal embryos are illegal. The United Kingdom allows for introduction of human embryonic cells and cells lines into animals (Bourret et al. 2016). However, it is illegal to transplant a chimeric embryo into an animal mother for further development. German law forbids combining a human embryo with animal cells, but not the introduction of human cells into an animal embryo (Bourret et al. 2016). There are no current federal U.S. laws that govern human-animal chimeric research. In 2005 the U.S. National Research Council and the Institute of Medicine recommended limits on such research, including that no human stem cells be added to primate embryos and that animal-human chimeras not be allowed to breed (Bourret et al. 2016). Japan currently limits research on human-animal chimeric embryos by not allowing the development of such embryos past a maximum of fourteen days post-fertilization and not allowing their transfer into an animal uterus (Bourret et al. 2016). Recently however, the Japanese Expert Panel on Bioethics supported the idea of creating a human–animal chimera and proposed that the Japanese research regulation permit flexibility to advance this research (Bourret et al. 2016).

What Is the Ethical Implication of Human-Chimeric Research on Animal Welfare?

The use of animals to genetically create new animal species raises serious ethical concerns for the welfare of animals participating in medical research. The USDA governs animal use in medical research through the Animal Welfare Act. The law requires that all animal research be reviewed and approved by an institutional review committee that evaluates the following requirements: (1) Animal research should not exceed a minimal amount of pain; (2) There is no alternative to using animals to achieve the end goal; and (3) The research involving any animal must be monitored by a veterinarian (Animal Welfare Act and Animal Welfare Regulations 2013). Presently, federal laws governing animal research are far more regulated and held to higher standards than for research conducted on human embryos and aborted fetal tissue. If animals are now endowed with human genetics and characteristics, then to what sort of protected status should they be entitled? Are such animals going to experience greater intelligence? Are they going to perceive pain and suffering differently if they now acquire human genetic traits? Lastly, can the same research outcome be achieved in animals without having to introduce human genetic elements? These issues need to be addressed before such research is allowed, and layers of safeguards would need to be implemented.

Is There an Alternative to Forming Human-Animal Chimeras Without Using Human Embryonic Stem Cells?

Even assuming that there was a compelling argument and sufficient safeguards to protect animal welfare to allow for

human-animal chimera research, it is still unnecessary to introduce human embryonic stem cells into animal embryos. Pluripotent stem cells can be created by means of induced pluripotent stem cells (IPSC). IPSC are created by the introduction of genetic factors that reprogram an adult cell into an embryonic-like stem cell without the need to use an embryo. IPSC have the same characteristics as an embryonic stem cell and can differentiate into all of the same specialized tissues as an embryonic stem cell. Recently a group of scientists created human-animal chimeras by combining human IPSC with pigs and cattle (Wu et al. 2017). Thus, IPSC would make human embryonic stem cells unnecessary for chimeric research.

Recommendation to Continue Moratorium on Human-Animal Chimeric Research

Based on the evidence that has been presented, it is my judgment that the moratorium on introducing human embryonic stem cells into animal embryos should remain. First, I believe it is premature to pursue human-animal chimeras until there is ample data collected utilizing large animal–small animal (mouse) chimeras. Second, it is concerning that the NIH allowed only a month of public discussion for this important and sensitive issue. This limited discussion creates a perception that the government is rushing to a decision without sufficient public discourse and evaluation and casts a bad light on the part of government. Third, there should be realistic expectations on the part of scientists and the general public that pursuing this research quite likely could not achieve the hype that advocates are currently portraying. Fourth, human-animal chimeras should not proceed until there are sufficient safeguards on the welfare of animals, and any such research must satisfy the current laws of the Animal Welfare Act. Lastly, if chimeric research is to be pursued, only human IPSC should be used and not human embryonic stem cells.

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