APPROACHING RELIGIOUS GUIDELINES FOR CHIMERA POLICYMAKING

by Stephen M. Modell

Abstract. Recent developments in the use of cow egg cells to clone human somatic cells, and the grafting by researchers at several universities of human neurons into mice, bring the notion of the chimera, a mixture of several living organisms, from myth into reality. In his article "Cross-Species Chimeras: Exploring a Possible Christian Perspective," Neville Cobbe considers the religious arguments overlying the creation of human-nonhuman chimeras. In my commentary I focus on the distinction between germline- and tissue transplant–related chimeric techniques implicit in Cobbe's essay and argue that the former poses more serious moral difficulties than the latter if the chimeric product is brought to term. The substantive view of the *imago Dei*, or image of God, serves as a scaffold by which to judge the permissibility of chimera creation using stem cell and other tissue implants. While useful for judging the rights of such artificially generated beings, I argue that specific criteria such as proportion of tissue uptake, mental capacity, and adherence with the organism's *telos* are more appropriately considered within a composite image of the living being reflecting its unique integrality. Human co-creativity with the Divine will inevitably prompt attempts to generate medically useful chimeras. Religious dialogue, combined with the categories of religious moral argument appearing in Cobbe's essay, will help to establish the outline of feasible policy guidelines addressing the complexities inherent in the creation of chimeras.

Keywords: chimeras; cloning; dialogue; ethics; gene therapy; genetics; *imago Dei* (image of God); morals; ontology; policy; religion; religion and medicine; reproduction; stem cells; transplantation; wholeness; xenotransplantation

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A new day dawned in the history of potential humankind on 11 November 1998 when a scientist at Advanced Cell Technology of Worcester, Massachusetts, slipped the nucleus of one of his cheek cells into an enucleated cow egg to yield a cluster of embryonic stem cells containing elements of two species (Wade 1998). The era of the human-nonhuman chimera, or cross-species entity, was born. The event created a ripple through time and space that erupted eight years later in Britain with a group of medical researchers applying to the Human Fertilization and Embryology Authority (HFEA) to employ the same procedure to develop stem cells for investigating and ultimately treating neurodegenerative disorders. Although the procedure was considered legal, decision making was halted while the HFEA engaged in public consultation on the controversial procedure (Coghlan 2007, 7). The very possibility of human-nonhuman chimeras, a subject of ancient Greek mythology, has prompted authors such as Neville Cobbe (2007) to contemplate the ethical and religious permissions and cautions of creating such entities.

In his timely article, Cobbe reviews the technical aspects of creating chimeras, then uses passages from the Bible as a platform for examining the spiritual-religious arguments underlying chimeric procedures. He considers chimera production using enucleated animal eggs to generate clones as a potential source for stem cells; recent experiments in generating mice with large shares of human brain tissue; and implications of using such maneuvers in closer human relatives, such as chimpanzees. These procedures elicit deep-minded questions concerning human nature in relation to the divine and human co-creativity with God. In the end, he concludes that some degree of license for beneficent experimentation is permissible under Christian morality but that careful evaluation on a case-by-case basis is needed.

Background

The timing of such an essay is appropriate given the desire of several British scientists to move ahead with projects using human-animal chimeras and their meeting this year with authorities in Australia to seek related collaborations. The number and variety of interspecies cloning and tissue-transplant experiments is mushrooming worldwide. It should be stated that countries have radically different positions on the acceptability of chimera production but that, like stem cell procedures, such knowledge exhibits the capacity to seep across national borders and attract varied interest according to the proposed application. Australia, for example, permits therapeutic cloning to generate human embryonic stem cells but has so far legislatively ruled out chimera production. Other countries display a tension of individualist and communitarian interests. The United States Human Embryo Research Panel noted the utility of chimeras combining

different strains of mice for clarifying cell lineage and elucidating molecular and physiologic processes. Chimeric fetuses containing both human and primate cells were viewed as "totally unacceptable from both a medical and ethical standpoint" (NIH 1994, 31). The U.S. President's Council on Bioethics later contended that there is nothing inherently wrong with mixing human and animal tissues in the context of therapy and preventive medicine (PCB 2004, 12). The Canadian Assisted Human Reproduction Act, on the other hand, banned certain types of chimera production, based on both specific moral arguments and more general concerns with "public welfare and human dignity" (Kopinski 2004, 1–2).

Religious Forerunners

The principle of human dignity is recognized by religious faiths far and wide. In the Vatican's "Instruction on Respect for Human Life," "human life must be absolutely respected and protected from the moment of conception" (Congregation for the Doctrine of the Faith 1987, 701). The statement representing the Vatican viewpoint is highly complicated by this line of research, because the distinction between human and nonhuman in the early chimera is blurred. Even fundamental biblical statements, such as Leviticus 19:19 cited by Cobbe ("Thou shalt not let thy cattle gender with a diverse kind: thou shalt not sow thy field with mingled seed," KJV), are unclear in their meaning when applied to chimeric research that does not involve the sexual transfer of genetic material. The proscription applied to plants in the field has been interpreted by some religious authorities to not apply to genetic engineering if the resultant plant is unable to grow and continue on its own into a fully flourishing entity, the case with many cloned cells and all stem cells (Wolff 2001, 5–6). Mosaic law allows latitude of interpretation, especially with subject matter so novel.

If the chimeric dilemma is foreshadowed in the Bible, it has sprung to real life with modern medicine. Developments like xeno (cross-species) transplantation, donor organ pigs with tissues expressing primate cell surface proteins (to avoid immune rejection), transgenic goats producing pharmaceutical compounds in their milk, and GloFish and rhesus monkeys with implanted jelly fish genes have all presaged the current chaos (Baumiller and Modell 1997, 289). Much of medical research accepts humanity's co-creativity with the divine as a working premise but gets stuck on questions of how far the co-creativity should extend. The range of applications in this new area falls along a spectrum from the clearly useful to the more expendable (uses, that is).

The rationale for consideration of primates in xenotransplants and chimera experiments is their similarity with humans at the genetic and tissue levels, though it must be conceded that for transplant organ purposes, pigs have an anatomy and physiology very similar to humans. The religious

implications of similar-species xenotransplants are significant. At the time of the baboon heart transplant into Baby Fae in 1984, Father Richard McCormick noted that in addition to the many hopes riding on the procedure, the possibility existed that members of the public might view the cross-species grafting as more profound than simply the insertion of a new heart pump. "Special concerns" might arise (McCormick 1985, 12). Further explication of this thought appeared in *Time* magazine: "Some sacred barrier between species had been broken, some principle of separateness between man and animal violated. Indeed, it is a blow to man's idea of himself to think that a piece of plastic or animal tissue may occupy the seat of the emotions and perform perfectly well" (Krauthammer 1984, 87). It should be reciprocally noted that many people also had feelings about the baboon having been made to donate its heart and that the author's comments about advocacy ethics for animal subjects have found much resonance with the public.

The heart may be the ancient postulated seat of the soul, but the blood circulates its life-giving force. Upon the death of the world's first baboon liver recipient, transplant surgeon Thomas Starzl discovered not only that a fungal infection had led to the patient's death but also that breakaway baboon liver cells had been working to help him. The migrated cells, which had settled in the patient's heart, lungs, kidneys, and lymph nodes, would have offered greater protection against immune rejection of the liver had the patient lived. Dr. Starzl's transplant patients had become the first definitive human-animal chimeras (Baumiller and Modell 1997, 290)!

There can be no doubt that both Baby Fae and Starzl's baboon organ recipients were in great need of transplants. Clearly they met the criteria for an organ recipient based on urgency. Many commentators also said that these investigational procedures were motivated by the ambition to advance science, albeit for a good cause. In investigational transplant procedures, and new genetic and reproductive techniques, chimeras included, a broader set of criteria than benefit to science should rule (Modell 1996, 235). The morality of the next step—more thoroughgoing human-simian combinations (discussed by Cobbe, but launched as a hypothetical by a French journal a century ago) through tissue transplantation or cloning—needs to be closely considered (Cobbe 2007, 606; Baumiller and Modell 1997, 291).

Chimeric procedures need an appropriate set of boundaries demanding input from fields beyond science, religion being an important contributor because it often affords the opportunity to look at the "big picture." Cobbe's article offers overall suggestions if one can just step back from the particular arguments. The first of his technical sections is titled "Animal Eggs for Human Cloning?" and the second "Animals with Human Brains?" The first deals with a procedure that alters the egg cell and the second with a tissue-transplant procedure. This division is also a natural one for gene

therapy techniques. The gulf between germline (reproductive) and somatic (bodily) cell gene therapy is widely appreciated by policymakers in a variety of disciplines. The World Council of Churches notes that for germline gene therapy (GLGT) to be successful it would require large-scale embryo experimentation and destruction, would affect the subject's descendents, and could result in discrimination against those held to be "defective" (1989, 14). The National Council of the Churches of Christ in the U.S.A. acknowledges that untoward mutations resulting from GLGT will "pass on irrevocably into future generations" (1986, 4). Both bodies cautiously endorse development of somatic cell gene therapy because it can alleviate disease without perpetuating mutational errors in future generations. Further, while Christian denominations may differ on the acceptability of therapeutic cloning to derive stem cells as opposed to reproductive cloning to pass on one's lineage, they all agree on the impermissibility of using cloning for reproductive purposes (Campbell 1997).

Meddling with the Germline

The seriousness of transgressing the reproductive ethical border is indirectly expressed by Cobbe in the arrangement of his essay. The major point is that the progeny of individuals or entities receiving transplants of liver, pancreatic, or neural cell lines will not inherit the transformations undergone by their parent, but cloned chimeras will. Religious policy statements suggest by inference that cloned chimeras should receive special attention if the possibility of future reproduction exists, with recourse to various levels of restriction. Cobbe's statement that chimeras with apparently human faculties would be denied a fundamental right if they were not allowed to reproduce (p. 619) begs the question of whether they should be created or allowed to go past the neural developmental stage to term in the first place (Streiffer 2005, 365) and is based on an ethic of individual autonomy that ignores public welfare and the interests of future generations, collectivities appreciated by the various faiths.

Level of risk is also mentioned in religious genetics-policy statements, particularly in sections commenting on gene therapy experimentation. Nuclear transfer from a human somatic cell to an enucleated animal egg introduces three potential sources of genetic error: (1) transformation of the donor haploid genome into a diploid genome, resulting in unpaired recessive genetic mutations; (2) methylation errors from the resetting of the donor nucleus's time clock by the recipient egg cell's cytoplasm; and (3) combination of donor nucleus with recipient cytoplasm, creating a mitochondrial mismatch (the latter two possibilities recognized by the author).

Let us concentrate on the third problem, mitochondrial mismatch. A species' mitochondrial DNA is evolved to provide the correct amount of

metabolic energy for the cell's operation, and if the introduced nucleus demands protein production at a rate unsustainable by the recipient cell's mitochondria the result may be deleterious for the entire organism. Research on children born from a related procedure, ooplasmic transplantation, has shown that newly introduced mitochondria can be sustained in the progeny's cells for more than a year (Barritt et al. 2001, 514–15). That is, if through cloning two species have been successfully merged into a single chimera, a mismatch in the resultant cells' energy-producing machinery will be sustained and perpetuated in the entity as it develops. Such mismatches may not be innocuous. One cause in animal models of Parkinson's disease, a neurodegenerative disorder earmarked as a target for chimera research, results from a mutation in the *PINK1* gene affecting mitochondrial function (Park et al. 2006, 1157, 1160).

These risks for a human-nonhuman chimera would become manifest once it was brought to term. Religious authorities who accept the use of cloning for therapeutic purposes might eschew chimera production if it involves human cells and can or is allowed to lead to a term delivery.

Tissue Transplanting to Form a Chimera

Side by side on the desk are two mouse articles, one showing a mouse with a human ear sticking out of its back (Toufexis 1995, 60) and the other, cited by Cobbe, picturing "neurospheres" in the brains of mice formed by the insertion of human fetal neural stem cells (Scott 2006, 489). One addition is visible and full size; the other is hidden and relating to an organ—the human brain—in miniature. The case of noncloned chimeras, entities that have achieved a hybrid status by virtue of tissue insertion during their development, presents a challenge in balancing experimental risks and a factor former President's Council on Bioethics chairman Leon Kass calls "the wisdom of repugnance" with the potential for human good (1997, 19–20). As these entities contain human elements, they are and should continue to be scrutinized by animal research oversight committees that share overlapping concerns with human institutional review boards (IRBs).

Baby Fae's transplant procedure underwent intense ethical scrutiny by multiple academic departments, administrative committees, and Loma Linda University's IRB, the latter composed of members of the Seventh-Day Adventist Church. IRBs generally contain at least one theologically trained member. Assuming an IRB with theologic input were to examine the chimeric tissue insertion experiments such as Stanford University researchers' ongoing colonizations of murine brains with human neural cells, what sorts of criteria would they consider as filters for research?

First would come a standard set of ethical criteria, such as individual risk, group benefit, and existence of alternative procedures. When medical researchers surgically implanted human fetal nerve cells into the

putamenal area of the brains of patients with severe Parkinson's disease, they were astonished to find that the cells grew too abundantly in 15 percent of the recipients (Freed et al. 2001, 710). The resultant writhing movements were quite aberrant and largely uncontrollable. It is possible that admixture of tissues from different species would overcome such problems by allowing early developmental coordination of interconnecting cells. Perhaps side-effect problems could be minimized by the early developmental timing of the experiments.

Chimeric experiments would also be gauged by their potential to lead to eventual therapeutic benefits for affected populations. Many of the experiments seem elemental, mostly seeking to either prove or track tissue migration, but it is possible that some will lead to medical discoveries down the road. In the interim, the media will pick up on the experiments. The perceived acceptability of the experiments by the public is heavily influenced by media reporting, which needs to be handled very carefully. When news about Dolly the cloned sheep hit the headlines, one Christian ethicist was reported in *Time* to have remarked, "The people doing this ought to contemplate splitting themselves in half and see how they like it" (Hopkins 1998, 9).

The existence of less risky alternative procedures is always a consideration. By way of analogy, many medical ethicists argue that gene therapy trials should not be conducted when preimplantation genetic diagnosis (PGD) could alternatively be used to bypass a genetic condition at the four- to eight-cell stage. Even PGD is considered ethically questionable for late-onset conditions. The Jackson Laboratory currently makes available genetic knockout mice with intentionally defective genes for research on Alzheimer's disease, Parkinson's disease, and a variety of carcinomas (Jackson Laboratory 2007). The United States National Human Genome Research Institute is itself engaged in a Knockout Mouse Project to create a vast collection of mice with a defect for every gene in the mouse genome (NHGRI 2005). Given the existence of non-chimeric mouse models for studying neurodegenerative disorders, the reasons for creating human-nonhuman chimeras to investigate such conditions would need to come under close scrutiny.

Suppose that chimera production passes standard review-committee criteria and poses unique opportunities to study the genesis of conditions afflicting a major portion of the population. With this realization would come plans for a vast variety of experiments, invoking the need for deeper moral reasoning (Robert 2006, 840). It is likely that standard ethical criteria will have only limited pertinence and that ethicists would need to explore religious considerations for matters dealing with human and animal identity and essence, as Cobbe has done. As he suggests, the analysis might initially boil down to "what proportion of human cells or which mental capacities in a chimera are morally significant" (Cobbe 2007, 616;

Streiffer 2005, 365). Cobbe's wrestling with DNA ratios (nuclear versus mitochondrial) shows the difficulty of classifying cells of different species based on quantitative figures, but this type of task is not unknown to science. Gene therapy for severe combined immune deficiency in the popularized Ashanti de Silva case was considered successful when her immune function was corrected and 20 to 25 percent of her T cells contained the gene introduced by retroviral transfer (Roberts 2002, 12). Therapeutic efficacy for hemophilia B is considered a success when clotting factor IX levels greater than 1 percent are achieved (gene therapy trials with one patient resulted in levels of 1.6 percent) (Stephenson 2000, 590).

If a scale for taxonomic classification exists, the difficulty in considering whether or not a chimera is substantially human originates with dependence on singular scales of judgment. Counterarguments can always be made that a given ratio of nuclear to mitochondrial DNA, size of brain lobes or density of cerebral folds, degree of spread of chimeric liver cells, measure of intelligence, or obedience to one's *telos* is or is not sufficient to classify the chimera in question as human. Any given scale will of necessity display overlap in classification (true of Linnaeus's taxonomy as well). Cobbe's arguments display this perplexity.

A human being, though, is more than the entirety of a gene sequence or the sum total of anatomic parts. The operating genome, as opposed to a linear gene sequence, is far from being understood and may never thoroughly be. The entire human being is a dynamic composite. Echoing Pope John Paul II, "The person is who he/she is, not because of what the person can do, in terms of mental or physical capacities or actions . . . but because of the very constitution of that which we know to be a distinctly human life" (Dailey and Leonard 2006, 114; John Paul II 1993, 50.1). This view is also Aristotelian, expressing that a living being as a whole is a new actuality, not to be found in any of its parts (Carroll 1994, 51). Mental and physical capacities, the latter being adapted to external needs and physiologic, are virtues of an integrated living entity.

The substantive *imago Dei* (image of God) view of the human being applies in this instance. God represents ultimate unification. The human being's constitution is a likeness of God, or a gestalt of God's unity. There are hints of this colinearity in Cobbe's references to the humanness of a single cell and the "wholesome future" of humanity as co-creator with God. The point of emphasizing the unity is not to make the concept of the human being so abstract that the problem of analyzing it will be washed away but to reemphasize that a single measure of achieved humanness is insufficient. In fact, any measure will fall short, but a practical measure will need to be a composite. Likewise, if one thumbs through journals describing humanity's divergence from its prehistoric forebears, one comes up with a variety of criteria: changes in brain size, the development of speech organs and ability, handiness with tools, and mobility. Policymaking

bodies and review committees will realistically need to consider a variety of measures to assess the ethics of an experiment leading to a human-nonhuman chimera. To constrain the measures to the strictly quantitative would be degrading. A committee would need to balance empirical factors with value judgments in an evidentiary way (Wilfond and Thomson 2000, 73).

From abstract philosophical-religious notions follow more hardened considerations, such as the attempt to stipulate proportionalities of tissues, or indications of morphologic closeness or similarity, that might indicate humanness and creational boundaries to be heeded. Perhaps the outcome, whether projected or actual, could be viewed along a normal curve. Chimeras on one end would simply be animals. Those in the middle (considering multiple characteristics) would be ambiguously human, deserving some rights but not others (embryonic development to the neural stage, birth, reproduction, and a full life being the main rights at stake); those on the other end would be more human than not. The question of whether God's image is mirrored in artificially created entities such as chimeras is philosophically challenging and difficult to resolve. Some religious authorities hold that God's image is also reflected in one's fellow man and woman; thus the command to treat one's neighbor as oneself (Benedict XVI 2005; Brachtendorf 2000, 5). In this sense, chimeras at the far end and in the midsection of the curve would be a dim reflection, or a distorted image, of God's vision for humanity. Chimeras on the near end would be viewed and treated as close to human.

To put the matter in religious perspective, the example of a mouse with a surgically implanted ear might fit onto the far end of the curve, and the case of the mouse with pockets of human neural tissue would be somewhere in the middle. The Roman Catholic tenet that personhood exists from conception onward is entirely relevant, but it is questionable whether many of the chimeras being described meet the criterion of humanhood. As the author points out, animals, too, have rights, but these rights need to be considered, if medical research is the topic, under a different umbrella, such as advocacy ethics.

Ethics of the Near Right

On the near right of the curve lie those chimeras bearing a significant resemblance by various standards to humans. Cobbe cites the example of primates receiving transplanted human cells (2007, 608). The converse would also apply: humans receiving transplanted closely related animal cells. Surgical procedures involving transplant of baboon hearts and livers and porcine heart valves into human recipients attracted considerable ethical attention, but in the end the urgency of these cases and the potential to help others in need proved overriding. Situations in which primates in the fetal state receive human stem cells, or in which humans in the fetal state receive animal, possibly primate, stem cells (analogous to in-utero gene

therapy for a clinically severe condition, but avoiding reproductive risks) are perplexing. More profound changes performed earlier still, at the embryonic stage, might fall under the same sort of ethical analysis as cloned chimeras.

In a 1994 paper dealing with the creation of human clones through blastomere (postconception) separation of cells (to be distinguished from the more recent expeditious but risky somatic cell nuclear transfer procedure) ethicist John Robertson proposed that the later born child, far from undergoing an identity crisis due to lack of uniqueness, would probably harbor feelings of closeness with the earlier, mirrored child—like relations between natural twins (Robertson 1994, 11). Apparently the thought of being twinned is not altogether dejecting, then. This angle has a religious side to it. A child born as an exact or proximal copy of another individual would be viewed as a reflection of the original person. A child born as a more patchy copy of another individual, however, would be viewed as a distortion of the original. In a less physical sense, one might be viewed as a reflection of the *imago Dei* and the other as a distortion of the divine image or plan. The latter case, to me, resembles the relationship between Isaac and Ishmael in the Old Testament. Abraham kept Isaac, born of Sarah, as his rightful heir, whereas Ishmael, born of Hagar, was cast off. There also may be psychological reasons for rejecting a being grossly similar to yet relationally distant from one's makeup, but the religious rationale does partly explain the caution that would surround the creation of a human-primate chimera that did not closely resemble a human being. Such a semihuman entity might be rejected or excluded. The precautionary principle mentioned by Cobbe would be appropriate for this branch of experimentation. Conversely, a human with a potentially fatal or severely debilitating genetic condition corrected by the addition of nonhuman tissue at an intermediate developmental stage would be viewed as human and not likely shunned. Chimera production would have achieved its intended therapeutic end.

One concern of reliably developing chimera procedures to a point where they achieve clinical efficacy is that they might be misapplied. The author paraphrases Thomas Berg: "could the creation of some human-nonhuman chimeras be 'at the service of the human person . . . ?'" (Cobbe 2007, 617) It must be understood that the purpose of the experiments discussed is to ameliorate disease, not to enhance some individuals' traits or characteristics, degrade others' status, or subjugate one being to another. The purpose is medical, not social. The complications of going beyond this point have been keenly portrayed in the popular literature (for example, Aldous Huxley's *Brave New World* [1989]) and incisively discussed in the bioethics literature. Religious-policy statements uniformly oppose the use of genetic and reproductive technologies for eugenic purposes or in ways that will lead to stigmatization and discrimination of individuals or groups.

Likewise, chimeras should not be followed through to term just to satisfy scientific curiosity or to try to determine whether they are more human or animal in capacity. Researchers should demonstrate substantial medical need and purpose (Robert 2006, 844). The personal integrity of all beings—that they are not just lumps of experimental material—is to be recognized.

Conclusion

Cobbe's essay raises issues that need to be explored. He treats biblical wisdom in a somewhat pedantic way, but I would argue that the stiff point-counterpoint is needed as a platform for further moral and intellectual inquiry. His suggestion that research protocols in this area should be examined on a case-by-case basis is well taken given the inherent moral complexity of the procedures. The U.S. National Academy of Sciences has proposed Embryonic Stem Cell Research Oversight (ESCRO) committees to perform institutional review (Robert 2006, 843). Recombinant DNA advisory committees and gene therapy commissions offer precedent in a closely related area.

Much can be gained also by applying religious precedent to the chimera scenarios he discusses. Religion can perform the role of establishing general boundaries in a way that self-interested science cannot.

There will, of course, be lingering areas for moral deliberation:

- the overall permissibility of creating chimeric clones to yield stem cells
- the point in utero beyond usefulness for stem cell generation at which human-nonhuman chimeric clones should ethically be terminated
- the moral rights of stem cell and tissue implant–generated (versus generating) chimeras whose ontology lies midway between animals and humans
- the impermissibility of some shades of human-simian chimera production

As with genetic technologies, religiously minded citizens and scholars must resist the temptation to proclaim sweeping, absolutist prohibitions of chimeric procedures. Areas of concern demand input of both experts and the public, with dialogue admitting secular and religious values (Modell 2007, 179–80).

The importance of dialogue using human-nonhuman chimeras as examples is highlighted by humanity's continued reshaping of its essential nature along the smallest (genetic) and largest (global) dimensions. Human engineering proceeds spontaneously because of our co-creative nature with the Divine, thus calling for a spark of divine wisdom.

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