Is It Ethical to Generate Human-Animal Chimeras?

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In 2003, *The American Journal of Bioethics* posted a cadre of responses to a target article discussing the ethics of human-animal chimeras.[1] I concur with the prominently expressed opinion that, should this sort of developmental manipulation generate an end product that is human or quasi-animal, its breach of the animal-human species boundary would be unethical. I take exception, however, to the flawed

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The query posed in the title of this article is a mixed question. Mortimer Adler argues that adequately answering a question of this kind requires a collaborative meeting of minds between scientists and philosophers. See *The Difference of Man and the Difference It Makes* (Bronx, NY: Fordham University Press, 1993), based on Adler's 1966 Encyclopaedia Britannica Lectures and first published in 1967. Ideally, this collaborative effort should be a case-by-case discussion where, *antecedent to* the actual generation of the chimera or hybrid, the researchers describe what would be involved in the generation of their prospective chimeric/hybrid entity and predict, as best they can, the biological nature of the resultant entity. Philosophers, for their part, should aid in evaluating not only the essential nature of the chimera/hybrid, but also the ethical significance of producing such an entity. The goal of this interdisciplinary exchange should be to equip researchers to decide whether what they intend to generate ought to be generated. In deliberations *subsequent to* completed research, such as the deliberations conducted here, the goal is to offer sound philosophical guidelines to assist researchers in deciding whether they ought to continue to generate chimeras/hybrids like those produced to date.

[1] Jason Scott Robert and Françoise Baylis, "Crossing Species Boundaries," *The American Journal of Bioethics* 3.3 (Summer 2003): 1–13. The term *chimera* is a reference to the mythical monster—part lion, part goat, and part dragon—that the Greek hero Bellerophon slew as he rode on the magical horse Pegasus. The following poem by Titus Lucretius Carus (50 B.C.) captures the fear and fascination that ancient Greeks had for such chimeric animals: "But still't must not be thought that in all ways / All things can be conjoined; for then wouldest view / Portents begot about thee every side; / Hulks of mankind half brute astarting up.… / And Nature along the all-producing earth / Feeding those dire

method by which various authors have argued this position.[2] By failing to demonstrate that the species boundary between animals and humans is real, the *American Journal of Bioethics* essays were unconvincing in their conclusion that crossing that barrier would be ethically dubious.[3]

Chimaeras breathing flame / From hideous jaws—Of which 'tis simple fact / That none have been begot." The poem is quoted in Phillip Karpowicz, Cynthia B. Cohen, and Derek van der Kooy, "Developing Human-Nonhuman Chimeras in Human Stem Cell Research: Ethical Issues and Boundaries," *Kennedy Institute of Ethics Journal* 15.2 (June 2005): 107. For definitions of human-animal chimeras and hybrids relevant to the scientific assays examined here, see Part III of this article.

[2] A recent report in *Science*, which discussed the moral issues involved in the grafting of human neural stem cells into nonhuman primates (by a panel of twenty-two primatologists, stem cell researchers, lawyers, and philosophers), seems to highlight the flawed methods of argument being used regarding this issue, and the ethical morass involved. Mark Greene et al., "Moral Issues of Human-Non-Human Primate Neural Grafting," *Science* 309.5733 (July 15, 2005): 385–386. The report is striking in its lack of consensus on just about every issue raised. A popular science magazine described the *Science* article this way: "Scientists don't know how their monkeying around might alter the intelligence and emotions of animals. The scientists admit they don't even know what really separates humans from our closest relatives, morally speaking, or how to measure any cognitive changes they might induce in an ape, monkey or other non-human primate.... [One *Science* author stated], 'cell biologists and neurologists couldn't specify limits on what implanted human cells might do, and the primatologists explained that gaps in our knowledge of normal non-human primate abilities make it difficult to detect changes. And there's no philosophical consensus on the moral significance of changes in abilities if we could detect them.'" Robert Roy Britt, "Moral Debate: Procedure Risks Making Monkeys More Humanlike," *Live Science* (July 14, 2005), http://www.livescience.com/animalworld/050714_monkeys_humans.html. Interestingly, the *Science* panelists expressed a principal fear of unintentionally altering an animal's normal cognitive capacity so that it caused suffering in the animal.

[3] This can be illustrated by four examples from *The American Journal of Bioethics*: (1) In "Defining Chimeras … and Chimeric Concerns" (17–20), Henry T. Greely never explains why people might be less concerned over "moving nonhuman parts into human beings" and more concerned over the reverse, "moving human 'parts' into nonhuman beings." Nor does he distinguish the basis for acceptance of the *former* from the basis for acceptance of moving human parts into nonhuman beings when, for example, "the result was a cell making human proteins for human medical use." In other words, he never defines how plants and animals differ from humans, so that we can judge whether public approbation or rejection of different forms of chimeras is based on something other than mere arbitrariness, or on a utilitarian, consequentialist, or emotivist ethics. (2) In "In Defense of Stem Cell Chimeras: A Response to 'Crossing Species Boundaries'" (W17–W19), Phillip Karpowicz comes closer to recognizing the idea of a radical difference between animals and humans when he argues that chimeras would be morally problematic only if they possessed functions that were necessarily associated with moral worth. But he fails to explain what those moral functions are and precisely why the morality of generating chimeras turns on whether the chimeric animal has the capacity for those moral functions. (3) In "A Scientist Crossing a Boundary: A Step into the Bioethical Issues Surrounding Stem Cell Research" (W15–W16), Nao R. Kobayashi weighs in by agreeing with Robert and Baylis that it is presumptuous to debate the morality of "crossing" species barriers when "there is no consensus among scientists about what *species in-*

Here, in an alternative approach, I appeal to the common-sense realism of Mortimer Adler's position on the specific difference between animals and humans.[4] I define the kind of difference that grounds the animal-human species boundary, identify the practical consequences that follow from this specific difference, translate these repercussions into ethical guidelines relevant to the production of human-animal chimeras and hybrids, and judge selected experiments by these principled criteria.

I. The Species Boundary between Animals and Humans

To argue his case, Adler turns first to science and to two of its widely held canons regarding the kind of difference that exists between animals and humans. The first, postulated by paleoanthropologists and evolutionary biologists, concludes that human life is in phylogenetic continuity with all other life forms. Accordingly, animals and humans are not different kinds of life forms but only different degrees along a single continuum of life.

The second canon is a consensus of behavioral scientists. The results of their empirical investigations demonstrate that human beings uniquely exhibit the twin behaviors of propositional language and the ability to mentally transcend the perceived present.[5] Animals, on the other hand, evidence only signatory cries and gestures, and are thus confined to the perceptual present of their immediate environ-

tegrity might mean." Kobayashi seems to be calling for a practical definition of a species boundary, since he argues that without one, scientists will have no way of knowing when they have created novel "human-animal beings." But then, in a bit of circular reasoning, the author—without a definition of a species boundary—concludes that when human-animal chimeras are "confined within the laboratory setting" and "benefit human beings" they, like any other animal, "do not share membership in human society." (4) In "Chimeras and 'Human Dignity'" (W6–W8), Josephine Johnston and Christopher Eliot make a case for judging the morality of chimeras on the basis of whether the chimeras represent an affront to human dignity. But failing to adequately ground human dignity in the difference of human nature, the authors fail to show cogently why defending dignity is of the essence in an ethical evaluation of human-animal chimeras.

[4] The inspiration for Parts I and II of this article is Adler's book *The Difference of Man and the Difference It Makes*. My presentation here is a synthesis of seminal ideas in Adler's book and does not, therefore, cite exact pages of the book. In short, the ideas I present are *passim*, that is, they appear throughout the book.

[5] Wolfgang Enard et al. have studied the *FOXP2* gene, the first gene found to be "relevant to the human ability to develop language." After sequencing the complementary DNAs that encode the FOXP2 protein in the chimpanzee, gorilla, orangutan, rhesus macaque, and mouse and then comparing them with the human complementary DNA, they concluded that the human *FOXP2* gene contains "changes in amino-acid coding and a pattern of nucleotide polymorphism, which strongly suggest that this gene has been the target of selection during recent human evolution." It is interesting that, although these investigators are not behavioral scientists, they acknowledge the uniqueness of human language. The opening statement of their abstract reads, "Language is a uniquely human trait likely to have been a prerequisite for the development of human culture." Wolfgang Enard et al., "Molecular Evolution of *FOXP2*, a Gene Involved in Speech and Language," *Nature* 418.6900 (August 22, 2002): 869–872.

ment. Furthermore, behavioralists infer that the power which grounds a human being's singular use of an abstract language is its tandem ability to think conceptually.

Since the consensus among these behavioralists acknowledges a behavior consistently found in humans but altogether lacking in animals, the investigators logically concede that, by virtue of this unique behavior, humans differ *in kind* from animals. They are quick to add, however, that this singular human behavior signifies only a *superficial* difference of kind, a difference which should be understood as one of degree.[6] In other words, comparative behaviorists argue that the same psychological processes and material factors that account for animal language also account for human language, only to a greater degree. Thus, humans communicate differently than animals merely by dint of possessing larger and more physiologically complex brains than those of animals.

Adler astutely unpacks the significance of the scientific conclusion that humans are the only linguistic/conceptualizing animals. He focuses on the uniqueness of human language as his point of departure, since its veracity can be proved philosophically, that is, by appeal to common human experience. Inspired by this dual verification, Adler asks: What is the psychic meaning behind the linguistic behavior which both science and philosophy concur is unique to humans?

In the first place, the ability to communicate through propositional language is the ability to name things and to utter sentences. To be able to utter sentences, Adler explains, is evidence of the capacity to connect name-words (nouns, adjectives, and verbs) by means of conjunctions, prepositions, and articles to form meaningful statements. Second, the psychological power behind the unique human ability to make meaningful statements about objects of perception is conceptual thought. For to name things and make judgments and inferences about those things is to engage in conceptual thinking: it is the mental process of abstracting the universal *quidditas,* or essential nature, of the objects of perception (whether they be concrete singulars, finite beings, or instinctual goals). To speak a human language or to freely pursue happiness as the goal of life is inextricably dependent on the power of abstract thought, the power to conceive the meaning of the world and life's goal, respectively. In using a propositional language and freely pursuing a conception of happiness as the end of life, the human being transcends the temporal, spatial, and volitional constraints of the perceptual or material present.

To contend that this unique capacity of propositional language—with its direct link to conceptual thought and human freedom—represents only a superficial difference in kind between animals and humans is, as Adler substantiates, untenable. To do so would be to insist that material factors such as the brain and its physiological processes can generate the immaterial activities of human conceptual thought and freedom of choice. But simple logic dictates that the perfection of effects can never exceed that of their cause. (That is, there cannot be an effect greater than its cause; conceptual thought exceeds that which can be produced by a material brain.) Therefore, since linguistic conceptual thought and free choice exceed the essential perfection of the material human brain and its sensate appendages, the behaviorist argument for the superficial difference of humans does not stand.

[6] Adler, *Difference of Man*, 122.

On the other hand, Adler admits it is perfectly reasonable to conclude that, insofar as human neurophysiological processes generate perceptual images from the particulars of sense data, the sense data provide the requisite material images for the formulation of concepts or ideas. The brain and its sensory appendages are thus the *necessary*, though not the *sufficient*, instruments of conceptual thought.[7]

Thus, to sufficiently account for the psychological process of conceptual thinking, Adler insists on the need to posit an *immaterial* cause. Adequately explaining conceptual thought demands that we attribute to the human being an immaterial causative factor, variably called the human intellect, reason, or intellectuality. Only an immaterial faculty like the intellect adequately explains the singular capacity of human beings to come to know the world around them by transcending the materiality and temporality of the perceptual present.

Adler underlines the point of convergence in his line of argumentation: to identify immaterial as well as material causative factors in the human being is also to identify the kind of difference that distinguishes human beings from animals. Whereas animals are completely defined by material forces, human beings are completely understood only if we appeal to *both* their material and immaterial dimensions.

In sum, humans differ from all other animals not superficially or by degree, but radically. Hence, even chimpanzees, members of the species *Pan troglodytes*, although closest to humans in evolutionary terms, are a radically different form of life from humans, members of the species *Homo sapiens*. Stated differently, given the unique human capacity for propositional language, with its direct links to both the capacity for conceptual thought and the immaterial causative power of the intellect, the human species, insofar as it cannot be sufficiently explained merely by material causes (such as the human brain and its sensory appendages), is discontinuous from all other species.

II. Practical Consequences

Adler's conclusion about human nature propels him logically toward fundamental socio-ethical considerations. The radical difference between human and animal natures, the real boundary between the human species and any other animal species, is precisely what informs the radically different ways we think about and treat human beings and animals.

[7] It is interesting that Adler's well-argued assertion—that there is no such thing as innate knowledge, since the spiritual human intelligence depends on the brain and the senses for information—is denied by both materialists and idealists. Also, Adler's point about the necessity but insufficiency of the brain for human intellectuality also raises the question of what the organ of central control is, *before* the presence of the developed brain. As Benedict Ashley, O.P., and Albert Moraczewski, O.P. argue, the primitive streak is the fourteen-day-old embryonic precursor to the brain. And, ultimately, in the zygotic human being, the nuclear DNA of the single cell contains all the information and power to direct the development of the brain in the service of our spiritual intelligence. "Cloning, Aquinas, and the Embryonic Person," *National Catholic Bioethics Quarterly* 1.2 (Summer 2001): 189–201.

Personhood. Humans, with their faculty of immaterial intellectuality, are moral beings or persons. While rooted in the natural world, the human being sounds through (*personare*) his or her body, thereby transcending his materiality.

In contradistinction, animals are totally defined by their materiality and circumscribed by the temporal, spatial, and determinative constraints of their sensate knowledge and behavior. They are a part of the objective world of things, not the subjective world of persons.

Self-Determination. Human beings, by virtue of their intellectuality, are emancipated from the determinative forces of basic instinctual drives toward food, sex, and drink. As a relatively free agent, then, the human person has the power to choose whether the satisfaction or denial of these instinctual goals—or even the renunciation of them for spiritual ends—is appropriate. Even more comprehensively, the human being has the power to conceive happiness as the ultimate goal of life, to consciously keep that end before his mind's eye, and to realize that goal by freely intending concrete human goods in his actions. Thus, in their free choices, human beings paint a moral portrait of themselves and, with relative emancipation from material constraints, move freely toward or away from happiness, the ultimate meaning of their existence.

Animals, by virtue of their total materiality, are limited by the physicality of perceptual knowledge and the determinative character of instinctual drives. No empirical evidence evinces the capacity in animals to transcend instinctual goals. Inferentially, then, we also conclude that an animal could neither conceive nor freely pursue a metaphysical, ultimate goal.

Dignity. Human beings, by virtue of their subjectivity, possess intrinsic dignity. As a subject, a human being is to be loved as an end in himself, never used as a mere means to someone else's end.

As part of the objective world, animals are not ends in themselves, but means to extrinsic human ends. Therefore, although the ontological worth of animals is inherent—animals have worth by virtue of being and existing—their principle worth comes from the fact that they have played a part in the historical development of the human species. Because of this, they are important instruments of human flourishing, providing food, clothing, and companionship to humans. Even more importantly, they provide us with objects of scientific study and contemplation through which we come to understand and appreciate our species more fully.

Rights. Human beings—embodied persons who are dignified by their freedom and intelligence—possess inherent rights, natural rights that are theirs by virtue of their being human. Since animals are not moral beings, they cannot possess inherent rights. It is good to note that, although Peter Singer has attributed rights to animals because they can feel pain, he fails to recognize that it is conscious intelligence and free will, not sensory consciousness, which forms the basis of human rights. Through their intelligent free behavior, human persons seek a common good that transcends the only goods that animals can attain—physical health and propagation of their species.

As the subject of rights, every human being has the corresponding responsibility to exercise those rights justly, that is, in ways that consistently honor the rights of other persons. Humans also have the responsibility to use animals, plants, and inani-

mate things in humane and intelligent ways. Animals, on the other hand, since they exercise no rights, have no responsibilities.

Equality. Accidental differences of race, gender, religion, developmental maturity, and acquired abilities notwithstanding, one human being is essentially equal to every other and shares equally in basic human rights. Even though human beings may not always treat one another in accord with this equality, a basic ontological equality of all humans is generally acknowledged.

Among animals, however, equality of this kind is nonexistent, and animals do not acknowledge an inner equality between themselves. Interspecifically, one kind of animal often preys on another. Even intraspecifically, one chimpanzee might be stronger, larger, or more aggressive than another, prompting the former to dominate, stalk, and perhaps even kill the latter, without remorse.[8]

III. Guidelines for the Evaluation of Human-Animal Chimeras and Hybrids

Since the capacity for conceptual thought is what sets human beings apart from animals, and since the human brain is the necessary (though not sufficient) physiological instrument for conceptual thinking (humans do not think with their brain, but cannot think without it), the moral evaluation of any chimeric or hybrid experiment turns on whether the experiment results in the production of a human-animal chimera or hybrid with a human brain or its primordia.[9] From a materialist perspective (the human brain is all that a human being needs for conceptual thought), the presence of a human brain would sufficiently define the human-animal chimera or hybrid as a member of the human species; from the realist position discussed above (the human brain is the necessary but not sufficient instrument of conceptual thought), the presence of a human brain is not sufficient requisite for humanhood. From the realist position, a chimera with a human brain would be able to think conceptually (become a rational animal, a member of the human species) only if God transformed it into a new kind of being by introducing the principle of rationality, a human soul. From either philosophical perspective, then, the presence of the human brain or its primordia defines a particular organism as a member of the human species—either necessarily or sufficiently. Hence, the following guidelines for evaluating the production of human-animal chimeras and hybrids are relevant.

In what follows, the term *human-animal chimera* designates an organism consisting of *a mixture of the cell types* of both originating species (animal and human) throughout some or all of its organs or tissues (a condition sometimes described as

[8] See Richard Wrangham and Dale Peterson, *Demonic Males: Apes and the Origins of Human Violence* (Boston: Mariner Books, 1997).

[9] The human brain's primordia are those early embryonic precursors that act as the organ of central control before the formation of the primitive streak; i.e., the nuclear DNA of the single-cell zygote, whose guiding developmental power is passed on in the DNA of a dominant group of cells in the morula, which develops into the inner cell mass (ICM) at the blastocyst stage.

cellular or tissue mosaicism). Here I will focus on human-animal chimeras produced by the transfer or fusion of human material into an animal, not the reverse. The three chimeric experiments I evaluate were carried out at different stages of the host animal's development: fetal, neonatal, and embryonic, respectively.

The term *human-animal hybrid* refers to an organism whose *every cell* contains a mixture of genetic material from both originating species.[10] The hybrid experiment I evaluate below is an embryonic hybrid produced by the fusion of human and animal material through nuclear transfer or cloning.

The production of a *human-animal chimera* would be ethical if :

A. The goal of the chimeric experiment promotes human health and well-being.

B. Researchers obtain informed consent for the donated human genetic material, and the material is obtained from licit sources.

C. Researchers honor all appropriate guidelines defining animal welfare.

D. The following guidelines are observed in experiments that generate *human-animal chimeric embryos* (mixed-species embryos).[11] These guidelines are intended to prevent two kinds of dangers: one to the human individual (by producing a chimera that seems to be an animal but is capable of abstract thought *or* by producing an embryonic human being [in vitro] from the human germ cells of male and female animal chimeras), and the other to the human species (by producing a chimera capable of passing its human genetic material, including any capacity for abstract thought, to its offspring):[12]

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[10] Definitions of *chimera* and *hybrid* were found in numerous sources. Dashka Slater's explanation was the most helpful: "HumouseTM," *Legal Affairs* (November/December 2002), http://www.legalaffairs.org/issues/November-December-2002/feature_slater_novdec2002.html.

[11] Phillip Karpowicz, Cynthia B. Cohen, and Derek van der Kooy, "It Is Ethical to Transplant Human Stem Cells into Nonhuman Embryos," *Nature Medicine* 10.4 (April 2004): 334.

[12] It appears likely that guidelines set forth by Karpowicz, Cohen, and van der Kooy, some of which are repeated officially in the National Academies Press's *Guidelines for Human Embryonic Stem Cell Research*, are coming from a materialist, and therefore simplistic, view of human intelligence. See ibid., 334, and Committee on Guidelines for Human Embryonic Stem Cell Research, *Guidelines for Human Embryonic Stem Cell Research* (Washington, DC: National Academies Press, 2005). In their fear that human-primate chimeras may be humanized—that is, may possess human brains—Karpowicz, Cohen, and van der Kooy are admitting that primate body plus human brain would produce a rational primate. Their philosophical position—that the human brain and its central nervous system is the *sufficient* instrument for human intelligence—demonstrates rejection, or ignorance, of the psychological difference between sensitive animal intelligence and abstract human intelligence and of the notion that human conceptual thought is a nonmaterial activity necessitating a nonmaterial (spiritual) principle or cause. But their fears of humanization in human-primate chimeras or hybrids are well grounded since, as I discuss below (note 17), the hylomorphic theory demonstrates that human ensoulment, or apt matter for rationality, is dependent on a material body that possesses at least the capacity for developing a human brain.

- Limit the number of human cells that are transferred to an animal host at its embryonic stage to the fewest number needed to reach the research goals.[13]
- Avoid the transfer of human pluripotent stem cells or non-embryonic stem cells, especially neural stem cells, into an embryonic or fetal chimpanzee, gorilla, or orangutan—animal hosts which, from a structural and functional perspective (especially that of the brain), are closely related to the human being.[14]
- Avoid insertion of human stem cells into the host embryonic/fetal animal until after its period of gonadal development, so that the animal's germ cells do not develop to incorporate human DNA and, in the event of any host animal producing progeny, the human genetic contribution is not passed on.[15]

[13] In an experiment in which they mixed the ICM of goats with blastocysts of sheep and then transferred the resultant embryos into sheep recipients, V. J. Polzin et al. demonstrated that increasing or decreasing the transplanted cells from the goat ICM biased the donor- or host-specific characteristics of the resultant animal: "There were several ways in which the foreign [goat] and 'host' [sheep] ICM of any injected blastocyst could potentially develop: if incorporation [of goat ICM] took place, a chimera would develop: if the injected ICM was excluded, a lamb would develop; and if the injected ICM [of the goat] replaced the [sheep] 'host' ICM, a kid would result." "Production of Sheep-Goat Chimeras by Inner Cell Mass Transplantation," *Journal of Animal Science* 65.1 (July 1987): 329.

[14] A multidisciplinary working group that studied the moral issues of engrafting human neural stem cells into great apes points out that "it is unlikely that the structural complexity needed for any significant degree of humanlike mental capacity can be achieved under tight size limitations"—the cranial cavity of a mouse, for example. Greene et al., "Moral Issues," 385–386; see note 3. The authors also note that, to a limited degree, the size of the brain can influence the size of the cranium—an effect observed in a hydrocephalic infant, for example. Thus, "a fetal marmoset engrafted with human neural cells might, to some extent, develop a larger brain than is typical for the species" (386). The cranial cavity of any of the great apes approximates that of humans. With this fact and the observation that brain size can increase the size of the cranium, one can see why this group reflected seriously on the likelihood that an ape engrafted with human neural cells could acquire moral status, especially one that models human neurological disease and injury, because the innate neural damage that such models exhibit "might allow greater scope for engrafted human neural cells to affect cognitive capacities" (ibid.). The National Academies' *Guidelines for Human Embryonic Stem Cell Research* seem to require more oversight of experiments producing chimeras in which human embryonic stem cells, their derivatives, or other pluripotent cells are introduced into nonhuman fetuses which are "allowed to develop into adult chimeras" (106, guideline 6.6). The Academies' rationale for requiring more stringent review for such experiments is that "the extent of human contribution to the resulting animal may be higher," especially "major functional contributions to the brain" (ibid.). I do not include the stipulation "allowed to develop into adult chimeras" in my guidelines, because I believe that as long as the scientist risks producing a chimera with capacities for human behavior, it is wrong to do so even when the intent is to destroy the chimera before it reaches maturity.

[15] The *Guidelines for Human Embryonic Stem Cell Research* state that "no animal into which [human embryonic stem] cells have been introduced at any stage of development should be allowed to breed" (99, guideline 1.2[c]3).

- Transfer dissociated human neural stem cells rather than large-area tissue transplants (whole regions of neural tissue, for example) into the more mature embryonic host.[16]

E. The host animal (whether embryonic, fetal, neonatal or mature) remains an animal of its kind despite the insertion of human genetic material. That is, the chimera's somatic developmental trajectory is only accidentally, rather than essentially, modified. Its neurological development results in an animal brain of its respective species, not in a human brain or its primordia.[17]

The production of a *human-animal hybrid* would be ethical if:

A. The goal of producing the hybrid is the promotion of human health and well-being.

B. Researchers obtain informed consent for use of the relevant human material, which is gotten from licit sources.

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[16] Greene et al. conclude that the issues of moral status in nonhuman primates engrafted with human neural stem cells is of greatest concern with experiments "in which human neural stem cells are engrafted into the developing brains of great apes *and constitute a large proportion of the engrafted brain*" ("Moral Issues," 386, my emphasis). They also reason that, besides the quantity of cells transplanted, the specific sites into which the human neural cells are engrafted could be morally significant. In this sense, engrafting human neural stem cells into the developing cerebellum might be less controversial than engrafting them into the cerebrum, the part of the brain associated with higher cognitive activities. Even here, however, they admit that, given the ability of stem cells to migrate to other parts of the brain, engrafting human neural stem cells in one section of a developing primate brain is no guarantee that the stem cells will not migrate and integrate into another part (ibid.). The study "Application of the Quail-Chick Chimera System to the Study of Brain Development and Behavior" describes how quail behavior was transferred to a chick through transplants of quail neural regions: "Hatched chicks with chimeric brains containing cells from both the domestic chicken (*Gallus gallus domesticus*) and the Japanese quail (*Coturnix coturnix japonica*) have been produced by transplantation of various regions of the neural tube at the 8- to 15- somite stage. The positions of host and donor cells relative to graft boundaries observed throughout embryonic development and after hatching implicated both radial and tangential cell movements in brain morphogenesis. In addition, transplants containing the entire quail mesencephalon and diencephalon *resulted in the transfer of certain aspects of species-typical* [quail] *crowing behavior*" (my emphasis). E. Blaban, M.A. Teillet, and N. Le Douarin, *Science* 241.4871 (September 9, 1988): 1339–1342.

[17] With this prescription, I am not implying that a human-chimpanzee or a human-gorilla chimera, for example, would become human merely by virtue of having a brain that is structurally human. I am suggesting that were such a chimeric animal to exist, its material body would include a structurally human brain with all of its neocortical complexity, and the animal could, therefore, become a rational animal, a human being, under divine causality. Consistent with the Adlerian analysis I have given above (the brain is the necessary but not sufficient instrument of rational intelligence), producing a higher primate with a structurally human brain raises the question of whether God would transform the primate into a new kind of being by introducing the principle of rationality, a human soul. According to guideline E, it is morally unconscionable for scientists to risk producing such an organism.

C. There is credible experimental evidence that researchers do not run the risk of producing a hybrid that would either (i) be human (by virtue of possessing a human brain or its primordia and its corresponding capacity for rational behavior) but have an animal phenotype; or (ii) be a new species altogether.[18]

Realistically, since the generation of human-animal hybrids, particularly for the derivation of human embryonic stem cells, has already been done in private U.S. laboratories and in laboratories outside the U.S., it is obvious that some researchers have jettisoned these criteria, especially (C). Hence, in the generation of human-animal hybrids under such circumstances in the future, ethical oversight including adherence to the following guidelines might at least limit the moral fallout:[19] (1) The production of hybrids by the combination of animal and human gametes is prohibited, (2) the in vitro development or manipulation of hybrids beyond fourteen days is prohibited, (3) the transfer of hybrids to a human or animal uterus is prohibited, and 4) the therapeutic transplantation of cells derived from human-animal hybrids to human beings is prohibited until its safety can be confirmed by the proper regulatory agency.

IV. Evaluation of Individual Cases: Human-Animal Chimeras

Case 1: The Generation of Human-Sheep (Xenograft) Chimeras

G. Almeida-Porada et al. transplanted human bone-marrow-derived stromal cell progenitors and human hematopoietic stem cells (hHSCs) together into fifteen immunologically naive fetal sheep that were of fifty-five to sixty days gestational

[18] Since there is so much we do not know about the consequences of mixing human and animal genomes, it is necessary to analyze the moral status of at least two of the myriad hypothetical outcomes. What would be the moral status, first, of a hybrid with animal phenotype and normal human intelligence resulting in humanly intelligent behavior and, second, of a hybrid with animal phenotype and subnormal human intelligence? In the first case, we would need to grant moral status to such an entity because it possesses that which sets the human being apart from animals, namely, the capacity for rational intelligence. Guideline C prohibits even the risk of producing such a creature, since it would constitute an assault on human dignity and would, therefore, be immoral. If the hybrid had an animal phenotype but subnormal intelligence, it would also, it seems to me, deserve moral status and protection, because it would retain the radical capacity for normal intelligence even though that capacity could not be realized optimally due to experimental injury. The principle behind the prohibition not to risk the production of such a hybrid is not implying that human beings who lack a complete brain or are intellectually impaired from birth are not human persons or should not be allowed to live. The guideline simply holds that for anyone to *deliberately* risk the production of a hybrid that has human intelligence is to act immorally.

[19] These were adapted from guidelines governing an experiment done in Shanghai, and are representative of guidelines for embryonic stem cell research issued by various academic and public committees entrusted with ethical oversight. Ying Chen et al., "Embryonic Stem Cells Generated by Nuclear Transfer of Human Somatic Nuclei into Rabbit Oocytes," *Cell Research* 13.4 (August 2003): 262.

age.[20] They also transplanted twelve sheep with hHSCs alone. They found that the co-transplantation of the two types of cells together resulted in higher levels of donor cell engraftment in the host sheep than transplantation of hHSCs alone. In the "cotransplantation" sheep, higher human donor cell activity was found in the peripheral blood circulation early in gestation, and greater numbers of human donor cells engrafted in the bone marrow at later points post-transplantation.

Thus, the collected data from this protocol demonstrate that the in utero co-transplantation of human stromal cell progenitors and hHSCs provides a micro-environment in the xenogeneic recipient (the human-sheep fetal chimera) which is more conducive to long-term engraftment of hHSCs than the transplantation of hHSCs alone, and could also reduce the period of time required for reconstitution of bone marrow blood tissue. Through human stromal cell promotion of hHSC engraftments and appropriate differentiation of the hHSCs, the investigators modeled a method which, if applied to clinical hematopoietic transplantation, could bring both in utero HSC transplantation (used to treat diseases such as X-linked severe combined immunodeficiency disease and thalassemia) as well as postnatal bone marrow transplantation (used to treat metabolic diseases, immune diseases, hematologic and solid tumor malignancies, and storage diseases such as Tay-Sachs and Gauchers) to greater levels of therapeutic efficacy.

Ethical evaluation:

A. The goal of improving both in utero and postnatal clinical hHSC transplantation to better treat an array of diseases is ethically laudable.

B. The "healthy donors" of bone marrow gave informed consent for their contributions.

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[20] Graça Almeida-Porada et al., "Cotransplantation of Human Stromal Cell Progenitors into Preimmune Fetal Sheep Results in Early Appearance of Human Donor Cells in Circulation and Boosts Cell Levels in Bone Marrow at Later Time Points after Transplantation," *Blood* 95.11 (June 1, 2000): 3620–3627. The transplantation of human stem cells into host animals—some of which are normal, others of which are disease models, especially for human neurodegenerative diseases—is common to the first two examples of chimeras that I consider. Human-animal stem cell chimeras are a preclinical tool used to test how human stem cells will migrate, proliferate, differentiate, and perhaps even transdifferentiate within the organic system of various live animal models. These chimeric experiments thus provide the means to develop reliable data that can be used to verify the safety and efficacy of specific clinical stem cell transplantations for the many human degenerative diseases under consideration. But this worthy goal does not give researchers cartes blanches to generate any and every human-animal stem cell chimera. The increased use of disease-model chimeras to study the repair capacity of human neural stem cells has forced us to focus, scientist and philosopher alike, on what it is that makes us human—which, predictably, has cast the spotlight on the necessity of the human brain or its primordia, and on the issue of human neural stem cell transplantation into our closest animal relatives, the great apes. The crucial question, then, is to describe under what conditions the transfer of human neural stem cells into primates would, in all probability, lead to transfer of human cognitive intelligence and behavior. Such conditions, if correctly identified and described, should be used as the basis for guidelines for all such chimeric experiments in the future. Such guidelines can be compared with my own in section III.

C. The manner in which investigators transplanted and sacrificed the sheep was indicative of humane use.

D. At various intervals post-transplantation, while investigators found human cells engrafted in bone marrow, thymus, liver, spleen, and peripheral blood, there was no mention of engraftment in gonadal tissue. A possible explanation for this is that the gonads are not hematopoietic target organs, and formation of the primitive gonadal crest occurs in sheep around the fourth week of gestation, that is, four weeks prior to the time of transplantation in this experiment. Thus, after the fourth week, it could be more difficult for the gonads to incorporate foreign cells.

E. The transplanted human cells were functionally integrated into the microenvironment of the sheep and positively affected bone marrow and peripheral blood development. In essence, the human hematopoietic cells and their progeny were functioning *like* their sheep counterparts already within the sheep body. For this reason, I conclude that while the transplanted human cells enhanced the natural hematopoiesis of the sheep and engrafted in various target organs and tissues (i.e., the sheep recognized these cells as their own), they did not alter the essential nature of the transplanted sheep before or after birth.

Therefore, the creation of preclinical human-sheep chimeras, large animal models of human hematopoiesis, by Almeida-Porada et al. appears to be a moral means to the good end of improving clinical human transplantation therapy.

Case 2: The Generation of Human-Mouse Chimeras

N. Uchida et al. isolated human central nervous system (CNS) stem cells from the fresh fetal spinal cord and brain tissues of approximately sixteen-to-twenty-week-old aborted human fetuses.[21] After considerable expansion in culture to verify monoclonal derivation, these stem/progenitor cells were transplanted into the lateral ventricles of the brains of developing newborn non-obese, diabetic mice with severe combined immunodeficiency disease (NOD-SCID mice). (I assume that the immunodeficient mice were used to prevent rejection of the human cells or to test whether the transplanted neural cells would form cancerous tissue within animmune-suppressed environment.[22]) The human CNS stem cells and their progeny engrafted not only in numerous sites of the murine brain but also in the murine olfactory system, demonstrating a wide (global) distribution of transplanted human neural cells throughout the brain. These human cells demonstrated continued self-renewal, migration, and neural differentiation for at least seven months, just as their mouse neural stem cell counterparts would do. Multiple cells in the murine olfactory system were found to be "double positive" for both animal and human neural markers. The results suggested that the structure of the mouse brains were composed of mostly mouse neural cells and

[21]Nobuko Uchida et al., "Direct Isolation of Human Central Nervous System Stem Cells," *Proceedings of the National Academy of Sciences USA* 97.26 (December 19, 2000): 14720–14725. Irving Weissman, who provided experimental oversight, confirmed in personal communication with me that the stem cells were obtained from aborted human fetuses.

[22] Karpowicz, Cohen, and van der Kooy, "It Is Ethical," 332.

a significantly lesser proportion of human neural cells. When analyzed seven to twelve months post-implantation, the human neural stem cells continued to respond to cues from the mouse microenvironment and did so without the formation of tumors.

Ethical evaluation:

A. A major objective in the creation of these human-animal chimeric mice was a worthy goal: to test, preclinically, whether the transplantation of clonogenic neural stem cells would constitute a safe and effective human therapy.[23] There is substantial evidence that neural cells isolated from the human brain may emulate the behavior of neural stem cells in lower mammals. Thus, the results described by Uchida and associates offer further confirmation that human patients suffering from neurodegenerative diseases involving cell and tissue damage or death could benefit from the post-transplant properties exhibited by human neural stem cells in this experiment, namely, engraftment, migration, and appropriate differentiation.

B. Uchida et al. report that the fresh human fetal spinal cord and brain tissues for their study were obtained from the company Advanced Bioscience Resources "in accordance with all state and federal guidelines." This mode of procuring aborted tissues includes soliciting consent from the woman who aborted. Although soliciting the latter's consent is legal, it is not moral. When a woman chooses to end the life of her fetus, she also abdicates her parental rights over her child, including donating, or giving proxy consent for the use of, tissues from her aborted fetus in experimental protocols.[24]

C. The researchers respected the canons of animal model research, treating the animals humanely and sacrificing them in a way that minimized pain.

D. Since the human neural stem cells were injected into neonatal mice after the time of gonadal formation, there was no possibility of human DNA engraftment in mouse gonadal tissue.

E. Evan Snyder (director of the stem cell program at the Burnham Institute, La Jolla, CA), who has conducted extensive neural stem cell research similar to that of Uchida et al., reports that his engrafted mouse chimeras "exhibited no behavioral abnormalities or other indications of neurologic dysfunction" following human neural

[23] As Karpowicz, Cohen, and van der Kooy explain, "For safety reasons, it is unethical to assay human stem cells in human patients until their function and tumorigenic capacity is tested. Preliminary in vivo studies of human stem cells in living animals provide a more accurate characterization of cells than in vitro studies. Some stem cells cannot even be cultured ex corpore. For instance, transplants of human blood stem cells into living organisms have provided the sole avenue through which long-term repopulating blood stem cell behavior can be examined" (ibid., 331).

[24] The investigators who used tissues from a directly aborted fetal human being are, objectively speaking, also complicit in the evil of abortion to the extent that they are intent that some woman somewhere donates aborted fetal tissues so they can carry out their experiments. Also, the argument could be made that, under certain circumstances, patients with neurodegenerative diseases who receive a transplant of stem cells derived from aborted fetal tissue would also be immorally cooperating with the evil of abortion.

stem cell transplants.[25] This would suggest the seamless integration of human neural stem cells into the murine microenvironment; i.e., these human cells and their progeny were accepted by the host animal as its own. Neural stem cells and their progeny, then, were functioning in the same way as their mouse counterpart cells. In short, the chimeric mouse was still a mouse, and his brain was structurally and functionally a mouse brain following transplantation—that is, the ontology of the mouse was only accidentally, or perhaps not at all, altered by the injection of human neural stem cells.

Therefore, this chimeric stem cell assay would be ethical if Uchida et al. had not derived the necessary stem cells from aborted human fetuses. Since an action must be good both essentially and accidentally, and since this experiment is immoral in the latter sense, the experiment taken as a whole is also immoral. However, if the fetal tissues used in this study were obtained from a miscarried pregnancy and were donated with parental consent, the experiment, taken as a whole, would be ethically unobjectionable.

3. The Generation of a Viable Human-Chimpanzee Chimeric Offspring

In 1997, Stuart Newman, a professor of cell biology and anatomy applied to the U.S. Patent and Trademark Office (PTO) for a patent to protect human-animal chimeric embryos, cell lines, and animals.[26] At the time of application, Newman admitted that he had not created these chimeric entities and had no plans to do so in the future. (U.S. patent law does not require an actual prototype of the invention at the time of application, "only that feasibility, novelty and utility be demonstrated."[27]) The intent in applying for a chimera patent was to "raise these issues before the public and the legal system in a particularly dramatic fashion"[28] (especially the issue

[25] Evan Y. Snyder, John H. Wolfe, and Seung U. Kim, *Engraftable human neural stem cells.* U.S. Patent 5,958,767, filed August 14, 1998, and issued September 28, 1999. U.S. patents and patent applications are available online at http://portal.uspto.gov/external/portal/pair.

[26] Stuart A. Newman, *Chimeric embryos and animals containing human cells*, U.S. Patent Application 08/993,564, filed December 18, 1997. A revised version (10/308,135) was filed December 3, 2002. Newman is a professor of cell biology and anatomy at New York Medical College, Valhalla, NY. The information in this section is based on communications from Deborah Crouch, patent and trademark examiner, to Newman, received by him March 24, 1999, June 5, 2003, August 4, 2004, and August 13, 2004. *Diamond v. Chakrabarty,* 447 U.S. 303 (1980), set the stage for the patenting of living organisms and "contributed to a climate of acceptance of privatization of naturally occurring cell types and DNA sequences.… [It also] enabled the issuance of patents on mice, pigs and cows, some containing introduced human genes, as well as naturally occurring human cells and nonhuman mammals containing such cells." In 1988, for example, the PTO granted Harvard University the first patent for a mammal—the Oncomouse—and its progeny. "The new 'composition of matter' was the Oncomouse—a strain of genetically modified mice that developed cancer at a rate of 40-fold that of the unmodified strain." Stuart A. Newman, "Averting the Clone Age: Prospects and Perils of Human Developmental Manipulation," *Journal of Contemporary Health Law and Policy* 19.1 (Spring 2003): 439–440.

[27] Ibid., 455.

[28] Ibid.

of whether society should permit technology "to blur the lines between human and nonhuman, person and artifact"[29]). Newman, with codesigner Jeremy Rifkin, planned to use approval for these human-animal chimera patents to prevent anyone else from creating or commercially exploiting them. In the same way, these applicants intended to use denial of a patent as a basis for further judicial appeal which could, in turn, lead to a legislative remedy: a U.S. federal law legally prohibiting production of such human-animal chimeras.[30] Recently, the U.S. Patent and Trademark Office rejected Newman's application on the grounds that his human-animal chimera innovations would be too closely related to a human to be patentable.

No one to date has produced the human-chimpanzee chimeric embryos and animals described by Newman, even though, given our current capacity for mammalian developmental manipulation, their creation is a logical possibility. It seems wise, then, to anticipate and evaluate the ethical issues raised by such chimeric experiments before society's good intention in asking the question "Should we?" is completely overpowered by fascination with the potential therapeutic benefits realized by such experiments.

Here I will focus on Newman's protocol for one of his inventions: the generation of embryonic stem cell (ESC)-derived human-chimpanzee chimeric embryos which would be brought to term and used as sources for human heart transplantation.[31] The embryos would be derived entirely from "early passage" human and chimpanzee ESCs (pluripotent stem cells that are permitted "only a few divisions in culture after the ES cell line is established"[32]). These human and chimpanzee stem cells would then be combined with developmentally compromised human or nonhuman tetraploid embryos (embryos produced by electric-pulse-mediated fusion of normal two-cell embryos).[33] Clumps of ten to fifteen ESCs, comprising a mixture of human and chimpanzee stem cells, would be sandwiched between two tetraploid embryos and placed in special culture wells overnight or longer.[34] "In such chimeras," Newman explains, "the tetraploid is selected against and [the mixed human-chimpanzee] ES cells differentiate normally, to form viable embryos."[35] The resultant human-chimpanzee chimeric embryos would be introduced into the uterus of "a hormonally prepared 'pseudopregnant' female."[36] This could be a human foster mother if the chorion

[29] Newman, "The Human Chimera Patent Initiative," *Medical Ethics* 9.1 (Winter 2002): 7.

[30] Jeremy Rifkin is a social critic and president of the Foundation on Economic Trends in Washington, DC. In a phone conversation with Newman on April 1, 2005, I got the impression that he and Rifkin were not going to appeal the PTO's recent rejection of their patent application.

[31] Newman, Patent Application 10/308,135: "Specification" (December 3, 2002), 14, 20.

[32] Ibid., 5.

[33] Ibid., 5, 18.

[34] Ibid., 18.

[35] Ibid., 5.

[36] Ibid., 7.

epithelium (a protective population of cells surrounding the embryo, which prevents recognition of the foreign fetus by the mother of the other species) were human-derived, thereby preventing the mother from rejecting the chimeric embryo as immunologically incompatible. A chimpanzee could be the foster mother if the chorion epithelium were chimpanzee-derived, thereby preventing the mother from rejecting the chimeric embryo as immunologically incompatible.[37] When brought to term, the human-chimpanzee chimeras would be a source of whole organs for transplantation to cardiac patients since, as Newman predicts, there is "a relatively high expectation" that such chimeric hearts would not be rejected by the human host.[38]

Ethical evaluation:

A. The goal of this patent initiative, or invention, is ethical from the general perspective of advancing xenotransplantation. Providing a source of transplant organs that are compatible with the human recipients' immune systems is *in se* a good end.[39]

B. As expected, a patent application for the generation of a living organism like the human-chimpanzee chimera does not discuss informed consent for the donation of the involved human genetic material. Newman, however, does stipulate that the human ESCs needed for the generation of human-chimpanzee embryos could be derived from either fresh or cryopreserved IVF embryos that are no longer needed for reproductive ends.[40] Any legal consent for the use of human embryos in destructive experimentation notwithstanding, the ethical reality is that the progenitors of these embryos are barred from giving such consent. The progenitors abdicate their right to do so by donating embryos to research that involves the direct destruction of the embryos.

C. Newman makes no specific mention in his application of how animal welfare guidelines would be observed in the generation of his prospective inventions. That they would be observed can be inferred from relevant discussion by the creators of the application within the application and elsewhere. The principal reason

[37] Ibid., 3.

[38] Ibid., 20.

[39] In explaining to Newman why certain of his patent claims were rejected, Deborah Crouch, the patent examiner, questioned Newman's claims about the immunological compatibility of the chimeric organs from human-chimpanzee chimeras without the need for immunosuppressive drugs: "Bartholomew [whose experiments Newman cites to support his claim of immune toleration] teaches methods to overcome host versus graft disease for replacement transplantation of organs between primates. This does not teach that left untreated, the transplanted organs would not be tolerated for some length of time in a non-immunosuppressed individual. Given Gustafson, and applicant's reliance on the reference, demonstrating that skin grafts from chimeric animals to its single species siblings are rejected, immunologically tolerated would mean tolerated for some period of time before rejection. Applicant's arguments hinge on a term, immunologically tolerated, that is not defined in the specification and is not defined in the art." Newman, 10/308,135: "Final Rejection" (August 11, 2004), 19–20. Many of Newman's research claims were similarly rejected as "not persuasive" precisely because they appeared to contradict the very research experiments that Newman cited to support the creation of his inventions.

Jeremy Rifkin gives for wanting to block the production of human-animal chimeras is his belief that "animals have the right to exist without being tampered with or crossed with another species."[41] In other words, if Newman were ever to generate the chimeras he describes (and we know his objective is to prevent all such production), it is likely that he would be sensitive to ensuring animal welfare, maintaining species identity, and preventing any blurring of the line between animal and human. If he shares Rifkin's views, Newman would perhaps exercise these precautions from the perspective of animal rather than human rights.

D. By using a host animal (the chimpanzee) that is structurally and functional close to the human being, and by generating a chimeric embryo derived from the fusion of 50 percent (or more) human stem cells with 50 percent (or less) chimpanzee cells, Newman would be increasing the risk of humanizing the final chimeric entity and producing a chimeric brain. Therefore, it would be reasonable to speculate that, if the human-chimpanzee chimera comprised patches of human DNA alongside patches of chimpanzee DNA (particularly within its organ of central control, the brain), the chimera would not be a human and it would not be a chimpanzee. It would be a new species. In other words, this human-chimpanzee chimera would be an organism that is essentially different from what a human embryo would have been without fusion with chimpanzee material.

However, two other scenarios are possible. If this chimeric organism possessed a brain (and its less developed precursors) that was structurally and functionally human and consisted only (or mostly) of human tissue[42]—in other words, a human brain—then the entity would be a human person with patches of transplanted chimpanzee tissue in its body. The latter chimeric organism would not differ essentially from what a human embryo would have been without fusion with chimpanzee material. If, on the other hand, the chimeric organism possessed a brain that was structurally and functionally a chimpanzee brain, then the entity would be a chimpanzee with patches of transplanted human tissue in its body. Obviously, the impossibility of predicting the final nature of the chimeric entity is indicative of the unethical nature of the assay.

E. Hence, given the structural similarity of humans and chimpanzees, if the human-chimpanzee chimera generated according to the Newman/Rifkin protocol had a functioning human brain, produced by human neural stem cells that had given

[40] Newman, 0/308,135: "Specification," 16.

[41] Maryann Mott, "Animal-Human Hybrids Spark Controversy," *National Geographic News*, January 25, 2005, http://news.nationalgeographic.com/news/2005/01/0125_050125_chimeras_2.html.

[42] Evan Snyder and his colleagues, after implanting human neural stem cells into the brains of twelve-week-old fetal bonnet monkeys in a 2001 study, and after examining the four-week-old aborted fetuses, discovered that the human cells had both migrated and differentiated into the neural cells of the cerebral hemispheres and the developing monkey cortex. The small scattering of human cells in the monkey brain was, in Snyder's mind, unable to transfer human behavioral traits. In other words, the monkey brain with a scattering of human neural

rise to human neural functions and human neural architecture, the chimera would be a human person (albeit with patches of human DNA and chimpanzee DNA in other organs and tissues) and could not be destroyed for its organs. Second, if the chimera had a functioning chimpanzee brain with patches of human and chimpanzee DNA in other parts of its body, it would be a chimpanzee and could be destroyed for its organs. Third, if the chimera had a brain that was neither totally human nor totally chimpanzee, it would most probably have to be granted at least a modicum of human rights, because of the likely presence of even limited human cognitive capacity. This means that the realization of the very goal of the chimera's creation according to Newman and Rifkin—to be sacrificed for its organs—would betray its right to life and integrity. What Newman says of human beings who are genetically manipulated during their developmental stages applies *a fortiori* to the human-chimpanzee embryos, fetuses, and neonates under consideration, because of the unpredictability of their resultant nature:

> During development ... tissues and organs are taking form ... and genes function in anything but a modular fashion. In development many, if not most, gene products can have multiple effects on the architecture of organs and the wiring of the nervous system, including the brain. Individuals produced by developmental intervention (particularly as it comes to extend beyond the single gene, to chromosomes or groups of chromosomes) could begin to approach the status of "experimental artifacts," in the sense that their bodies and mentali-

stem cells was architecturally indicative of a sixteen-week-old fetal monkey brain with the capacity to function as such and no more. Regarding this study, Snyder says, "Even if I were to make a monkey with a hippocampus composed entirely of human cells, it's not going to stand up and quote Shakespeare. Those sophisticated in human functioning know that it's more than the cellular components that make a human brain. It's the connections, the blood vessels that feed them; it's the various surfaces on which they migrate, the timing by which various synaptic molecules are released and impact other things, like molecules from the bloodstream and from the bone." Quoted in Jamie Shreeve, "The Other Stem-Cell Debate," *The New York Times Magazine*, April 10, 2005, http://www.nytimes.com/2005/04/10/magazine10CHIMERA.html?ex=1133586000&en=5fae08061e77697f&ei=5070. Echoing Snyder's nuanced understanding of human brain function, Karpowicz, Cohen, and van der Kooy explain why it is highly doubtful that a human neural stem cell transplantation into mice or monkeys would produce a human brain: "Both the mouse and the monkey chimeras would have to possess heads swollen many times their ordinary size to be able to accommodate a human brain. This scenario is unlikely. It is far more likely that human tissue would develop into the host's native form and would have no effect on the mouse or monkey's neural capacities. Even a monkey chimera whose thalamus and cortex were largely human-derived would not possess human capacities if the human neurons were to lie in different, nonhuman, functional networks. The same is true of even the closest relatives of the human, such as the chimpanzee, whose brain does not possess the same architecture and organization as the human brain. The reasons why human networks differ from those of nonhuman primates are not known. It appears to have little to do with brain size itself, but instead with the time span of overall neuronal development, and increases in the frequency of cell division of the neuronal progenitors that contribute to specific regions of the cortex during development." "Developing Human-Nonhuman Chimeras," 125–126.

ties could be quite different from those of anyone generated by processes using the standard starting materials generated by evolution (including IVF).[43]

Therefore, since the generation of human-chimpanzee chimeras as envisaged by Newman and Rifkin could result in human beings or quasi-animals (which would be transferred to human or chimpanzee foster uteruses) and since the human material would be obtained in an unethical manner, this experiment would trivialize human dignity and equality, and would therefore be an immoral means to the good end of medical therapy and heart transplantation. In addition, given the unpredictability of whether the chimeric entity would be essentially chimpanzee (which could, in principle, be sacrificed for its organs), this experiment would be unethical, no matter the nature of its final chimeric entity.

V. Evaluation of Individual Cases: Human-Animal Hybrids

4. The Generation of Human-Rabbit Hybrid Embryos

Dr. Ying Chen et al., researchers at the Center for Developmental Biology at Shanghai Second Medical University, in China, reported the successful generation of human-rabbit hybrid embryos (or human-rabbit nucleocytoplasmic hybrids) by fusing human fibroblast somatic cells and their nuclei with enucleated New Zealand rabbit oocytes.[44] In other words, these researchers (1) successfully reprogrammed human somatic nuclei with rabbit ooplasm; (2) derived nuclear transfer embryonic stem cells (ntESCs) that possessed the properties and phenotypes of conventional human ESCs (sustained growth in an undifferentiated state and formation of densely packed embryoid bodies) and maintained a normal karyotype; and (3) induced the human ESCs to engage in multilineage cellular differentiation (neuron, muscle). Initial analysis of the ntESCs used in situ hybridization, PCR (polymerase chain reaction), and immunohistochemistry with probes that distinguish between the various species, and showed that the nuclear DNA was human and the mitochondrial DNA (mtDNA) of their cytoplasm consisted of both rabbit mtDNA and human mtDNA.

Technically, the product of this experiment cannot be considered a true hybrid, because the nuclear DNA does not combine between the two species (because the oocytes were enucleated prior to insertion of the somatic nuclear DNA). However, the product can be considered a "quasi-hybrid," as two species of DNA are present (nuclear DNA from one species and mitochondrial DNA from the other species' oocyte) in each of the cells of the resultant embryos, even though there is probably no fusion of their genetic material. I will still label the product a hybrid for the purposes of this paper.

Ethical evaluation:

A. The principal goal of this study was worthy: to help solve the problem of immune incompatibility that plagues allogeneic stem cell transplants. Generating autologous cells and tissue (reprogramming the nuclear DNA of cells from transplant recipients by means of enucleated ooplasms), as these investigators did, could solve

[43] Newman, "Averting the Clone Age," 452–453.

[44] Chen et al., "Embryonic Stem Cells Generated by Nuclear Transfer," 251–263.

the problem of immune rejection. The researchers also used the early stages of these developing hybrid (human-rabbit) cloned embryos for another good goal: the study of the molecular mechanisms governing pluripotency, reprogramming, differentiation, and genomic imprinting, in hopes of eventually applying the accumulated data to the improvement of human health.

B. Although not stated explicitly, the probable reason for using rabbit ooctyes was to avoid the health and discriminatory hazards that hyperovulation poses for women who agree to donate their eggs for use in a human cloning protocol. Researchers did obtain informed consent for the use of somatic nuclear DNA from two kinds of post-surgical tissue that would have ordinarily been discarded: foreskin tissue from four male patients, and facial skin tissue from a female patient.

C. The Shanghai investigators referred to the fused entities of their human-rabbit nuclear transfer protocol as "nt-units." One can only speculate about their rationale for describing these entities as artifacts. In all likelihood, the authors figured that the term "nt-unit" would not provoke the controversy surrounding more accurate scientific terms, such as "human-animal hybrids" or "cloned human embryos." As a result of the euphemistic terminology, however, only careful examination of the experimental results can uncover the species identity of these "nt-units."

It is possible to derive human pluripotent stem cells from complex human tissue that does not constitute a human organism (e.g., from a teratoma). So the fact that these investigators derived human ntESCs from the "nt-units" does not necessarily prove that the "nt-units" were human. One could reasonably argue, however, that the cloned hybrids were one of two kinds of organisms: either (1) human (i.e., human clonal hybrids with rabbit mitochondria) or (2) quasi-human entities, neither human nor rabbit. The first category seems the most plausible, based on the following facts reported by the investigators: the blastocyst hybrids, when analyzed by in situ hybridization, hybridized to both probes (human and rabbit), showing that the blastocyst cells contained a complete human genome (by virtue of nuclear DNA and human mitochondria) as well as rabbit mtDNA. These data suggest that the resultant hybrids were human organisms and that the extra rabbit mtDNA did not essentially change their species identity.[45]

Applying the guidelines for the production of human-animal chimeric embryos to these hybrid embryos, one could conclude that the large number of human nuclear genes that were entered into the rabbit oocyte upon fusion of the two cells significantly increased the risk of humanization in the resultant embryonic hybrid, giving rise to the possibility that, if allowed to develop, the entity could develop a human brain or its primordia.

[45] The role of mitochondria is that of supplying cell energy in the form of adenosine triphosphate (ATP). Since ATP produced by rabbit mitochondria is the same as ATP produced by human mitochondria, there is evidence for the conservation of mitochondria over long periods of evolutionary development. Therefore, "as the ancient strangers within our cells," the presence of mitochondria from both rabbits and humans may not cause adverse developmental or phenotypical events.

D. The Shanghai researchers did not intend to produce a viable cloned human offspring. Nevertheless, based on knowledge gained from clonal mammalian precedents, they must have known that they were producing a hybrid embryo which, if left to further development and growth, could very well be characterized by any number of gross fetal, neonatal, and adult abnormalities. And since we cannot currently predict with any certainty whether or what developmental misadventures result when a researcher permits such human-rabbit blastocysts to develop to term, it is immoral to risk those results in the production of such a hybrid.[46]

Focusing on the generation of hybrid embryos for their stem cells, the investigators were operating within the hypothesis that "mechanisms regulating early embryonic development may be conserved among mammalian species."[47] By developing human-rabbit hybrid clones to their blastocyst stage only, the researchers were reasonably confident that the clones would yield normal human pluripotent stem cells. But even here, the investigators had to admit that the principal goal of their experimental manipulation, producing autologous stem cells for prospective transplants, was not assured: "Although the fate of the mitochondria (rabbit/human) in these human ES cells remains unresolved, it is *possible* that these cells will be recognized as 'self' when transplanted back into the same patient."[48] This much is certain: the clinical use of stem cells like those produced in this experiment would be prohibited by the U.S. Food and Drug Administration until it could be proved that the "fate of the mitochondria (rabbit/human)" would not jeopardize the safe use of these cells for transplant purposes.

Therefore, the Shanghai protocol fails to honor the personhood, dignity, equality, and rights of the resultant human hybrid (whether we characterize it as human or a new species), especially its right to life and integrity. Since the process of deriving nuclear transfer stem cells destroyed human beings in their blastocyst stage, the experiment is also immoral because of the way the stem cells were obtained. The experiment failed to recognize or treat the early human (hybrid) embryo, despite its nascent stage of development, as "one of us," that is, equal before the law like any mature human being.

The Chen study is unethical because, while it was done for a worthy end, and proper informed consent was solicited, it failed to respect the life and bodily integrity, and therefore the dignity, equality, and basic rights, of the resultant human or quasi-human (hybrid) embryonic organisms.

[46] See note 16.

[47] Chen et al., "Embryonic Stem Cells Generated by Nuclear Transfer," 252.

[48] Ibid., 262 (my emphasis).