Harvard Journal of Law & Technology
Volume 21, Number 1 Fall 2007

HUMAN-NONHUMAN CHIMERAS IN EMBRYONIC STEM CELL RESEARCH

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I. INTRODUCTION

Myths of different cultures speak of creatures that combine species. In Greek mythology, we find the Chimera, a fire-breathing she-monster represented either as having a lion's head, a goat's body, and a serpent's tail, or as having a lion's body and head with a goat's head

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rising from the back.[1] The Chimera created havoc and inspired terror until Bellerophon slew it.[2]

The big "C" Chimera of lore has given way to the small "c" chimeras of laboratories. In contemporary scientific parlance, the term chimera applies to various entities that contain cells from two or more individuals of the same or different species.[3] Chimeras differ from transgenic plants and animals in that the latter have genes from two or more species.[4] Examples of chimeras include: (1) a cross between a male of one species and a female of another species;[5] (2) a fetus that results from the fusing of fraternal twins;[6] and (3) nonhuman animals that contain selected human cells, tissues, or organs.[7]

Creating and using the third type of chimera would have significant benefits. Human-nonhuman chimeras could, for example, be effective testing models for future therapies. The Food and Drug Administration ("FDA") requires that any new drug or therapy undergo extensive testing in animals before allowing human trials to commence.[8] Pharmaceutical companies spend a great deal of money

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1. WEBSTER'S THIRD NEW INTERNATIONAL DICTIONARY 389 (Philip Babcock Gove unabridged ed. 2002).

2. *Id*. at 201. Hesiod and Homer tell of the Chimera and its death. *See* HESIOD, *Theogony* 319–25, *in* HESIOD'S THEOGONY 48 (Richard S. Caldwell trans., Focus Info. Group 1987) (Greek original late 8th century B.C.E.); HOMER, THE ILIAD 201 (Robert Fagles trans., Penguin 1990) (Greek original c. 8th century B.C.E.).

3. *See* ESSENTIALS OF STEM CELL BIOLOGY 522 (Robert Lanza et al. eds., 2006) [hereinafter STEM CELL BIOLOGY] (defining a chimera as an "[o]rganism made up of cells from two or more different genetic donors").

4. *See* GLOSSARY OF BIOTECHNOLOGY FOR FOOD AND AGRICULTURE (A. Zaid et al. eds., 2001) [hereinafter FAO GLOSSARY], http://www.fao.org/biotech/find-form-n.asp (search for "transgenic") (defining transgenic as pertaining to an individual "in which a transgene has been integrated into its genome"). In contrast to this Article, the FAO GLOSSARY does not indicate that the transgene must be derived from a different species from that of the recipient. *See id.* ("Often, but not always, the transgene has been derived from a different species than that of the recipient.").

5. "Cross" refers to a mix of two species produced by biotechnological or surgical intervention. *Cf.* Carole B. Fehilly et al., *Interspecific Chimaerism between Sheep and Goat*, 307 NATURE 634, 636 (1984); Jason Scott Robert & Françoise Baylis, *Crossing Species Boundaries*, 3 AM. J. BIOETHICS, Summer 2003, at 1, 2. Mixed-species creatures that result not from biotechnological or surgical intervention but from the fertilization of an ovum from a member of one species by a sperm cell from a member of a different species (whether as a result of sexual intercourse or an assisted reproduction technique), where both species occur in nature, are "hybrids" rather than chimeras. Examples of hybrids include mules, geeps, ligers, and wolphins.

6. *See* Claire Ainsworth, *The Stranger Within*, NEW SCIENTIST, Nov. 15, 2003, at 34.

7. A prominent example of such animals is the SCID-hu mouse (resulting from engraftment of human fetal liver hematopoietic cells, human fetal thymus, and human fetal lymph nodes into mice with severe combined immunodeficiency syndrome). *See* Mark Jagels, Note, *Dr. Moreau Has Left the Island: Dealing with Human-Animal Patents in the 21st Century*, 23 T. JEFFERSON L. REV. 115, 132 (2000); Donald E. Mosier et al., *Transfer of a Functional Human Immune System to Mice with Severe Combined Immunodeficiency*, 335 NATURE 256, 256–59 (1988).

8. *See* Martin S. Lipsky & Lisa K. Sharp, *From Idea to Market: The Drug Approval Process,* 14 J. AM. BD. FAM. MED. 362 (2001).

conducting pre-clinical trials on each new drug. Still, the main reason drugs fail to be approved is that they are found to be unsafe or ineffective in human beings, even though they perform well in animal studies.[9] Thus, conventional animal models are often inadequate for testing pharmaceutical safety and effectiveness. Nonhuman animals that carry "humanized" organs or tissues are likely to demonstrate a more human response to new drugs and therapies than their unmodified brethren.[10] In addition to their use as testing models, chimeras potentially could be employed to "farm" human organs and tissues; those organs and tissues could then be transplanted into human beings.[11] Such organs and tissues are likely to have a lower risk of rejection than tissues or organs provided by an unrelated donor, particularly if they are grown using the patient's own stem cells.[12] Furthermore, human-nonhuman chimeras created using human embryonic stem cells ("hESCs") may prove useful in testing the pluripotency[13] of existing hESC lines, in overcoming immunological barriers to xenotransplantation,[14] and in preventing cross-species viral diseases.[15]

Many scientists believe that putting hESCs or their differentiated derivatives into an adult animal, if done at the right time, is unlikely to affect radically the resulting chimera's appearance or cognitive abilities, while still affording the opportunity for experimental control of the chimera and the chance to observe cellular behavior.[16] In fact, scientists can create human-nonhuman chimeras in many ways. For example, scientists can insert hESCs or their differentiated derivatives

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9. *See* Carol Cruzan Morton, *Fashions Change in Modeling Disease*, FOCUS, Dec. 17, 2004, http://focus.hms.harvard.edu/2004/Dec17_2004/scientific_symposium.html (quoting Richard Roman, professor of physiology and medicine at the Medical College of Wisconsin, as saying, "Ninety percent of drugs fail in clinical trials, half for efficacy and half for safety. . . . All are efficacious and safe in animal studies. Genetically, rodents are 90 percent identical to humans. Why then do they have only 10 percent predictive power for responses in humans?").

10. *See* Nicole E. Kopinski, Note, *Human-Nonhuman Chimeras: A Regulatory Proposal on the Blurring of Species Lines*, 45 B.C. L. REV. 619, 630 (2004).

11. *See* Christopher Thomas Scott, *Chimeras in the Crosshairs,* 24 NATURE BIOTECH. 487, 488 (2006).

12. *See* Kopinski, *supra* note 10, at 630.

13. *See* STEM CELL BIOLOGY, *supra* note 3, at 527 (defining pluripotency as "ability to differentiate cells varieties of cells that belong to all three germ layers").

14. *Cf.* SILKE SCHICKTANZ, ORGANLIEFERANT TIER? MEDIZIN- UND TIERETHISCHE PROBLEME DER XENOTRANSPLANTATION (2002) (investigating the risks and biomedical/animal-ethical aspects of xenotransplantation). Xenotransplantation is the transfer of tissue or organs from a member of one species to a member of a different species. FAO GLOSSARY, *supra* note 4.

15. One way of preventing cross-species viral diseases is to observe when such diseases occur in chimeras, identify the path of infection, and then determine ways to block that path.

16. *See*, *e.g.*, Jamie Shreeve, *The Other Stem-Cell Debate*, N.Y. TIMES MAG., Apr. 10, 2005, at 42, 44, 47, *available at* http://www.nytimes.com/2005/04/10/magazine/10CHIMERA.html (reporting the views of Dr. Eugene Redmond on the insignificant cognitive effects of transplanting immature human neural cells into the brain of a vervet monkey).

into enucleated animal ova, blastocysts, embryos, fetuses, or adults.[17] They can also reverse the order by inserting nonhuman embryonic stem cells ("ESCs") or their derivatives into human enucleated ova, blastocysts, embryos, fetuses, or adults. Some believe that, in such experiments, an animal embryo or fetus would be more likely than an adult animal to become "humanized" — that is, to become less like a nonhuman animal and more like a human being.[18] And some think that the earlier in gestation one introduces the human stem cells, the more humanized the animal is likely to become.[19] Yet because different animals have different gestation periods, it is hard to decide when is "too young" and when is "old enough." In part for these reasons, most stem cell researchers in the United States currently shy away from putting hESCs into animal blastocysts even though there is no legal prohibition against doing so.[20]

It requires little imagination or political attunement to see why the topic of human-nonhuman chimeras is hotly debated. First, such chimeras contain a mix of cells from human and nonhuman species, which some people regard as contrary to God's will, immoral, or at least imprudent.[21] Second, human-nonhuman chimeras are linked to the abiding controversy over hESC research.[22]

This Article has three main tasks: (1) devising a framework for thinking about human-nonhuman chimeras and using that framework to analyze cases that raise moral problems; (2) building on that framework to evaluate and shape social policy; and (3) employing the framework to assess existing law and a legislative proposals. The Article mainly addresses hESC-derived human-nonhuman chimeras, but the moral, social, and legal analysis developed here also applies for the most part to human-nonhuman chimeras created without using hESCs. To keep the inquiry manageable, I assume that hESCs in a laboratory dish have no moral status that makes it wrong to use them in research and that existing regulations on the use of animals in research are morally, socially, and legally justified.[23]

My primary thesis is that the moral, social, and legal concerns about human-nonhuman chimeras are so complicated that, though one

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17. *See id.* at 44–47 (discussing the research of Dr. Ali Brivanlou, Dr. Irving Weissman, and Dr. Esmail Zanjani).

18. *Cf.* Natalie DeWitt, *Animal-Human Chimeras: Summary of UK Academy of Medical Sciences Report,* NATURE REP. STEM CELLS, Aug. 2, 2007, http://www.nature.com/stemcells/2007/0708/070802/full/stemcells.2007.67.html.

19. *See* Scott, *supra* note 11, at 490.

20. *See, e.g.*, Shreeve, *supra* note 16, at 45 (reporting the disinclination of the Geron Corporation and Dr. Robert Lanza to "pursue inter-species stem-cell chimeras").

21. *See* Scott, *supra* note 11, at 490.

22. *See* Robert Streiffer, *At the Edge of Humanity: Human Stem Cells, Chimeras, and Moral Status*, 15 KENNEDY INST. OF ETHICS J. 347, 348 (2005).

23. These are highly controversial assumptions, but defending them here would take us well outside the scope of the present inquiry.

can illuminate these concerns, one cannot categorize the creation of human-nonhuman chimera as either permissible or impermissible. It is simply beyond the current state of scientific knowledge and moral thinking to formulate a set of necessary and sufficient conditions that could be used for sorting all cases into morally permissible and morally impermissible categories, without leaving any cases undecided. One can, however, shed a great deal of light on these concerns. Specifically, it is possible to create a multi-element framework that contains some sufficient conditions for morally permissible chimeras, to illuminate many cases with the framework by identifying the relevant issues and resolving them, and to use other cases to suggest ways of improving the framework.

Furthermore, with regard to social policy, I argue that one commission report by the President's Council on Bioethics, Reproduction and Responsibility is unduly narrow in concentrating chiefly on human-nonhuman chimeras created by intervening at the stage of fertilization.[24] A later report prepared by a board acting on behalf of the Institute of Medicine makes sensible recommendations on chimeras created using hESCs.[25] Finally, I consider the legal issues surrounding chimeras and contend that Congress, FDA, and/or the United States Department of Agriculture ("USDA") should regulate hESC-derived human-nonhuman chimeras. No current federal statute or regulation addresses this matter. I argue that the bills proposed by Senator Sam Brownback (R-Kan.) are helpful in some respects, but are misguided in others and remain incomplete.[26] I suggest a different regulatory approach. I also argue that some human-nonhuman chimeras should be patentable.

The inquiry takes the following path. Part II explains my approach to morality and moral appraisal. Part III develops and defends a moral framework for analyzing human-nonhuman chimeras, applies that framework to six cases, and then revisits the framework to see whether the examination of particular cases gives any reasons for adjusting it. Part IV discusses social policy. It pays critical attention to the policies embedded in two major commission reports on chimeras and suggests how improvements could be made on those reports. Part V turns to chimeras and the law. It addresses the legal regulation and patentability of human-nonhuman chimeras. Part VI concludes the inquiry.

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24. *See* PRESIDENT'S COUNCIL ON BIOETHICS, REPRODUCTION AND RESPONSIBILITY: THE REGULATION OF NEW TECHNOLOGIES 222 (2004) [hereinafter COUNCIL REPORT], *available at* http://www.bioethics.gov/reports/reproductionandresponsibility/index.html.

25. *See* BD. ON LIFE SCI., NAT'L RESEARCH COUNCIL & BD. ON HEALTH SCI. POLICY, INST. OF MED., GUIDELINES FOR HUMAN EMBRYONIC STEM CELL RESEARCH 6–8, 17, 30, 39–41, 116 (2005) [hereinafter NRC/IOM GUIDELINES].

26. Human Chimera Prohibition Act of 2005, S. 659, 109th Cong. (2005); Human Chimera Prohibition Act of 2006, S. 1373, 109th Cong. (2005).

This Article, therefore, involves a mix of the concrete and the abstract. It combines moral theory as well as practical social and legal investigation. To launch this project, I begin by first laying the foundations of my approach to moral philosophy.

II. FOUNDATIONS: AN APPROACH TO MORALITY AND MORAL APPRAISAL

There are many competing approaches to morality and moral appraisal, and I wish to state forthrightly how my approach compares with others. Moral philosophers often distinguish between consequentialist and nonconsequentialist approaches to morality. The former holds that the morality of actions should be judged by their consequences. Prominent among consequentialist approaches are various forms of utilitarianism. In utilitarianism, the supreme goal is the promotion of "utility," which is often defined as happiness, preference-satisfaction, or the balance of pleasure over pain.[27] In contrast, nonconsequentialist approaches to morality stress one or more principles that are generally either duty-based or right-based. Approaches relying on duty-based (deontological) principles are common. Noteworthy among them is Kant's moral philosophy with its categorical imperative: "Act in such a way that you always treat humanity, whether in your own person or in the person of any other, never simply as a means, but always at the same time as an end."[28] J.L. Mackie, in contrast, argues that morality is right-based or, more precisely, that we should invent a right-based morality.[29] Other contemporary nonconsequentialist theories include the theories of Charles Fried and Alan Gewirth.[30] There are, of course, mixed ("pluralist") approaches that contain either (1) both consequentialist and nonconsequentialist principles, (2) nonconsequentialist principles that can sometimes be overridden by the adverse consequences of adhering to those principles, or (3) consequentialist principles that are constrained by nonconsequentialist rights or duties.[31] The principles offered below for human-

27. *See, e.g.*, JEREMY BENTHAM, AN INTRODUCTION TO THE PRINCIPLES OF MORALS AND LEGISLATION (J.H. Burns & H.L.A. Hart eds., Univ. of London the Athlone Press 1970) (1789); J.S. MILL, UTILITARIANISM (Samuel Gorovitz ed., Bobbs-Merrill Co. 1971) (1863).

28. IMMANUEL KANT, GROUNDWORK OF THE METAPHYSIC OF MORALS (1785), *translated in* THE MORAL LAW 96 (H.J. Paton trans., Hutchinson's Univ. Library 1948) (emphasis and footnotes omitted). This formulation is known as the "formula of the end in itself."

29. J.L. Mackie, *Can There Be a Right-Based Moral Theory?*, 3 MIDWEST STUD. IN PHIL. 350, 355–56 (1978).

30. *See* CHARLES FRIED, RIGHT AND WRONG (1978); ALAN GEWIRTH, REASON AND MORALITY (1978); ALAN GEWIRTH, THE COMMUNITY OF RIGHTS (1996).

31. *See*, *e.g.*, LAWRENCE C. BECKER, PROPERTY RIGHTS: PHILOSOPHIC FOUNDATIONS 32–80 (1977) (offering arguments based on utility, labor, and political liberty for the moral foundations of property rights).

nonhuman chimeras are ultimately defended using a pluralist approach.

Moral appraisal often — but not always — involves evaluating human actions based on their impact on society. Evaluation of this sort can inform social and legal policy. Alternatively, sometimes individuals want to appraise the morality of their actions irrespective of the social impact of those actions. A scientist who asks, "Should I engage in hESC research that creates human-nonhuman chimeras?" could be seeking purely personal moral guidance. In this case, the scientist is not asking the question because she is necessarily troubled by the general social implications of doing the research, for she knows that other scientists would step in and do the work if she chose not to conduct the research. Instead, the scientist is asking the question because she wants to know whether she will be acting in accord with her own moral principles in doing the work.

The personal dimension evident in the scientist's moral appraisal of her actions enables one to see that morality deals not only with actions but also with virtues and ideals. As the term is used in this Article's framework, a virtue is an abiding character trait that disposes a person to think or act in ways that are generally beneficial both for the person having the trait and for others. A virtue either enhances some positive feature or corrects or modifies some shortcoming of human beings. An ideal, as understood in this Article, is a way of living that is extraordinarily good, worthy of emulation by others, and yet beyond the call of duty.

The scientist researching human-nonhuman chimeras in the example above might also wonder whether her research would foster good character traits such as respect for truth and a concern for helping patients or would instead cultivate callousness toward the organisms she produces. She might also ask whether her research would embody the selfless pursuit of knowledge that is both good in itself and useful to others or would instead drive her away from other, nobler ideals. Of course, the selfless pursuit of knowledge is not necessarily at odds with other, nobler ideals. Yet, it would be difficult for all but the most energetic individuals to always pursue both knowledge and such ideals simultaneously throughout life.

III. MORALITY AND HUMAN-NONHUMAN CHIMERAS

A. Six Cases

Chimera development is a new and growing field, and bioethicists are divided on many issues raised by chimera research. Yet, one cannot know what sort of moral framework is needed for analyzing these issues without first having a concrete idea of some of the problems the

framework is supposed to solve. In this Section, I discuss six cases that illustrate some of the issues posed by chimera research. The cases include modifications of actual research projects and hypothetical situations that currently verge on science fiction. These widely varying examples are useful for teasing out our moral intuitions and revising moral principles that we can then apply to evaluate the creation and use of human-nonhuman chimeras. In each case, one should ask, "Morally permissible or not?"

(1) Scientists insert hESCs into postnatal mice and tag the cells for identification. The researchers take effective steps to prevent the stem cells from "humanizing" the creatures in regard to appearance, mental ability, and emotions. They ensure that these cells will differentiate only into hematopoietic (that is, blood-forming) stem cells. The resulting chimeras look like mice and are not allowed to breed. They have the cognitive and emotional life of normal laboratory mice. The aim of this research is to see how the cells migrate into various parts of the body, differentiate into more specialized cells, and interact with other systems in the animal body. Some of the longer-term implications of this research include determining how stem cells respond to cues emanating from their cellular niches,[32] identifying their potential to replace or repair damaged tissue, and exploring "their potential for creating animal models that more closely mimic humans."[33]

(2) A research team creates mice that have complete human, rather than murine, immune systems. The researchers accomplish this feat by injecting hESCs into the developing lymphatic system of murine fetuses and coaxing the stem cells into differentiating into lymphocytes and related immune cells. The team wants to study HIV in nonhumans, and the mice are cheaper than other species of laboratory animals while still remaining a useful model for humans. The organisms look like mice, are sterile, and have no capacity for thought, language, or the higher emotions beyond those of ordinary mice.

(3) A team of veterinarians and developmental biologists introduces hESCs and human embryonic germ cells ("hEGCs") into carefully selected parts of the fetuses of large primates. The aim of the research is to examine the development of the reproductive system in both large primates and humans. Specifically, the team seeks to better understand the formation of ovaries and testes in fetuses and the maturation of these organs in offspring. The team takes effective measures to prevent hESCs and hEGCs from differentiating into any cells besides those ordinarily found in the ovaries and testes. As the primate-human chimeras reach sexual maturity, the team pays close attention

32. A niche is a "[s]tructural and biological entity where stem cells are located, proliferate, and differentiate." STEM CELL BIOLOGY, *supra* note 3, at 526.

33. Streiffer, *supra* note 22, at 349 (internal citations omitted) (describing a similar experiment using differentiated bone marrow stem cells).

to the formation of ova and sperm. It finds, as predicted, that the mature gonads produce both primate and human ova in females and both primate and human sperm in males. The research protocol allows the chimeras to mate.

(4) Scientists integrate hESCs into a fetal primate at various stages. They want to study the effect of hESCs on the primate's mental and emotional capacities. The result is an obedient, cheerful chimera with an IQ in the range of 35–40 to 50–55, which is capable of communicating in language and will do simple household chores.[34] The chimera has the appearance of a medium-sized nonhuman primate.

(5) Scientists stimulate hESCs *in vitro* to develop into human neural precursors.[35] They then insert these precursor cells into a developing chimpanzee such that the chimera, though it cannot speak and has no more linguistic capacity than a chimpanzee, has some human, or humanlike, vocalizations. For example, the chimera can sob and laugh, not just hoot and pant. From ordinary observation, no one can tell what the chimera's inner experience or feelings are when it sobs or laughs. This chimera is not allowed to breed. It looks like a chimpanzee, and primatologists can determine that it has no greater cognitive capacities than an ordinary chimpanzee.

(6) A research team coaxes hESCs *in vitro* into differentiating into various sorts of skin cells as well as cartilage cells. The team then seeds a biodegradable scaffold with these various cells. The result is an external ear (auricle) that, when fully developed, will be appropriate in size and shape for a human child. The researchers graft the auricle onto the back of a mouse.[36] The aim of the experiment is to

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34. Humans with an IQ in this range are at the upper band of "moderate" mental retardation and the lower band of "mild" mental retardation. As children, they would likely have some developmental delays and learning difficulties. As adults with "mental ages" from about six to ten years, most could communicate adequately, work with some guidance, and form social relationships. *See* AM. ASS'N ON MENTAL RETARDATION, MENTAL RETARDATION: DEFINITIONS, CLASSIFICATIONS, AND SYSTEMS OF SUPPORTS 104 (10th ed. 2002) (presenting the World Health Organization classification in Table 7.2). However, Case (4) simplifies the concept of intelligence in animals because most contemporary ethologists doubt that it is possible to measure animals' IQs since animal species vary greatly among themselves and with respect to humans in their sensory apparatus and processing of information. *See, e.g.*, LESLEY J. ROGERS, MINDS OF THEIR OWN: THINKING AND AWARENESS IN ANIMALS 56–57 (1997).

35. *Cf.* Václav Ourednik et al., *Segregation of Human Neural Stem Cells in the Developing Primate Forebrain*, 293 SCIENCE 1820 (2001) (describing human neuronal progenitors transplanted into the forebrain of fetal bonnet monkeys to assess stem-cell function in primate brain development).

36. *See* Sarah Franklin, *Drawing the Line at Not-Fully-Human: What We Already Know*, 3 AM. J. BIOETHICS, Summer 2003, at W25, W25 (describing the work of Linda Griffith-Cima and Charles Vacanti and including a photograph of the grafted auricle). Linda Griffith-Cima and Charles Vacanti's work rests on Yilin Cao et al., *Transplantation of Chondrocytes Utilizing a Polymer-Cell Construct to Produce Tissue-Engineered Cartilage in the Shape of a Human Ear*, 100 PLASTIC & RECONSTRUCTIVE SURGERY 297 (1997).

develop a mirror-image auricle for a child, now eight years old, who was born with only one external ear.

B. A Proposed Moral Framework and Its Defense

These cases will spur reflective readers to think about distinctions and factors that seem relevant to the moral analysis of these situations. For instance, a reader might distinguish between the creation and the use of a particular chimera; perhaps a reader would find a chimera's creation morally permissible even if she concluded that some uses of it were impermissible. A reader might identify uncertainty as an important factor; perhaps creating a particular chimera would be morally permissible if scientists knew all of the consequences and knew that the consequences were benign, yet creating the same chimera would be impermissible or at least problematic if the consequences were unknown or largely unpredictable. The number of different possible distinctions and factors might leave even a thoughtful reader unsure how to craft a set of moral principles for dealing with these and other cases.

In this Article, I concentrate almost entirely on human-nonhuman chimeras created by hESCs or their derivatives. The integrated framework I propose consists of three different sets of elements: (1) distinctions, (2) factors, and (3) principles. Each is explained in greater detail below; distinctions and factors both appear in certain principles. In this context, a "distinction" is an element that separates two or more things that might appear conflated but in fact require discrimination. A "factor" is an element that seems to be a morally relevant consideration, even if the exact weight it should be given is unclear. A "principle" is an element that states that a particular action is required, forbidden, or permitted, or that gives priority rules in case other principles conflict.

At the end of this Section I defend the framework. The defense is not part of the framework itself but reasons for accepting it. Only as the inquiry unfolds will the full significance of the distinctions, factors and principles emerge.

1. Distinctions. An important component of any analysis is the separation of elements that some thinkers might overlook or conflate but are in fact different.

The first distinction separates the cognitive levels of human-nonhuman chimeras into three categories: basic, enhanced, and dramatically enhanced. I define these levels as follows:

- Basic human-nonhuman chimeras ("basic chimeras") have some human cells, some nonhuman cells, and, in special cases, some hybrid human-nonhuman cells. Some

tissues or organs in these chimeras may consist entirely of human, nonhuman, or hybrid cells, while other tissues or organs may consist of a mixture of these cells. Basic human-nonhuman chimeras do not have cognitive capacities higher than those of a dog or a pig.

- Enhanced human-nonhuman chimeras ("enhanced chimeras") have cognitive capacities roughly equivalent to those of a chimpanzee — which is selected as the definitional threshold for enhancement because of its relative proximity to human cognitive capacities in the animal order.[37]
- Dramatically enhanced human-nonhuman chimeras ("dramatically enhanced chimeras") have cognitive capacities — including intelligence, linguistic capacity, self-awareness, emotions, and the ability to form and maintain social relationships — that approximate the capacities of a human being.[38]

One significant qualification applies to the expression "cognitive capacities" in the foregoing definitions: these capacities are assessed in relation to tasks characteristically performed by humans. A growing consensus among ethologists holds that each species is "adapted to its particular environmental niche and performs 'intelligently' in that niche."[39] Thus, one cannot rank "all species on the same scale of intelligence."[40] Nevertheless, if one focuses on tasks characteristically performed by humans, non-human primates perform fairly well, or at least better than other nonhuman animals.[41]

Next come some distinctions that are likely to be more familiar. One distinction is between creating a chimera and using it. Another distinction is between ways of creating chimeras: cellular creation versus anatomic creation. In cellular creation, scientists mix cells from human and nonhuman animals, often during embryonic or fetal stages of development. In anatomic creation, scientists attach a human organ

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37. The word "enhanced" is used as a term of art. If a human-chimpanzee chimera has a human liver and a chimpanzee brain, and if its cognitive capacities remain those of an ordinary chimpanzee, the creature qualifies as an "enhanced human-nonhuman chimera" even though the creature's *brain* has not been enhanced in any way.

38. The expression "dramatically enhanced" is also used as a term of art. Suppose that a person has a transplanted porcine organ or body part, such as a pig's liver or heart valve. This person qualifies as a "dramatically enhanced human-nonhuman chimera" even though, as a matter of ordinary English, we would not say that its *brain* has been dramatically enhanced in any way. It lies beyond the scope of this inquiry to consider human-nonhuman chimeras whose cognitive capacities far outstrip those of human beings.

39. *See, e.g.*, ROGERS, *supra* note 34, at 57.

40. *Id; accord* STEPHEN BUDIANSKY, IF A LION COULD TALK: ANIMAL INTELLIGENCE AND THE EVOLUTION OF CONSCIOUSNESS 16 (1998).

41. *See, e.g.*, ROGERS, *supra* note 34, at 191 (comparing the performance of Chantek, a signing orangutan, with that of human children on the Bayley Scale of Infant Development).

or body part onto the body of a nonhuman creature or vice versa. Something akin to anatomic creation occurs today when porcine heart valves are used to replace defective human heart valves.

Still another distinction is between breeding and non-breeding chimeras. If human-nonhuman chimeras are not allowed to breed, there is no need to worry about the characteristics of offspring. But if they are allowed to breed, we must worry about the consequences, both when the characteristics of offspring are known and when they are unknown.

Yet another distinction is between traits and appearance. Roughly, the "traits" of a chimera include its physical size and shape and its cognitive and emotional capacities. The "appearance" of a chimera is the way it looks in relation to humans. This is not a sharp distinction, but it incorporates some visceral reactions that people can have to humanlike parts on animals that otherwise look nonhuman. People are apt to react differently, for example, to human skin on the mostly hairless belly of a dog than to a human face on a sheep.

2. Factors. Chief among the factors in the moral analysis of human-nonhuman chimeras are the following: purposes, benefits, costs, uncertainty, risk, risk assessment, and risk distribution.

Purposes are resolute intentions related to the creation and use of chimeras. Purposes can be narrow or broad, and targeted at basic research or therapeutic advances. Ordinarily, scientists have purposes and funding agencies or bioethicists assess them. Purposes are germane to the analysis under almost all approaches to morality — consequentialist, nonconsequentialist, and mixed. Other things being equal, under a consequentialist theory, having a resolute intention (purpose) to do an action usually increases the probability that the action will be done and bring about the consequences often caused by that action. For example, an accountant who resolutely intends to embezzle funds (his purpose) is more likely than other accountants to embezzle and cause financial loss to his employer or client. In a nonconsequentialist theory such as Kant's, the accountant who resolutely intends to embezzle treats his employer or client simply as a means, and thus violates the categorical imperative. Purposes are also relevant to pluralist moral theories because such theories involve a mix of consequentialist and nonconsequentialist principles.

Benefits and costs are factors that offset each other in chimera research. However, unless they offset each other equally, there will be either a net benefit or a net cost. Both benefits and costs can be further categorized as anticipated (what is predicted) or actual (what emerges from the research). In the case of chimera research, typical benefits could include more accurate characterizations of hESCs in living chi-

meras than can be obtained from *in vitro* studies.[42] Typical costs include researchers' salaries, funds for laboratory animals and equipment, operating overhead, and any adverse outcomes. If the anticipated costs exceed the anticipated benefits, there is a compelling reason for not doing the research. If actual costs exceed actual benefits, there is a strong reason for designing future research projects differently.

Uncertainty is a lack of knowledge regarding the outcome of particular chimera research. Uncertainty varies greatly in degree. If outcomes were known in advance, there would be little reason for experimentation, save for instructional purposes. If uncertainty is low, we can expect that the actual benefits and actual costs are very likely to be similar to the anticipated benefits and anticipated costs. If uncertainty is high, it may be difficult to decide whether the proposed research should go forward. Given that research on human-nonhuman chimeras is in its infancy, uncertainty could bedevil decisions on whether a particular experiment should proceed. If there is a way to quantify uncertainty, we may be able to speak of uncertainty costs and include these costs in a cost-benefit analysis.

The last three factors — risk, risk assessment, and risk distribution — are obviously related. Risk is the product obtained by discounting (multiplying) the gravity of an adverse outcome by the probability of that outcome. This "product" is often only quasi-mathematical. Sometimes we can both put a value on the gravity of an outcome and specify its probability. Sometimes we can put a value on gravity or probability, but not both, and sometimes we can do neither. In those cases, we can only make a rough estimate of risk or provide a range of its expected values. Risk assessment compares the risk of one adverse outcome with the risk of other possible harms and benefits. Risk distribution specifies the individuals or groups that bear a given risk.[43]

Risk, risk assessment, and risk distribution are relevant to decisions about the creation and use of chimeras because this type of research requires us not only to identify risks but also to engage in risk assessment. Assessing risk is especially difficult when the variables that define it — probabilities, the nature and gravity of adverse outcomes, precaution costs, and pertinent benefits — are unknown. The difficulties mount when we consider risk distribution. Although the issue is beyond the scope of this Article, I doubt that decisions involv-

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42. *See, e.g.*, Phillip Karpowicz, Cynthia B. Cohen & Derek van der Kooy, *It Is Ethical to Transplant Human Stem Cells into Nonhuman Embryos*, 10 NATURE MED. 331, 331–32 (2004); *see also* Morton, *supra* note 9; Kopinski, *supra* note 10; Phillip Karpowicz et al., *Developing Human-Nonhuman Chimeras in Human Stem Cell Research: Ethical Issues and Boundaries*, 15 KENNEDY INST. OF ETHICS J. 107 (2005).

43. These distinctions partly follow James E. Krier, *Risk Assessment*, *in* 3 THE NEW PALGRAVE DICTIONARY OF ECONOMICS AND THE LAW 347–50 (Peter Newman ed., 1998).

ing such uncertainties surrender entirely to consequentialist considerations, such as maximizing average or aggregate preference-satisfaction. Instead, decision-making that occurs when there is uncertainty about the harm from and to chimeras and research on them, should consider the effects on particular individuals or groups. Above all, such decisions should take into account the effects on the life prospects of the least well off in society and on those most burdened by decisions about chimeras.[44]

3. Principles. The principles in the framework make use of the distinctions and factors just discussed. The following principles aim to help someone applying the framework decide when the creation of chimeras is morally permissible or impermissible. The principles are also intended to help determine when the use of chimeras is morally permissible or morally impermissible. I apply the principles to the six cases introduced above.

Principle 1: The creation of human-nonhuman chimeras is morally permissible, subject to Principles 3 and 4, if all of the following conditions are satisfied: (1) the projected use of the chimera in research serves a defensible purpose, such as the promotion of human health; (2) chimeras that are classified as enhanced or dramatically enhanced will not experience substantial and enduring physical or emotional pain; (3) chimeras will not breed among themselves, with humans or with other animals; and (4) chimeras will not be created that have linguistic or other cognitive capacities greater than those of a chimpanzee.

A justification for condition (3) in Principle 1 (no-breeding) is that the risks to the offspring of the chimeras, their breeding partners, and humans are unknown. Risks to the offspring include further unintended mutations. Among the risks to breeding partners and humans is the transmission of diseases that are ordinarily confined to animal species. A justification for condition (4), the chimpanzee language-threshold condition, is that this characteristic marks one division between the linguistic capacity of humans and that of the most advanced primates. The capacity to communicate through language, as distinct from other forms of communication, is preeminently, though not quite uniquely, human.[45] A justification for the other part of condition (4), the "other cognitive capacities" condition, is to protect chimeras that have remarkable mechanical, architectural, artistic or other abilities even if the chimeras do not use language.

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44. In effect, I am sympathetic to Rawlsian and Scanlonian approaches to these decisions. *See* JOHN RAWLS, A THEORY OF JUSTICE (1971); THOMAS M. SCANLON, WHAT WE OWE TO EACH OTHER (1998).

45. *See, e.g.*, GEORGE PAGE, INSIDE THE ANIMAL MIND 141–60 (1999).

Together these conditions are sufficient for moral permissibility. Of course, these conditions may not be jointly or individually necessary for moral permissibility. In other words, saying that if all these conditions are satisfied, then the creation of the chimeras is morally permissible is *not* to say that if one or even all of these conditions are *un*satisfied then the creation of chimeras is not morally permissible.

Principle 2: The use of chimeras is morally permissible, subject to Principles 3 and 4, if all of the following conditions are satisfied: (1) the use of the chimera respects the chimera's biological nature and the nature of the chimera's bodily parts; (2) needless physical and emotional pain is prevented; and (3) if the chimeras are classified as enhanced or dramatically enhanced, due respect is given to their elevated moral status.

A justification for condition (2) of Principle 2 is that chimeras ought not to be exposed to unwarranted pain, harm, or disrespect, or to unwarranted risks thereof.[46]

As with the conditions that comprise Principle 1, the conditions in Principle 2 are jointly sufficient for moral permissibility, but may not be jointly or individually necessary. Similarly, to say that if all of these conditions are satisfied, then the use of the chimeras is morally permissible does not mean that if one or all of these conditions are unsatisfied, then the use is not morally permissible.

Principle 3: The creation of chimeras classified as enhanced or dramatically enhanced is morally impermissible unless important, highly promising research cannot be performed without them.

A justification for Principle 3 is that bringing such chimeras into being is tantamount to making new species with cognitive abilities roughly equivalent to those of a chimpanzee. To require that research on these chimeras be both important and highly promising recognizes these chimeras' enhanced moral status. Principle 3 mirrors current law, under which chimpanzees receive greater protection than any other species.[47] Furthermore, Principle 3 recognizes that chimpanzees are social creatures. If enhanced chimeras are also social creatures, Principle 3 requires that scientists create enough of them to form a social unit; otherwise, the treatment of the chimeras will not recognize their enhanced moral status.[48]

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46. I believe that this justification is consistent with current U.S. law, although whether laboratory practice in the United States is always compatible with U.S. law is another question.

47. *See* Chimpanzee Health Improvement, Maintenance, and Protection Act of 2000, 42 U.S.C. § 287a-3a (2000).

48. Feeling lost, alone, or lonely adversely affects many social and familial animals; even predominantly solitary animals spend more time together than is often supposed. *See, e.g.*, JEFFREY MOUSSAIEFF MASSON & SUSAN MCCARTHY, WHEN ELEPHANTS WEEP: THE EMOTIONAL LIVES OF ANIMALS 52, 97–98 (1995).

Principle 4: It is morally impermissible to create dramatically enhanced chimeras if doing so substantially alters the cognitive capacities of the chimeric creatures from what they would have been otherwise.

To be explicit, this principle applies to the intentional, knowing, reckless, or negligent creation of such chimeras. It does not say that creating them by non-negligent accident is morally wrong. Nevertheless, if any were created accidentally, Principle 5 would apply to them, as explained below.

By definition, chimeras classified as dramatically enhanced would have an intelligence, linguistic capacity, self-awareness, emotions, and ability to form social relationships that approximate those of humans. In accord with Mark Greene and his colleagues, I highlight several biological factors that bear on the development and continuation of chimeric experience above the level of chimpanzee experience: the nature of the contributing species (especially human and primate), the percentage of engrafted human cells, the engraftment site(s), the extent of neural development, the size and structure of the brain, and any brain pathology.[49] The behavioral and experiential correlates of these biological factors include the use of language, the existence of the higher emotions and reactive attitudes (e.g., guilt, shame, resentment), the forming of social relationships, and self-awareness.[50] The benefits of producing such an organism would probably never outweigh the harms. Were the harms outweighed by the benefits, that would still not suffice to justify creating this organism, for a significant risk exists that others would fail to treat it as an end in itself.

Principle 5: If, despite Principle 4, dramatically enhanced chimeras are created, treatment of them must reflect their elevated moral status.

A justification for Principle 5 is that any chimera classified as dramatically enhanced has the approximate moral status of a human being. The dramatically enhanced chimera therefore ought to be treated in approximately the same way we treat human beings. For instance, these chimeras could be research subjects only with their voluntary, informed consent.

Principle 6: Subject to Principle 7, when the outcome of research on chimeras is reasonably predictable, it is morally permissible to create and use the chimeras only if the anticipated benefits exceed the anticipated costs of the research.

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49. *See* Mark Greene et al., *Moral Issues of Human-Nonhuman Primate Neural Grafting*, 309 SCIENCE 385, 386 (2005).

50. Self-awareness involves the ascription of mental experiences to oneself and not simultaneously to others. Examples of self-awareness include having memories of which one is aware and recognizing oneself in a mirror. *See, e.g.*, ROGERS, *supra* note 34, at 20, 23, 30.

The justification for Principle 6 is thoroughly consequentialist. It differs in that respect from the preceding principles, which are not easily defended solely on consequentialist grounds. The "subject to" language in Principle 6 accounts for the situation in which the anticipated benefits only slightly exceeds the anticipated costs. In that case, a risk assessment should be performed in accordance with Principle 7. A justification for this gloss on Principle 6 is that in such borderline cases, it is not clear without a risk assessment whether the anticipated benefits will exceed the anticipated costs once risk is also taken into account. Because assessing risk is not costless, performing a risk assessment adds to the anticipated costs of the research.

Principle 7: In cases where uncertainty exists and the risk of the research on chimeras is not reasonably predictable, it is morally permissible to create and use the chimeras only if: (1) a risk assessment performed using a cost-benefit analysis indicates that it is rational to proceed; and (2) the risk distribution does not violate any moral principles.

The justification for condition (1) of Principle 7 is consequentialist. Condition (1) requires a comparison of the risks of the projected research to the risks of alternative research projects and to the status quo. It is rational to proceed if the assessment indicates that the projected research is, on a risk-adjusted basis, the best alternative. The justification for condition (2) could be considered consequentialist, too. Economists, mathematicians, and to a lesser extent philosophers, have shown how to calculate the consequences of different risk distributions. For me, however, condition (2) is not wholly consequentialist, because special consideration must be given to particular individuals and groups. This is one of the ways in which the framework takes nonconsequentialist considerations of fairness into account.

Principle 8: In cases of conflict between or among the foregoing principles, Principle 7 has priority over Principle 6. Principles 1–5, whether individually or in combination, have priority over Principles 6 and 7.

Principle 8 is a set of priority rules. These priority rules are only rules of thumb or rough guidelines, rather than priority rules in Rawls's sense (which specify lexical precedence).[51] In contrast, Principles 1–7 are more nearly strict rules.

4. Defense of the Framework. People can, and should, question any proposed moral framework. In this case, it is appropriate to ask

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51. *See* RAWLS, *supra* note 44, at 42–45, 243–51, 298–303, 541–48; STEPHEN R. MUNZER, A THEORY OF PROPERTY 303 (1990) [hereinafter MUNZER, THEORY OF PROPERTY]. For a general treatment of conflict between moral principles and its resolution, see *id.* at 292–314.

why the framework is the right one, or even a plausible one, for thinking about hESC-derived, human-nonhuman chimeras? To be convincing, the answer can hardly rest on mere assertion. While it is impossible to construct an entire theory of ethics from the ground up in this Article, a defense of the framework is essential. I defend it on the following bases.

First, the framework's principles rest on a broader theory of moral philosophy developed elsewhere.[52] That theory maintains that no single principle, nor any supreme principle, governs moral analysis — be it the principle of utility in some form of consequentialism, Kant's categorical imperative, or any other principle. Instead, morality is pluralist: it is governed by multiple irreducible principles that sometimes conflict. Although priority rules resolve some conflicts, they may not resolve all of them. For example, consider the moral theory of property rights. This theory rests on three irreducible principles: a principle of utility and efficiency, a principle of justice and equality, and a principle of desert based on labor.[53] This theory provides ways of analyzing many moral problems: the justifiability of property rights in human body parts, the rights of homeless persons and day laborers in urban public spaces, the intersection of tort law and intellectual property in genetically altered crops, and law and biotechnology generally.[54]

Second, this Article's framework is specifically designed for human-nonhuman chimeras. This design is evident not only in the principles but also in the distinctions and factors. The distinctions and factors extract features of cases and research projects considered relevant to the moral analysis of chimeras.[55] Some might object that introducing these features relies on moral intuitions. This objection, however, ignores the reality that it is impossible to engage in moral philosophy without some appeal to substantive moral intuitions —

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52. The wellsprings lie in Stephen R. Munzer, *Persons and Consequence: Observations on Fried's* Right and Wrong, 77 MICH. L. REV. 421 (1979) (defending a mixed theory in which otherwise deontological principles can to some extent be qualified or overridden by consequences); *see also* Stephen R. Munzer, *Intuition and Security in Moral Philosophy*, 82 MICH. L. REV. 740 (1984) [hereinafter Munzer, *Moral Philosophy*] (arguing that there is an unavoidable need to rely on substantive moral intuitions).

53. For a systematic exposition and defense, see MUNZER, THEORY OF PROPERTY, *supra* note 51, at 3–12, 191–314.

54. *See*, *e.g.*, Stephen R. Munzer, *An Uneasy Case Against Property Rights in Body Parts*, 11 SOC. PHIL. & POL'Y, Summer 1994, at 259; Stephen R. Munzer, *Ellickson on "Chronic Misconduct" in Urban Spaces: Of Panhandlers, Bench Squatters, and Day Laborers*, 32 HARV. C.R.-C.L. L. REV. 1, 3 (1997); Molly A. Holman & Stephen R. Munzer, *Intellectual Property Rights in Genes and Gene Fragments: A Registration Solution for Expressed Sequence Tags*, 85 IOWA L. REV. 735, 825–26 (2000); Stephen R. Munzer, *Plants, Torts, and Intellectual Property*, *in* PROPERTIES OF LAW: ESSAYS IN HONOUR OF JIM HARRIS 189 (Timothy Endicott et al. eds., 2006) [hereinafter Munzer, *Plants*].

55. *See* Greene et al., *supra* note 49; Cynthia B. Cohen, *Creating Human-Nonhuman Chimeras: Of Mice and Men,* AM. J. BIOETHICS, Summer 2003, at W3.

whether broad intuitions, such as the principle of utility, or narrow ones, such as Principle 4 in this Article, which forbids the creation of dramatically enhanced chimeras.[56]

Third, the entire framework is subject to revision under a variant of wide reflective equilibrium.[57] Wide reflective equilibrium is a method for justifying morality that seeks coherence in a set of moral judgments, a set of moral principles, and a set of background theories. As to chimeras, the set of moral judgments consists of intuitions about particular cases; I will turn to some of those cases shortly. The set of moral principles consists of Principles 1–8 that I just formulated. The set of background theories includes the distinctions and factors introduced earlier. Applying wide reflective equilibrium to a framework requires one to move back and forth among the moral judgments, moral principles and background theories to achieve consistency. For instance, as one forms moral judgments about particular examples of creating or using chimeras, it might prove necessary to adjust the principles, the background theories, or both.[58] Even if a "true" or "correct" or "objective" moral theory of human-nonhuman chimeras exists, convergence under the wide reflective equilibrium method is neither necessary nor sufficient to establish that we have found that theory; however, such convergence gives a reason for accepting the theory.[59]

Let's discuss the cases.

C. The Analysis of Cases

1. Morally permissible. Cases (1) and (2) are two examples of human-nonhuman chimeric creation that seem morally permissible.

In the terminology of the framework, Case (1) involves basic human-nonhuman chimeras because the chimeras have no distinctively human intellectual, emotional, or linguistic capacities.[60] The framework draws attention to their murine appearance, the cellular mode of their creation, and their use in research. These basic chimeras do not breed either among themselves or with regular mice. In essence, in Case (1) we have little more than mice with some human hematopoietic stem cells and their differentiated progeny inside them. Case (1) satisfies Principles 1, 2, and 6 and does not violate the other principles. Thus, the creation and use of the mice is morally permissible.

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56. *See generally* Munzer, *Moral Philosophy*, *supra* note 52.

57. This idea has its roots in RAWLS, *supra* note 44, at 48, and receives powerful development and expression in Norman Daniels, *Wide Reflective Equilibrium and Theory Acceptance in Ethics*, 76 J. PHIL. 256 (1979).

58. For use of the method of wide reflective equilibrium in the theory of property, see MUNZER, THEORY OF PROPERTY, *supra* note 51, at 308–10.

59. *See id*. at 309 (explaining the same point in relation to property).

60. *See supra* text accompanying notes 32–33.

Robert Streiffer has discussed a somewhat similar case. The leading difference is that Streiffer's example employs hematopoietic stem cells from the beginning, whereas Case (1) starts with hESCs. With regard to his example, Streiffer remarked that neither researchers nor bioethicists would regard it "as especially or distinctly problematic."[61] Although Case (1) differs slightly from Streiffer's, there are compelling reasons for concluding that the creation and use of these chimeras is morally permissible. Although Case (1) states that the scientists ensure that hESCs will differentiate only into hematopoietic stem cells and will not "humanize" the mice, some might raise a question about risk: can we be certain that scientists can and will make these limitations on the chimeras effective? If the scientists can and will, then the case remains unproblematic. If they cannot or might not, then under the framework it would be necessary to identify the probability and gravity of adverse outcomes. It would also be necessary to assess the scientists' ability to deal with such outcomes in accordance with Principle 7.[62] As these questions suggest, Case (1) as constructed is morally permissible. However, by changing certain details, such as the likelihood and gravity of adverse results, it is possible to construct a variation that could be morally problematic.

Case (2) also involves basic human-nonhuman chimeras.[63] They are murine in appearance and unable to breed. The human cells active in the chimeras are unrelated to upper-level human functions. Apart from the chimeras' immune systems, they are functionally equivalent to mice. Their creation is morally permissible under Principle 1 because all of the conditions contained in that principle are met. Their creation is also permissible under Principle 6 because the outcome of the research is reasonably predictable and the anticipated benefits exceed the anticipated costs. The result under Principle 6 derives in part from the starting assumption that current treatment of research animals is morally acceptable. Although the research project involves exposing the chimeras to HIV and, possibly, to pain and death,[64] this type of experiment lies within current regulations concerning the use of animals in research. Case (2) is morally permissible under Principle 2, since needless physical pain to the chimeras is avoided.

2. Morally impermissible. Now consider two examples in which the creation or treatment of human-nonhuman chimeras seems morally impermissible.

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61. Streiffer, *supra* note 22, at 349.

62. *See supra* p. 17.

63. *See supra* p. 8.

64. For a real-world example of the transmission of HIV to chimeras with human immune systems, see Shreeve, *supra* note 16, at 4.

Depending on the type of large primate used, Case (3) involves basic or enhanced human-nonhuman chimeras. In Case (3), researchers inject hESCs and hEGCs into primate fetuses to examine the development of the reproductive systems of primates and humans. This *use* does not seem to violate any of the conditions of Principle 2 because there is no evidence that this procedure inflicts needless physical or emotional pain on the chimeras. Further, scientists confine their research to the chimeras' reproductive systems and take steps to prevent the formation of cells not ordinarily found in the ovaries and testes. Thus, the scientists respect the chimeras' biological nature and the nature of their bodily parts. As described, Case (3) seems unlikely to enhance the cognitive or emotional capacity of the chimeras beyond their natural state. Consequently, even if the large primates employed were gorillas or orangutans, the resulting chimeras would probably have capacities that fall below those of chimpanzees. Were chimpanzees employed, the chimeras would qualify as enhanced, yet Case (3) suggests that the treatment reflects the chimeras' elevated moral status. Therefore, if all of the conditions of Principle 2 are met and if they indeed jointly suffice for moral permissibility, then the use of the chimeras seems morally permissible.

The *creation* of this chimera, however, is suspect. Although Case (3) satisfies conditions (1), (2) and (4) of Principle 1, it does not satisfy condition (3), the no-breeding condition. This feature of Case (3) is not sufficient to show that the creation of these chimeras is morally impermissible. Nevertheless, it is enough to prompt a more careful examination of the case to determine if the breeding of these chimeras creates a moral problem.

This subsidiary examination begins by evaluating the research proposal. Aside from the part allowing chimeras to breed, the rest of the research design could quite easily satisfy Principles 1, 2, and 6. The part of the research protocol that requires more careful analysis is the provision allowing the chimeras to mate.[65] As described, the facts of Case (3) do not expressly state what research purpose is served by breeding or attempting to breed the chimeras. If the breeding protocol springs from sheer scientific curiosity, the framework requires us to determine whether Principle 7 applies, which would require a risk assessment to be performed. Recall that Principle 7 applies when the outcome of a particular type of research on chimeras is not "reasonably certain." In Case (3), it is quite possible that the chimeras would prove unable to breed. Even if a female carried the fetus to term and delivered it successfully, the offspring might turn out to be a chimera just like the parents. As these hypotheticals suggest, the results of the

65. Any offspring would be the result of sexual reproduction. The offspring would not be hybrids because the chimeras do not occur in nature. *See supra* note 5.

breeding attempts are not reasonably predictable, so Principle 7 does apply.[66]

Risk assessment under Principle 7 should take into account all possibilities. For instance, it should consider alternative procedures. In this case, the breeding of chimeras could be done adequately with existing chimeras or hybrids that have no human cells, such as ligers and geeps. Because the chimeras of Case (3) produce some gametes identical to those of humans,[67] their offspring could theoretically be fully nonhuman primate, chimeric, or fully human. In Case (3), if a male and a female chimera were to have a fully nonhuman primate or chimeric infant, the outcome seems unlikely to distress the parents or the offspring because the offspring would have the primate appearance and capacities of the parents.

But what if the offspring were a fully human baby? The offspring would not have the primate appearance of its parents, and the chimeras might notice that difference. As the baby develops, the parents might notice, as through a glass darkly, that the child's intellectual and linguistic capacities are greater than theirs and that its emotions and moods differ from their own. The possible effects on the parents pale in comparison to the possible effects on the offspring.[68] Even though separation from one's parents can cause great distress, it would be unethical to leave a human baby solely with its chimeric parents forever. One could reduce the degree of distress through a weaning process, with continued access to the parents at intervals. But one must ultimately confront the moral issue of removing it from its parents and placing it with human adoptive parents.

This parade of difficulties leads to the moral judgment that basic and enhanced chimeras that produce some gametes identical to those of humans should not to be allowed to breed. This conclusion does not entail that *all* human-nonhuman chimeras should be prevented from

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66. *See supra* p. 17. Of course, results that are not reasonably predictable at one time might become reasonably predictable at a later time. Hence, it is possible that at some future time Principle 7 would no longer apply.

67. These chimeras probably exhibit a condition called "gonadal mosaicism." The term "gonadal mosaicism" is ambiguous. Sometimes it applies to a condition in which some but not all of an individual's gametes (sperm or oocytes) carry a genetic mutation. At other times, the term applies to a condition in which tissue in a gonad (testis or ovary) contains some normal gonadal cells and some cells that are not normal because of genetic mutation, chromosomal anomaly, or cellular anomaly (such as cells from two different zygotes). *See, e.g.*, STEDMAN'S MEDICAL DICTIONARY 982–83 (William R. Hensyl 25th ed. illus., 1990); JURG OTT, ANALYSIS OF HUMAN GENETIC LINKAGE 270–71 (3d ed. 1999); Joël Zlotogora, *Germ Line Mosaicism*, 102 HUMAN GENETICS 381 (1998). A highly interesting type of gonadal mosaicism (or related condition) would be a situation in which gonads — either ovarian or testicular tissue — produce both normal human and nonhuman gametes. This variant is interesting because it presents the possibility of two mating human-nonhuman chimeras having fully human offspring.

68. *Cf.* Tiffany S. Perkins et al., *Children of Mothers with Intellectual Disability: Stigma, Mother-Child Relationship, and Self-Esteem*, 15 J. APPLIED RES. IN INTELL. DISABILITIES 297 (2002).

breeding with each other. But it casts doubt on any research protocols allowing these human-nonhuman chimeras to breed, at least until the results can be predicted accurately and the predicted results are shown to be benign.

Observe that this conclusion and Case (3) involve basic and enhanced chimeras. The same verdict does not apply to dramatically enhanced human-nonhuman chimeras. Their cognitive capacities approximate those of humans. They should, in relevant respects, be treated the same as humans. Although many disagree about what moral rights humans have, many hold that they have a moral right to procreate. If so, it would seem that dramatically enhanced chimeras also have a right to procreate with any reproductively compatible species, including another chimera of the same type. What might the offspring of a dramatically enhanced chimera be like? We have no idea.

At this point it is crucial to distinguish between having a moral right to procreate and its being morally permissible to exercise that right. For example, a man and a woman who consult a medical geneticist might be told that were they to have a child together, the infant would only live a few years and experience great pain during its short existence. The geneticist might then warn them not to have a child together. One plausible position on this example is that although the man and the woman have a moral right to procreate with each other, it would be morally wrong to exercise this right.[69] If there were evidence that a dramatically enhanced chimera and its intended mating partner would have offspring that suffer unbroken pain during a short life, the chimera might have the moral right to procreate with its intended partner even though it would be morally wrong to do so.

Case (4) involves enhanced chimeras. Both the creation and use of these chimeras are morally impermissible. In Case (4), researchers produce an obedient, cheerful chimera with an IQ of 35–40 to 50–55 that is capable of communicating in language and performing household chores.[70] Principle 3 is violated, because it has not been shown that important, highly promising research cannot be performed without the chimeras.

Case (4)'s use of the chimeras also violates Principle 2 because the research does not give due respect to the chimeras' elevated moral status, and their creators have not taken appropriate measures to prevent immoral use and treatment. Indeed, Case (4) raises the specter of using chimeras as forced labor because they have just the right combination of sunny disposition, intelligence, and docility. Consider that many people would like to have their housework done for them. Of course, they could hire a live-in human maid or contract with a house-

69. *Cf.* Jeremy Waldron, *A Right to Do Wrong*, 92 ETHICS 21 (1981) (drawing this distinction at a general level).

70. *See supra* text accompanying note 34.

cleaning service. But that could be expensive, and the hired workers might be nosy, sullen, or uncooperative. They could also annoy the homeowner by demanding higher wages. So what is a frustrated homeowner to do? The docile housework chimera with the happy disposition might seem to be the ideal solution to the homeowner's problems. Of course, creating an intelligent organism for the purpose of forced labor is morally odious. A language-using creature with the level of intelligence specified in Case (4) is midway between a chimpanzee and a human being in cognitive and linguistic abilities. It is above the level of a guide dog. Consequently, even if the chimera were given some degree of comfort, independence, and respect, which is how we aspire to treat guide dogs, that would not accord it the respect required under the framework.

3. Morally debatable but ultimately morally permissible. The permissibility of the remaining two cases is debatable.

Case (5) involves what seems to be an enhanced human-nonhuman chimera. At first, our framework might seem to throw little light on Case (5), in which researchers create a chimera with some humanlike vocalizations.[71] The human-chimpanzee chimera does not differ in appearance from ordinary chimpanzees. Moreover, its creation and use do not run afoul of any of our principles. The only difference that stands out is the chimera's ability to sob and laugh in a fashion similar to humans. We seem, in short, to have an enhanced human-nonhuman chimera,[72] although what underlies the sobbing and laughter is as yet unknown.

Case (5) is unsettling because it exceeds what Jamie Shreeve has referred to as the "squirm threshold."[73] It is not clear, however, that this reaction is *moral* squirming. People who watch contestants dunk their heads in a tank of eels on the television show "Fear Factor" might squirm, but the squirming does not appear to be a distinctively moral reaction. Biological anthropologist Terrence Deacon argues that creating a human-chimpanzee chimera that can sob or laugh would be "highly unethical."[74] The reasons behind his conclusion, though, are unclear. In Case (5), since we do not know what the chimera's mental states are when it sobs or laughs, we cannot know whether these acts are expressing distinctively human reactions or emotions, or whether the sobbing and laughter are just "stray" humanlike vocalizations.[75]

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71. *See supra* text accompanying note 35.

72. *See supra* note 37 and accompanying text.

73. Shreeve, *supra* note 16, at 47.

74. *Id*.

75. On emotions in animals, see MARC BEKOFF, ANIMAL PASSIONS AND BEASTLY VIRTUES: REFLECTIONS ON REDECORATING NATURE 23–31 (2006); MASSON & MCCARTHY, *supra* note 48.

Like Case (3), Case (5) indicates that our framework requires a closer look at the facts. One way to make progress on Case (5) is to examine the circumstances in which the chimera sobs and laughs. To determine if those acts should be considered "distinctively" human, we could observe the chimera's reactions in situations in which humans would be likely to sob or laugh. For example, if the death of a companion or the capture of a very young chimpanzee by another social group immediately precedes sobbing, we might interpret the chimera's reaction as a sign of grief or deep distress. If another chimpanzee takes a pratfall or starts gobbling up food that almost all chimpanzees consider hardly worth eating, and the chimera immediately begins to laugh, we might think that it has a more developed sense of humor than other chimpanzees. Another way to unravel Case (5) might be to conduct PET or functional MRI scans of the chimera's brain when it sobs and laughs. It would be telling if such tests showed activation of those areas of the chimera's brain that correspond to the areas of the human brain that show activity when a human being sobs or laughs.

Such results from these observations would provide reasons for believing that the chimera has a richer emotional life than other chimpanzees and that it possesses certain traits that make it more like human beings. In that event, under Principles 2, 3, 6, and 7, researchers should alter the treatment of the chimera to reflect its elevated moral status. For example, under the framework researchers should not stage unhappy events just to see whether the chimera will sob.

If, however, the sobbing and laughter were found to occur randomly, or if the chimera sobs when chimpanzees would hoot and laughs when chimpanzees would pant, then we should treat the chimera's sounds as little more than stray humanlike vocalizations.

Under this analysis, creating such an enhanced chimera is morally permissible, subject to a caveat regarding the treatment of the chimera if its sobbing seemed likely to be an outward sign of grief or deep distress. In that case, the researchers should not cause the chimera to sob without very strong reasons. Under Principle 3, causing such distress might still be permissible if the research were important and highly promising and could not be done without this chimera. In contrast, researchers would not face a similar restriction on staging events that might make the chimera laugh, if the laughter were found not to be a stray vocalization.

The treatment of Case (5) underscores the reality that one cannot apply moral principles to some situations without carefully digging into the facts. Even then, areas of correspondence among human, chimpanzee, and chimeric brains may be difficult to identify, and there is some risk of homocentrism in expecting chimpanzees and

chimeras to have the same sense of humor and expressions of sadness as humans.

Case (6) involves a basic human-nonhuman chimera. The framework helps analyze Case (6), in which researchers graft a synthetic auricle onto the back of a mouse.[76] In particular, the framework makes clear that this basic human-nonhuman chimera results from both cellular and anatomic modes of creation. Both the creation and use of the chimera are permissible under Principles 1 and 2. Principle 3 is inapplicable because the chimera is basic rather than enhanced. Principles 6 and 7 are also relevant to this example; it is through these principles that the framework considers risk versus benefit. The commendable benefit sought is providing a child who has a disfiguring congenital condition (the lack of an auricle), with an external ear designed to be the mirror image of the child's other ear.

One factor that Principles 6 and 7 highlight is risk. In addition to the risk that the experiment might fail, there is a risk that bacteria or viruses common in mice might spread to the engrafted auricle and through it to the child, causing harm.

What arguably stands out the most, however, is the appearance of this chimera. Case (6) involves a "visible chimera" — namely, a creature with a viewable, ostensibly human part.[77] Dr. William Hurlbut argues that "[h]uman appearance is something we should reserve for humans. Anything else that looks human debases the coinage of truth."[78] This statement, though perhaps plausible, is more nearly an assertion than an argument. Yet, if we switch from an external ear on a mouse's back to "a sheep with a human face,"[79] the case might seem to cross a line, even if that line cannot be drawn precisely. It is not plain, however, that it is a moral requirement to reserve a human ear or face for humans, rather than simply a prudent practice so we can avoid becoming upset. Dr. Hurlbut's metaphor about debasing coinage is rhetorically adept, but it is only a metaphor. Furthermore, the visibility of the ear seems critical to Hurlbut's reaction. If a body part of a member of one species is wholly within the body of a member of another species, the reaction might be indifference or even gratitude. For example, the late Senator Jesse Helms had a defective heart valve

76. *See supra* text accompanying note 36.
77. *See* Streiffer, *supra* note 22, at 351 (discussing a variant of this case).
78. Shreeve, *supra* note 16, at 45 (quoting Hurlbut).
79. *Id.*

replaced with a pig valve.[80] He is quoted as saying that "[e]very time I pass a plate of barbeque, I cry. It might be one of my relatives."[81]

Given that Case (6) involves a chimera with only a human external ear, rather than a human face, I do not see why its distinctly odd appearance should make either its creation or its use morally impermissible under the framework. To say otherwise, on the basis of Dr. Hurlbut's claim that human appearance is something we should reserve for humans, is to rest the case on metaphor and assertion rather than argument. A chimera with a human auricle might elicit reactions of anxiety, unease, or even disgust from some people. I acknowledge that these reactions could matter morally to consequentialists who count avoidance of subjective discomfort as a moral value. But they are not distinctively or exclusively moral reactions in the eyes of nonconsequentialists. In light of the beneficent purpose of the experiment in Case (6), the creation and use of the chimera are morally permissible.

D. Revisiting the Moral Framework

The goal of analyzing these cases was to produce coherence among our moral judgments, the eight moral principles, and our background theories about chimeras. What do the six cases say about the framework? First, they reveal that the first four cases are fairly easy and that the framework handles them nicely. Second, they show that the last two cases are hard and require fresh thinking. The difficulty of the latter cases and the need for additional analysis outside of the principles and background theories indicate that the original framework may be incomplete. In particular, it may be necessary to revise the principles to account for the moral aspects of breeding chimeras and of endowing them with recognizable human body parts.

Constructing and justifying a complete moral framework for analyzing all cases of human-nonhuman chimeras are beyond the scope of this Article. Still, I will indicate some of the steps needed to improve on the framework.

The first necessary step is to think more deeply about human traits and the emergence of noticeable or detectable human features in chimeric creatures. Cases (5) and (6) display this need. The thinking should not, however, be confined to reflections about morality and the reactions of present-day Westerners to this subset of chimeras. Reflec-

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80. I assume that Sen. Helms' pre-surgery cognitive capacities were typical of humans and that receipt of the porcine heart valve did not diminish these capacities. Given these assumptions, the post-surgery Sen. Helms was a dramatically enhanced chimera. *See supra* note 38.

81. Walter Truett Anderson, *Science Steps Across the Animal-Human Boundary: Fears of the Chimera Reemerge*, JINN MAG., June 12, 1995, http://www.pacificnews.org/jinn/stories/columns/heresies/950612-animal.html (quoting Helms).

tion should also extend to literary, anthropological, and social psychological studies. A notable feature of legendary creatures that mix animal and human species is that they can inspire fear and often meet an untimely end. Consider, for example, the Minotaur, the mythical creature with the body of a man and the head of a bull, which appears in Greek mythology and the paintings of Picasso. The Minotaur terrorized the citizens of Crete until Theseus, one of his human would-be victims, slew him. It is important to plumb the depths of the apprehension and often horror that surround the mixed-species creatures of myth in many cultures in order to gain a clearer understanding of contemporary Western reactions.[82]

We must also reckon with the risks of chimera research. Parasites, bacteria, and viruses that are harmless in one species might be harmful or even fatal to another.[83] Before experiments can proceed, we must be sure to protect chimeras and humans from cross-species diseases (zoonoses). Examples of diseases that began in nonhuman animals but now affect humans include HIV/AIDS (from monkeys), hantavirus pulmonary syndrome (from mammals), avian flu (from chickens, ducks, and geese), and the influenza virus of 1918 (from birds).[84] Such diseases, or the agents that cause them, can move from animals to humans through contact, xenotransplantation, and infusion of animal cells into human embryos, fetuses, or adults.[85] Diseases and the agents that cause them can also move from humans to animals,[86] including to human-nonhuman chimeras, though movement in this direction is less well documented. Mixing human and animal genetic

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82. Preston Ascherin has pointed out to me that many Asian religions and myths view certain mixed-species creatures favorably. In Hinduism, the Lord Ganesha, a major deity who has the head of an elephant and an otherwise human body with four arms, is the eldest son of the Lord Shiva and the Divine Mother Parvati. Ganesha is seen as the height of perfection. *See* ROBERT L. BROWN, GANESH: STUDIES OF AN ASIAN GOD (1991) (discussing Ganesha in Hinduism, Jainism, and Buddhism); PAUL B. COURTRIGHT, GANEŚA: LORD OF OBSTACLES, LORD OF BEGINNINGS (1985) (recounting the iconography of Ganesha, the myths surrounding his birth and exploits, and the worship of Ganesha as a Hindu deity). In Thai mythology, Garuda is a deity with the head, wings, talons, and beak of an eagle and otherwise the body and limbs of a man. Garuda, the offspring of a sage and a princess, is respected by all as brilliant, beautiful, and good. Today the image of Garuda appears on the royal flag and Thai bank notes. *See* CAROL ROSE, GIANTS, MONSTERS, AND DRAGONS: AN ENCYCLOPEDIA OF FOLKLORE, LEGEND, AND MYTH 133 (2000).

83. *See* Margaret A. Clark, *This Little Piggy Went to Market: The Xenotransplantation and Xenozoonose Debate*, 27 J.L. MED. & ETHICS 137, 139–40 (1999).

84. *See id.* at 139 (citing these and other examples). Clark identifies pigs as the source of the 1918 flu pandemic, but later research indicates the ultimate source was birds, although the matter is still disputed. *See, e.g.*, Ann H. Reid & Jeffrey K. Taubenberger, *The Origin of the 1918 Pandemic Influenza Virus: A Continuing Enigma*, 84 J. GEN. VIROLOGY 2285 (2003).

85. *See* Louisa E. Chapman, *Xenotransplantation*, *in* THE EMERGENCE OF ZOONOTIC DISEASES: UNDERSTANDING THE IMPACT ON ANIMAL AND HUMAN HEALTH WORKSHOP SUMMARY, *from* FORUM ON EMERGING INFECTIONS 17, 17 (Nat'l Academy Press 2002).

86. *See, e.g.*, A. Fritsche et al., *Mycobacterium Bovis Tuberculosis: From Animal to Man and Back,* 8 INT. J. TUBERCULOSIS & LUNG DISEASE 903 (2004).

material, as contemplated by the creation of human-nonhuman chimeras, raises the ominous specter of new diseases, along with the possibility of heightened susceptibility to existing maladies, opportunistic infections, and parasites. Humans, animals, or chimeras might host the mutant viruses or bacteria that could pose a new health risk.[87]

Additionally, a complete moral framework for human-nonhuman chimeras cannot rest content with a consequentialist balancing of benefits and risks. Instead, the framework should proceed to nonconsequentialist considerations. Nowhere is this recommendation more important than in the case of dramatically enhanced chimeras, which are similar to human beings in the level of self-awareness, intelligence, higher emotions, linguistic capacity, and social relationships. Kant famously gave various formulations of his (nonconsequentialist) categorical imperative. One of them, the formula of the end itself, requires that you act so that "you always treat humanity, whether in your own person or in the person of any other, never simply as a means, but always at the same time as an end."[88] A dramatically enhanced chimera is partly human. This chimera's human aspects are in no respect more salient than in its cognitive capacities and thus in its rationality and fitness to be treated as an end. Accordingly, were Kant to consider a dramatically enhanced chimera, he might well agree that, because of its increased cognitive capacities, it should be treated as an end in itself rather than simply as a means to benefit oneself or others.[89]

Another point concerns the chimeras themselves. Some writers suggest that chimeras resulting from human-animal experimentation might exist in horrible agony, become humans manqués trapped in animal bodies with no way out, or find themselves emotionally isolated in the world.[90] This suggestion warrants respect, even though

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87. Jonathan D. Moreno, *Congress's Hybrid Problem*, HASTINGS CTR. REP., July–Aug. 2006, at 12, 12–13 (analyzing Senator Brownback's bill to prohibit chimera threats to public health).

88. KANT, *supra* note 28, at 96. For discussion of Kant's understanding of "humanity," see Thomas E. Hill, Jr., *Humanity as an End in Itself*, 91 ETHICS 84 (1980); Christine M. Korsgaard, *Kant's Formula of Humanity*, 77 KANT-STUDIEN 183 (1986).

89. For an effort to show how, in a different context, Kant would likely adapt his views to advances in biology, see Stephen R. Munzer, *Kant and Property Rights in Body Parts*, 6 CAN. J.L. & JURIS. 319, 326–28 (1993).

90. *See* Jamie Shreeve, *I, Chimera*, 186 NEW SCIENTIST, June 21, 2005, at 39, 43. Shreeve writes,

> But what if [the chimera] were trapped between those two worlds, able neither to realize its humanity, nor to live in peace with its animal self? Such a creature would be as wretched as the one crafted by the hand of Doctor Moreau, 'thrown out to live a year or so, to struggle and blunder and suffer'. Perhaps the best argument against too potent a mix of human and animal would be the emotional torment suffered by a being so unspeakably alone in the world.

Id.; see also Bernard E. Rollin, *Ethics and Species Integrity*, 3 AM. J. BIOETHICS 15, 15–16 (2003) (discussing the dangers and ethics of creating hybrids).

one should proceed cautiously in developing and applying it. Any time scientists mix species there will be risks for the resulting chimeras. This point holds, above all, for human-nonhuman animal chimeras that have larger brains than the great apes and whose brains contain many human neurons. The development of self-awareness, higher emotions, linguistic capacity, and relationships with humans and perhaps other chimeras of the same type takes us well beyond current laboratory experiments. Under Principle 4 of the framework, it is morally impermissible to create such dramatically enhanced chimeras. *A fortiori*, it would be wrong to impose a risk of a life of agony or emotional deprivation on these creatures. If, contrary to the framework, scientists did develop them, under Principle 5 such creatures ought to be treated with the respect demanded by their elevated moral status.

A final issue is whether there is a counterexample to Principle 4, which states that it is morally impermissible to create dramatically enhanced chimeras if doing so substantially alters the cognitive capacities of the chimeric creatures from what the capacities would have been otherwise.[91] Consider this example: A scientist is searching for a treatment for Alzheimer's disease. In pursuit of his research, he injects hESCs into the brains of early fetal chimpanzees *in utero*. The results of his experiments are invariably human-nonhuman chimeras whose brains have some chimpanzee neurons but contain mostly human neurons. Despite the high proportion of human neurons, these chimeras are only advanced, for the structure of their brains is almost identical to that of typical chimpanzee brains, which limits the chimeras' cognitive capacities to the level of chimpanzees. So far, the scientist has not violated Principle 4. It turns out to be technically unfeasible to separate the chimpanzee neurons from the human neurons while keeping the human neurons in a suitable condition for transplantation into a human brain. The scientist now joins forces with a neurologist and a neurosurgeon, who transplant the mix of chimpanzee and human neurons into various areas of the brain of a permanently demented Alzheimer's patient. Before the operation, the patient is permanently demented in the sense that she will never recover without extraordinary external assistance, and she has no ability to remember, speak, read, write, follow a conversation, or recognize others. After the operation, her body does not reject the transplanted cells — not even the small proportion of chimpanzee neurons. Further, she now has regained all of the cognitive capacities typical of humans and of her own pre-Alzheimer's existence. We can thus identify three stages in the history of this individual: at time t_1 she is a normal human being, at t_2 she is a permanently demented member of

91. *See supra* text accompanying notes 49–50.

the species *Homo sapiens*, and at t_3 she is a dramatically enhanced human-nonhuman chimera with normal human cognitive capacities. So the scientist, neurologist, and neurosurgeon have created a dramatically enhanced chimera in violation of Principle 4. They have altered her cognitive capacities from what they would otherwise have been — permanent dementia. The point of this case as a *counter*example is that it does not seem morally impermissible, despite what Principle 4 says, to have restored to this patient the cognitive capacities which Alzheimer's had destroyed.

There are at least two ways of responding to this putative counterexample. One is to play a game of "fix-it" and restate Principle 4 more carefully so that, once reformulated, it no longer forbids the creation of this dramatically enhanced chimera. This response is likely to yield a rather cumbersome principle, and it might require further tweaks if people later on devise other, more ingenious counterexamples. A better response is to be intellectually honest and recognize this case as a justifiable exception to Principle 4 as it is currently stated. What makes this case exceptional is that our scientific-medical trio is *restoring* to this patient cognitive capacities that she once possessed. For the better part of her life (t_1) she had entirely normal human cognitive capacities. Only when Alzheimer's thrust her into permanent dementia (t_2) did she lose those capacities. So now (t_3) they are only giving back to her capacities that she possessed earlier. This case differs sharply from the standard profile of dramatically enhanced human-nonhuman chimeras that we rightly wish to prohibit – namely, those in which we begin with a nonhuman animal at t_1 and by adding human cells at t_2 manage to enhance its cognitive capacities dramatically. In the standard-profile case we are *endowing* a creature with humanlike cognitive capacities that it never had before and would not otherwise have acquired, whereas in the alleged counterexample we are *restoring* cognitive capacities that a particular individual once had. In short, this is a principled exception to Principle 4, not an ad hoc manipulation of the language of Principle 4.

IV. FROM ETHICS TO SOCIAL POLICY

Morality, understood in the way sketched in Part II, has some dimensions that often lie outside the bounds of social and legal policy. Virtues, vices, and moral ideals are not always amenable to policy discussions. Furthermore, I do not assume that morality, even when it evaluates actions with regard to their impact on society, should be enacted into law either as a general matter or in the case of human-nonhuman chimeras. As a result, the proper social policy towards chimeras may differ from the moral framework developed in Part III.

A. General Considerations

So far as human-nonhuman chimeras are concerned, the position I expressed above cuts in two different directions, depending on the situation. On the one hand, creating some human-nonhuman chimeras or treating them in certain ways may be morally impermissible. Yet, this moral impermissibility does not mean that we should have a social or legal policy against the creation and use of such chimeras. Contract law provides a distant analogy. Specifically, contract law enforces only promises that are backed by consideration or that induce reasonable detrimental reliance by the promisee. Suppose that you promise to take your children to Disneyland on Saturday. It may be morally wrong for you not to honor your promise, but the law of contracts would not enforce your promise to take your children to Disneyland on Saturday — and with good reason. Enforcing all intrafamilial promises would consume substantial resources and intrude into private family relationships.

On the other hand, sometimes creating human-nonhuman chimeras or treating them in certain ways may be morally permissible. Yet, despite the moral permissibility, for prudential reasons it might make good sense for social or legal policy to prevent the creation and treatment of those chimeras. Few need reminding that hESC research is a tricky, even explosive, moral and political issue.[92] Both supporters and opponents of such research might want medical groups to ensure that their members never carry out research that comes within a country mile of moral wrongdoing, and research into the creation of human-nonhuman chimeras could conceivably come within that bound. Likewise, social conservatives and liberals alike might agitate for legal regulations that forbid research that carries the faintest odor of immorality.

This point is not intended to be a slippery slope argument. Rather, I argue only that sometimes it is imprudent to incur the high political costs of trying to get social policy or the law to conform exactly to morality. The costs of attempting to achieve that conformance include both the difficulties of getting social policies or legal regulations implemented and the potential loss of faith in public institutions (reputational costs).

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92. Some of the controversy about hESC research turns on the moral status of the blastocyst. *Compare* POPE JOHN PAUL II, THE GOSPEL OF LIFE ¶¶ 58–63 (1995) (condemning research that destroys embryos on the ground that a fertilized oocyte is already a human life), *with* Bonnie Steinbock, *The Morality of Killing Human Embryos*, 34 J.L. MED. & ETHICS 26, 33 (2006) (contending that an embryo outside the womb has no "valuable future" and so has no moral status); *see also* RUSSELL KOROBKIN, STEM CELL CENTURY: LAW AND POLICY FOR A BREAKTHROUGH TECHNOLOGY 26–61 (2007) (providing a vivid account of the moral, social, and political controversies surrounding hESC research).

Although no bright line separates social policy from legal policy as a general matter, I differentiate between the two in this Article as follows. By "social policy" I mean centrally the reports, proclamations, and guidelines of official commissions on human-nonhuman chimeras. By "legal policy" I mean centrally the statutes, administrative regulations and actions, and judicial decisions about such chimeras, together with the broader spirit or purposes that inform these laws and decisions. The distinction matters here. The law may establish a basic framework for regulating human-nonhuman chimeras. Within this framework, the non-legal policies of official commissions may both set aspirational standards and fine-tune the details of permissible chimeric research. In sum, the law would provide a baseline for the analysis, but social policy would offer significantly more guidance and restrictions.

B. Social Policy in Commission Reports

Two prestigious commissions have grappled with the issues raised by the creation of human-nonhuman chimeras. I concentrate on their reports because they offer exceptionally thoughtful discussions of many issues related to this Article. I use the moral framework developed and applied in Part III as part of my basis for analyzing and developing a social policy on human-nonhuman chimeras. As a result, I am occasionally critical of these reports' conclusions.

In 2004, the President's Council on Bioethics concluded that mixing human and animal tissues is not morally objectionable in the abstract.[93] It endorsed xenotransplantation — the transplantation of an organ, organ part, or tissue from one species into another species.[94] It also endorsed the insertion of animal genes into humans or human fetuses in order to prevent genetic disease.[95] The Council recommended, however, a prohibition on "the production of a hybrid human-animal embryo by fertilization of human egg by animal sperm or of animal egg by human sperm"[96] as well as a prohibition on "the transfer, for any purpose, of any human embryo into the body of any member of a nonhuman species."[97] Despite initial discussions, the Council ultimately decided to omit a recommendation prohibiting the combination of human and nonhuman embryos. Some members sug-

93. *See* COUNCIL REPORT, *supra* note 24, at 220; *see also* Kopinski, *supra* note 10, at 642–46 (explaining that the Council "did not want to judge the humanity or moral worth of a hybrid entity, and . . . did not want . . . ambiguously human life to have nonhuman ancestors" and believed that "humans should be placed only in human wombs").

94. *See* COUNCIL REPORT, *supra* note 24, at 220.

95. *See id*.

96. *Id*. at 221.

97. *Id*. at 220–21; *see also* Consolidated Appropriations Act, 2006, Pub. L. No. 109–149, § 509 (2005).

gested that such a prohibition required further consideration of the potential scientific and therapeutic benefits of human-nonhuman embryonic chimeras.[98]

The purpose of this Article and the purpose of the Council report, though not identical, are related. This Article concentrates chiefly on human-nonhuman chimeras created using hESCs or their differentiated derivatives and deals with the moral, social, and legal aspects of these chimeras. The Council report addressed reproductive technology generally, did not consider hESC-derived chimeras, and made recommendations of social policy with a less probing analysis of the specific moral and legal issues than that attempted here.

I agree with the Council regarding xenotransplantation and transgenic research. Xenotransplant research is useful for studying tissue rejection and graft-versus-host disease.[99] The most conspicuous employment of xenotransplants in current medical practice is the use of porcine heart valves to replace diseased human cardiac valves. The closest example discussed in this Article is Case (6), the grafting of a hESC-derived external ear onto the back of a mouse, which I argued is morally permissible under the framework. Likewise, I agree with the Council report's conclusion that transgenic research is permissible. As I emphasized earlier, chimeras have *cells* from different species whereas transgenic creatures have *genes* from different species.[100] Generally, research on the latter poses fewer moral and social problems than does research on the former.[101]

The Council report is also right to recommend a prohibition on "hybrid human-animal embryo[s]" created at fertilization and a prohibition on putting a human embryo into the body of "any member of a nonhuman species."[102] The first prohibition addresses one type of human-nonhuman chimera. It is not the type with which I am centrally concerned because no hESCs or their derivatives are directly

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98. *See* President's Council on Bioethics, Session 3 and Session 4: Biotechnology and Public Policy: Proposed Interim Recommendations, III and IV (Oct. 16, 2003), http://www.bioethics.gov/transcripts/oct03/session3_4.html.

99. *See, e.g.*, Joanne L. Zahorsky-Reeves et al., *The Xenoantibody Response and Immunoglobulin Gene Expression Profile of Cynomolgus Monkeys Transplanted with hDAF-transgenic Porcine Hearts*, 14 XENOTRANSPLANTATION 135 (2007); Rozemarijn S. van Rijn et al., *A New Xenograft Model for Graft-Versus-Host Disease by Intravenous Transfer of Human Peripheral Blood Mononuclear Cells in RAG2-/-γc-/- Double-Mutant Mice*, 102 BLOOD 2522 (2003).

100. *See supra* text accompanying notes 3–4.

101. *See* William Saletan, *Making Manimals*, WASH. POST, June 24, 2007, at B2 (contrasting the widespread use in biomedical research of transgenic animals carrying human DNA with the reluctance of ethicists to condone mouse/human chimeras resulting from the insertion of human stem cells into developing mouse brains); *see also* Donna Greene, *Dr. Stuart A. Newman: Drawing a Line in Genetic Engineering*, N.Y. TIMES, May 31, 1998, at 14WC (highlighting both Newman's opposition to some chimeras and his support for using transgenic animals for the advancement of health care).

102. COUNCIL REPORT, *supra* note 24, at 221.

used to create it. Nevertheless, the Council report's human-animal chimera would likely run afoul of Principle 3 or 4 of the framework because the chimera could well turn out to be enhanced or dramatically enhanced. The moral analysis proposed by this Article, therefore, confirms the verdict of the Council in its report. The second prohibition — against implanting a human embryo into the womb of a nonhuman animal — is not specifically addressed by the framework for the straightforward reason that the framework is designed to deal with hESC-derived, not embryo-derived, chimeras. Yet I agree with the Council report on two grounds. First, if the result is indeed an embryo-derived chimera, then it could be enhanced or dramatically enhanced. Principle 3 would regulate the former and Principle 4 would forbid the latter. Second, if the result is not a chimera but instead a human being, the implantation into a nonhuman animal could have grave consequences, such as the transmission of diseases harmful to humans. The implantation could also run afoul of Kant's formula of the end in itself if the developing fetus or baby were used to replace organs or tissues in existing humans who are ill.

I shift now to guidelines for the scientific community issued in April 2005 by the Committee on Human Embryonic Stem Cell Research of the National Research Council and the Institute of Medicine ("NRC/IOM"). The NRC/IOM report included guidelines for human-nonhuman embryonic chimera research.[103] The Committee recommended prohibiting any research in which hESCs are introduced into nonhuman primate blastocysts or in which any nonhuman ESCs are introduced into human blastocysts.[104] It also recommended that "no animal into which [hESCs] have been introduced at any stage of development should be allowed to breed."[105] The NRC/IOM report aimed to prevent a scenario in which a human oocyte is fertilized by a human sperm and the resulting human embryo is inserted into an animal's womb. The Committee stated that any experiments in which hESCs, their derivatives, or other pluripotent cells are introduced into nonhuman fetuses or adult animals need more careful consideration because of the extent of the human contribution to the resulting animal's brain.[106] More generally, it recommended that introduction of hESCs into nonhuman mammalian blastocysts should be considered only as a last resort when no other experiment can provide the information needed.[107] This recommendation is a less precise way of stating my third principle.

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103. See NRC/IOM GUIDELINES, *supra* note 25, at 105–06.
104. *See id*. at 99.
105. *See id*.
106. *See id*. at 106.
107. *See id*.

The framework comes to much the same conclusions as the NRC/IOM report's guidelines. The guidelines' categorical no-breeding restriction may be well-founded, although my framework does not forbid chimeric breeding in all cases. Similarly, the guideline's restriction on functional humanization of a nonhuman brain is in accord with my third principle and Case (4). The guideline's restriction on introducing hESCs into nonhuman mammalian blastocysts is also well-founded. Although none of the cases discussed in this Article introduces hESCs at such an early stage, the discussion regarding possible revisions to the framework suggests reasons for being careful about such experiments.

The NRC/IOM report recommended prohibiting research in which hESCs are put into primate blastocysts or nonhuman ESCs are put into human blastocysts.[108] This recommendation, based on those organizations' deep familiarity with ESC research and the possible outcomes of such experiments, seems wise. It is also compatible with my framework. However, one cannot necessarily derive this recommendation from the framework. One could, of course, appeal to the enhanced-chimera condition of Principle 1, the respect for the biological nature of chimeras advocated in Principle 2, or the risk assessment contemplated in Principle 7.[109] But the outcome of the research described might not be an enhanced or dramatically enhanced chimera, which makes it difficult to appeal to Principle 1. Principle 2 is not necessarily applicable because it addresses the *use* rather than the *creation* of chimeras. Finally, this hypothesis is too speculative to apply Principle 7. Unlike the NRC/IOM report, the framework does not clearly rule out either the insertion of hESCs into primate blastocysts or the insertion of nonhuman ESCs into human blastocysts. Perhaps some highly nuanced application of the framework, fortified by reliable information on experimental outcomes and risks, could rule out these experiments. For the purposes of the present discussion, it warrants notice that informed social policy sometimes requires something in addition to acute, clear-headed moral philosophy.

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108. *See* NRC/IOM GUIDELINES, *supra* note 25, at 99. The Human Fertilisation and Embryology Authority in the United Kingdom drew the opposite conclusion with respect to closely related research. *See infra* note 131; *see also* Kopinski, *supra* note 10, at 662–64. Kopinski explains:

> A research proposal to create a mouse with human neurons in its brain received publicity, but did not generate much disapproval. A research proposal transferring human brain tissue into a *primate,* however, would cause more serious ethical concerns because of the similarities between the two species. Thus, chimeras made by moving human parts into nonhuman beings raise concerns when the transfer is significant enough to cast doubts on the humanity of the recipient.

Id. at 663.

109. *See supra* pp. 14–17.

Stepping back from the details of the Council report and the NRC/IOM report provides a general perspective on the subject. The recommendations of both groups bespeak a middle-of-the-road consensus. Most types of research that these committees would prohibit are far removed from current hESC research. Hence, the prohibitions would not likely have any substantial impact on the development of stem cell therapies. Additionally, the final three NRC/IOM recommendations discussed above (gametes, brain, and last resort)[110] appear to be more like standards than clear rules. They provide significant discretion to Institutional Review Boards ("IRBs") to permit important experiments if the experiments are carefully designed to avoid a limited number of specific problems.

The NRC/IOM recommendations are quite sensible guidelines given the state of such research in the United States at this time. They prohibit much research that would be morally impermissible while allowing a good deal of research that would be morally permissible under the framework developed in this Article. The President's Council and especially the NRC/IOM Committee display commendable prudence in prohibiting, or at least restricting, research that even approaches what is morally impermissible. As I have argued, it is sound judgment to avoid incurring high political costs solely for the sake of getting social policy to square exactly with morality. It is better to err on the side of caution than to condone research that might trigger considerable political fallout.

The qualifying phrase "in the United States at this time" merits explanation. Perhaps the residents of some countries, especially city-states such as Singapore or Vatican City, already have a general consensus on the morality of creating and using human-nonhuman chimeras. The United States does not; too much division and debate remain in this country for that to be possible just yet.[111] The spirited intellectual exchanges over these chimeras might eventually produce a coherent view. In the years to come we are likely to see more uses for and risks from human-nonhuman chimeras. It makes sense to wait before setting any United States social policy in stone. Otherwise, efforts to fix social policies in the reports of elite commissions could, depending on the exact nature of the policies, either allow questionable chimeric research or unjustifiably inhibit permissible research on chimeras.

Nevertheless, once a general consensus on human-nonhuman chimeras exists in the United States, I suggest that the President's Council on Bioethics, the Institute of Medicine, and related bodies and organizations address the moral character, not just the actions, of the researchers who use chimeras in their work. This suggestion de-

110. *See supra* text accompanying notes 106–107.

111. *See* KOROBKIN, *supra* note 92, at 26–91 (describing the "embryo wars" and the political and legal debates over human "cloning").

rives from my view, expressed in Part II, that morality encompasses virtues and ideals as well as actions. To researchers who work with animals, including human-nonhuman chimeras, desensitization is a potential pitfall. It is quite easy to lose interest in an animal's pain, emotions, and moods, and eventually not to be aware of those aspects of the animal at all.[112] For this reason the virtuous researcher should fight against disinterest and lack of awareness. He should instead cultivate such character traits as kindness toward chimeras and gratitude for the role chimeras play in scientific research. The model researcher, moreover, should exemplify some ideal appropriate to his calling — for instance, a devotion to truth and discovery no matter who gets credit or a burning desire to aid human patients. Evidently, this devotion and the cultivation of kindness and gratitude could cut against each other.

This point has implications for social policies associated with the training and development of research scientists who work on human-nonhuman chimeras created through hESCs or other methods. Plato was of the view that virtue cannot be taught.[113] Aristotle believed that intellectual virtues, such as the pursuit of truth, could be taught. He believed that moral virtues, such as fortitude and temperance, were acquired by "training" (*ēthikē*, sometimes translated as "habit" or "habituation").[114] Presumably, scientists would argue that if virtue can be taught to lawyers,[115] it can certainly be taught to research scientists. Scientists who work with chimeras — somewhat like physicians, dentists, and veterinarians — need to be desensitized in some respects and sensitive in others. To do their jobs properly, all of these professionals require some professional distance from their research subjects and patients. A scientist who cannot perform a necessary procedure on a basic human-nonhuman chimera because it would cause modest but unavoidable pain would be no more useful than a physician who is incapable of giving an injection, a dentist who cannot extract an infected tooth that is beyond saving, or a veterinarian who is unable to euthanize a dog racked by pain from incurable cancer. These analogies are imperfect because they all involve inflicting pain on a person or animal for its own benefit, whereas it is not clear that this would be the purpose of a procedure being performed on a chimera. A more

112. *See* Roger E. Ulrich, *Animal Rights, Animal Wrongs, and the Question of Balance*, 2 PSYCHOL. SCI. 197, 198 (1991).

113. PLATO, *Meno*, *in* 1 THE DIALOGUES OF PLATO 265–301 (Benjamin Jowett trans., Clarendon Press 4th ed. 1953).

114. ARISTOTLE, NICOMACHEAN ETHICS 1103a14–1103b19, *in* 2 THE COMPLETE WORKS OF ARISTOTLE 1729, 1742 (Jonathan Barnes ed., Princeton Univ. Press 1984). In this view, a person develops fortitude by acting courageously and temperance by practicing moderation. *Id*.

115. *Cf.* Amy Gutman, *Can Virtue Be Taught to Lawyers?*, 45 STAN. L. REV. 1759 (1993).

useful analogy, in some respects, is our readiness to quarantine healthy animals and human carriers of disease, in spite of their experience of loss or psychic pain, to secure the safety of others.

And yet, this desensitization must be limited for all of these professionals because otherwise they will lack necessary compassion in their work. Some medical schools now have ceremonies at the end of their medical dissection classes in which students express gratitude for the cadavers on which they worked and which instructed them.[116] By the same token, research scientists who use laboratory animals, including basic and enhanced human-nonhuman chimeras, can be taught — or, if you agree with Plato, exhorted and shown by example[117] — to have a concern and gratitude for the organisms that make scientific progress possible. Perhaps not everyone will respond to such teaching, exhortation, and exemplary behavior. Those who fail to respond ought not, for this reason alone, to be barred from chimeric research. It does, however, make sense to limit the laboratory access of scientists who disdain animals or take delight in causing them pain.

V. CHIMERAS AND THE LAW

A. Regulation

Legal regulation of human-nonhuman chimeras is in a parlous state. Current federal statutes, and agency rules issued pursuant to these statutes, are largely silent about chimeras. Two bills proposed by Sen. Brownback are unsatisfactory. We need a different approach.

1. Existing Federal Regulations. Such pertinent federal administrative rules as there are date to the 1980s, when it became clear that new developments in biotechnology required new regulations. In 1984, the Office of Science and Technology Policies ("OSTP") published the Proposal for a Coordinated Framework for Regulation of Biotechnology, which was intended to index U.S. laws related to biotechnology and clarify the policies of regulatory agencies.[118] In 1986, OSTP published the Coordinated Framework for Regulation of Biotechnology,[119] which sketched the coordination and relationships

116. *See* Am. Med. Students Assoc., Funeral Service for Cadavers, http://www.amsa.org/dd/cadavers.cfm (last visited Dec. 1, 2007).

117. *See* PLATO, *supra* note 113, at 265–301.

118. *See* Mary Jane Angelo, *Regulating Evolution for Sale: An Evolutionary Biology Model for Regulating the Unnatural Selection of Genetically Modified Organisms*, 42 WAKE FOREST L. REV. 93, 112–13 (2007). Megon J. Walker aided my understanding of the current regulatory framework.

119. Coordinated Framework for Regulation of Biotechnology, 51 Fed. Reg. 23,302 (June 26, 1986); *see also* Angelo, *supra* note 118, at 112–13; Rebecca M. Bratspies, *Glowing in the Dark: How America's First Transgenic Animal Escaped Regulation*, 6 MINN. J.L. SCI. & TECH. 457, 471–72 (2005) (contending that the Federal Food Drug and Cosmetic Act

among federal agencies authorized to regulate biotechnology. Three agencies have primary regulatory authority over various aspects of biotechnology: the Environmental Protection Agency ("EPA"), the United States Department of Agriculture ("USDA"), and FDA. As a strategy of exposition, one could proceed by examining the role of either agencies or statutes. It is clearer to do the former and point out along the way which agencies have authority under which statutes. The picture that emerges from examining the role of agencies and the relevant statutes is one of agencies empowered to regulate assorted aspects of genetically modified organisms ("GMOs"), including transgenic animals and the risks associated with them, but with scant attention to either chimeras in general or human-nonhuman chimeras in particular.

EPA is the main federal agency charged with regulating activities that create environmental risks. Its authority to do derives from three key statutes. The Federal Insecticide, Fungicide, and Rodenticide Act[120] ("FIFRA") empowers EPA to govern the manufacture, sale, and distribution of pesticides and to address pesticide health risks. Additionally, EPA's authority to govern human health risks of pesticides in food comes from the National Environmental Policy Act.[121] Under the Toxic Substances Control Act ("TSCA"),[122] EPA has authority to regulate substances that do not fall within the jurisdictional bounds of other agencies.[123]

None of these statutes expressly addresses GMOs, but EPA has interpreted these statutes as providing authority to regulate certain categories of transgenic organisms. Its regulation of GMOs covers three classes of organisms: genetically altered microbes that function as pesticides under FIFRA and the Federal Food, Drug, and Cosmetic Act[124] ("FDCA"); genetically altered plants that act as pesticides under the same statutes; and genetically altered microorganisms lacking pesticidal characteristics under TSCA.[125] EPA has no rules governing GMOs other than microbes,[126] and it has promulgated no regulations covering genetically modified plants or animals under TSCA, despite repeated statements of its intent to do so.[127] Thus, it would seem that the EPA is a long way from regulating chimeric animals.

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is not well suited to regulate transgenic animals); Gregory N. Mandel, *Gaps, Inexperience, Inconsistencies, and Overlaps*, 45 WM. & MARY L. REV. 2167, 2216–17, 2229 tbl. 1 (2004) (displaying table of agencies and statutes governing transgenic plants and animals).

120. 7 U.S.C. §§ 136–136y (2000).

121. 42 U.S.C. § 4321 (2000).

122. 15 U.S.C. §§ 2601–2629 (2000).

123. Angelo, *supra* note 118, at 114–15.

124. 21 U.S.C. §§ 30 1–399 (2000).

125. Angelo, *supra* note 118, at 118–31.

126. *Id*. at 131.

127. *Id.* at 118, 131 & n.158. *See also* TSCA Policy Statement on Oversight of Transgenic Organisms (Including Plants), 70 Fed. Reg. 27,631 (May 16, 2005) (mentioning EPA

Under several statutes, USDA has the power to regulate agricultural plants, domestic livestock, and poultry.[128] It is responsible for protecting and promoting American agriculture and for preventing the release and spread of plant pests into the environment. Genetically modified plants could pose a risk to agricultural crops, although the gravity of that risk is hotly disputed.[129] USDA thus oversees the agricultural safety of the movement, importation, and field testing of transgenic plants. Additionally, the Animal and Plant Health Inspection Service ("APHIS") of USDA must give its approval before transgenic plants can be grown outside the laboratory.[130] The Food Safety and Inspection Service ("FSIS") of USDA is responsible for the safety of food products prepared from domestic livestock and poultry.[131] The Federal Meat Inspection Act and the Poultry Products Inspection Act require FSIS inspection of cattle, sheep, swine, goats, horses, and poultry, together with the resulting food products that are intended for human consumption.[132] Furthermore, USDA administers the Animal Welfare Act of 1970,[133] which governs animal research and the treatment of laboratory animals.[134] It has also promulgated regulations under this statute.[135]

And yet, neither EPA nor USDA has tried to regulate "higher" transgenic animals. Indeed, no federal statutes directly govern the creation, use, or release of such animals.[136] FDA is the only federal agency to have asserted any authority over them,[137] and so we must next examine FDA regulations and practices.

FDA is responsible for ensuring the safety of all food products, other than meat and poultry, that are on the market in the United States. To carry out its mandate, FDA must provide voluntary pre-

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position that transgenic animals that are not under the jurisdiction of FDA appear to be subject to TSCA).

128. Mandel, *supra* note 119, at 2223–28.

129. *See* Munzer, *Plants*, *supra* note 54, at 197–215.

130. APHIS's regulatory authority comes from the Plant Protection Act of 2000. 7 U.S.C. §§ 7701–7772 (2000, Supp. I. 2002 & Supp. I. 2004).

131. 9 C.F.R. § 300.1–.3 (2006); *see also* 21 U.S.C. §§ 451, 1031 (2000); 21 U.S.C.A. § 601 (West 2007).

132. 21 U.S.C. §§ 451, 601, 1031; Mandel, *supra* note 119, at 2223–28.

133. 7 U.S.C. §§ 2131–2159 (2000).

134. *See* Chad West, *Economics and Ethics in the Genetic Engineering of Animals*, 19 HARV. J.L. & TECH. 413, 433–34 (2006). The National Institutes of Health ("NIH") and its policies govern much treatment of laboratory animals, but they offer nothing on human-nonhuman chimeras. *See, e.g.*, National Institutes of Health Revitalization Act of 1993, 42 U.S.C. § 283(e) (2000); OFFICE OF LAB. ANIMAL WELFARE, NIH, PUBLIC HEALTH SERVICE POLICY ON HUMANE CARE AND USE OF LABORATORY ANIMALS (2002), *available at* http://grants.nih.gov/grants/olaw/references/phspol.htm.

135. *See* JORDAN CURNUTT, ANIMALS AND THE LAW 431–526 (2001) (discussing legal protections for laboratory animals).

136. *See* Mandel, *supra* note 119, at 2209 & n.229 (explaining that FDA has exerted authority over transgenic animals).

137. *Id*.

market consultations with food companies, seed companies, and plant developers. The FDA's statutory authority derives from the FDCA and the Public Health Service Act.[138] Neither of these statutes nor FDA regulations expressly cover GMOs. Even FDA regulations governing human drugs and biologics fail to address many advances in biotechnology, including chimeras.[139]

Despite the absence of express authority to regulate GMOs, FDA has been more aggressive than EPA or USDA. For example, when genetically modified salmon overproduced a growth hormone, FDA was the lone agency that sought, under the FDCA, to regulate the transgenic salmon. It did so on the footing that the salmon amounted to a "new animal drug."[140] To ground its actions in its statutory authority, FDA performed some giddy trapeze-work. Its analysis began with the text of the FDCA that defines drugs to include products "intended to affect the structure or any function of the body of man or other animals."[141] FDA reasoned that the foreign gene and its protein product were intended to alter the "structure or . . . function" of the salmon.[142] It likened the alteration to the action of a veterinary drug. So the transgenic salmon, according to EPA, are themselves new animal drugs, which EPA has express authority to regulate.[143]

Doubts about FDA's reasoning abound. When Congress enacted the FDCA, the process for inserting transgenes was unknown, so it is questionable whether Congress intended FDA to regulate transgenic salmon.[144] Further, it has been argued that FDA lacks the institutional competence to regulate transgenic fish or other genetically modified animals.[145] Professor Mandel contends that even if the transgenic salmon qualify as a "drug":

> [FDCA's] definition of "new animal drug" refers to substances not generally recognized as safe (GRAS), and a growth hormone already present in the salmon likely does not fit this bill. The FDA's reasoning —

138. Public Health Service Act, 42 U.S.C. §§ 262, 264 (2000); Angelo, *supra* note 118, at 131–34; Bratspies, *supra* note 119, at 471–72; Mandel, *supra* note 119, at 2218–21.

139. Mandel, *supra* note 119, at 2221.

140. *Id.* at 2209.

141. *See* 21 U.S.C. § 321(g)(1)(C) (2000) (defining "new animal drug").

142. Bratspies, *supra* note 119, at 472; *see also* Lars Noah, *Managing Biotechnology's [R]evolution: Has Guarded Enthusiasm Become Benign Neglect?*, 11 VA. J.L. & TECH. 4, ¶ 55 (2006), http://www.vjolt.net/vol11/issue2/v11i2_a4-Noah.pdf ("The FDA has decided to regulate GM livestock using its authority over 'animal drugs' (on the theory that the introduced genetic material and expressed protein affect the animal's 'structure or function' in much the same manner as conventional veterinary drugs might do), demanding proof of safety, at least when these qualify as 'new' animal drugs used in species intended for consumption by humans." (internal footnotes omitted)).

143. Bratspies, *supra* note 119, at 472.

144. *See id*; Mandel, *supra* note 119, at 2210.

145. Bratspies, *supra* note 119, at 472–75.

> that the increased protein production is not GRAS — is particularly questionable considering the FDA's conclusion in the transgenic crop arena that inserted genetic material is GRAS because all that is produced as a result of the insertion are proteins and other substances already commonly found in food.[146]

Of course, FDA regulates "medical devices"[147] and "combination products"[148] as well as drugs. Yet it is implausible to include chimeras in the definition of medical devices. Nor it is evident that they are combination products as that term is understood in FDA regulations.[149] Chimeras might, however, be "biological products" (or "biologics," for short), which FDA is authorized to regulate under the Public Health Service Act.[150] However, this statute, and the regulations promulgated under it, seem more directed at xenotransplants than chimeras, although the line between the two is not always clear.[151] Although this Article chiefly addresses human-nonhuman chimeras created by ESC research, such organisms created using xenotransplantation would also qualify as chimeras. It would thus seem that FDA could regulate these chimeras, even if it has not yet done so.[152]

As biotechnological innovation continues, scientists may develop new hybrids as well as chimeras in order to model human diseases in laboratory animals for research purposes, to engineer livestock that produce human proteins,[153] and to create xenotransplant animal donors that produce organs for human use.[154]

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146. Mandel, *supra* note 119, at 2210 (footnotes omitted).

147. 21 U.S.C. § 331(a) (2000) (prohibiting "[t]he introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded"); *see also id*. § 321(h) (defining "device").

148. *Id.* § 353(g) (2000).

149. 21 C.F.R. § 3.2(e) (2006) (defining "combination products" as including such combinations as drug/device, drug/biologic, and device/biologic).

150. Public Health Service Act, 42 U.S.C. § 262 (2000).

151. *See id.* §§ 262, 351. For current FDA guidelines and statements, see FDA, Tissues, http://www.fda.gov/cber/tiss.htm (last visited Dec. 1, 2007) and FDA, Xenotransplantation, http://www.fda.gov/cber/xap/xap.htm (last visited Dec. 1, 2007); *see also* Kopinski, *supra* note 10, at 638–39. Xenotransplants usually involve the grafting of an organ, organ part, or tissue from a member of one species into the body of a member of another species. The hESC-derived human-nonhuman chimeras discussed here rarely involve xenotransplants. But some medical usage allows for an overlap between xenotransplants and chimeras. *See* STEDMAN'S MEDICAL DICTIONARY 288 (25th ed. 1990).

152. *See* U.S. CONST. art. I, § 8; *see also* Kopinski, *supra* note 10, at 638–41; Gregory J. Rokosz*, Human Cloning: Is the Reach of FDA Authority Too Far a Stretch?*, 30 SETON HALL L. REV. 464, 492–96 (2000). There remains the issue of whether existing federal legislation under the commerce clause relating to FDA already empowers it to regulate human-nonhuman chimeras.

153. Noah, *supra* note 142, at ¶ 58.

154. *See* Monique A. Spillman & Robert M. Sade, *Clinical Trials of Xenotransplantation: Waiver of the Right to Withdraw from a Clinical Trial Should Be Required*, 35 J.L.

Human-nonhuman chimeras introduce special concerns. Many anthropocentric objections have focused on the possibility of chimeras with human-like consciousness,[155] which scientists could potentially create using procedures such as human-nonhuman primate neural grafting.[156] In this procedure, scientists would introduce human stem cells into a developing animal fetus; the animal's brain structure and function would be altered by the human stem cells that ultimately develop into human brain cells. Under the FDCA definition, the foreign genetic material and expressed proteins created by the grafting of human stem cells probably qualify as a drug. What might restrict the ability of FDA and USDA to regulate human-nonhuman chimeras is the requirement that the chimeras affect the food supply or be intended for human consumption.

In sum, EPA, USDA, and FDA currently have little to say about human-nonhuman chimeras. Whether any of these agencies *could* say more than they do under existing legislation is an open question. New legislation may be necessary. For that reason, proposed legislation is well worth investigating.

2. The Brownback Bills. Sen. Brownback introduced two bills, both titled the Human Chimera Prohibition Act of 2005, in the 109th Congress.[157] The first, S. 659, was introduced on March 17, 2005, and the second, S. 1373, was introduced on July 11, 2005. Neither bill came to a vote, and so far, neither version has been introduced in the 110th Congress. Although I will point out similarities and differences between the bills, my analysis will focus on the second, S. 1373. Not only do I find that S. 1373 is more rigorously drafted, but I argue that it is the only piece of legislation addressing chimeras that would possibly be worth reintroducing in the Senate.[158] While many are hardly

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MED. & ETHICS 265 (2007) (describing how the United States Code of Federal Regulations and FDA require life-long surveillance of xenotransplant recipients because of the risks to public health posed by xenogeneic infectious diseases).

155. *See* Darian M. Ibrahim, *Reproduce, Refine, Replace: The Failure of the Three R's and the Future of Animal Experimentation*, 2006 U. CHI. LEGAL F. 195, 224 (2006); *see also* D. Scott Bennett, Comment, *Chimera and the Continuum of Humanity: Erasing the Line of Constitutional Personhood*, 55 EMORY L.J. 347 (2006) (proposing tests for determining constitutional personhood for chimeras); *cf.* Lesley J. Rogers & Gisela Kaplan, *Think or Be Damned: The Problematic Case of Higher Cognition in Animals and Legislation for Animal Welfare*, 12 ANIMAL L. 151 (2006) (advocating better treatment for animals capable of higher cognition).

156. Noah, *supra* note 142, at ¶ 58 & n.213.

157. Human Chimera Prohibition Act of 2005, S. 659, 109th Cong. (2005); Human Chimera Prohibition Act of 2005, S. 1373, 109th Cong. (2005).

158. The first bill, S. 659, contained a defective definition of a chimera that led to a strong critique by the American Society for Biochemistry and Molecular Biology:

> [Sen. Brownback's] bill defines "chimera" as including not only crosses between humans and non-human species, but also crosses between humans. . . . This phrase — "a human embryo that consists of cells derived from more than 1 human embryo, fetus, or born individ-

fans of Sen. Brownback or his bills, right now his proposed legislation is the only game in town.

Both bills propose amending Part I of Title 18 of the United States Code by adding a new Chapter 16 entitled "human chimeras." This Chapter would prohibit creating or attempting to create human chimeras, which are defined as beings with human and nonhuman tissue as specified and defined in the Act. The bills also prohibit transferring or attempting to transfer a human embryo into a nonhuman womb, or a nonhuman embryo into a human womb; and transporting or receiving a human chimera.[159] Violators would be subject to a $1,000,000 fine, or up to ten years in prison, or both.[160]

To appraise these bills fairly requires some knowledge of the underlying concerns. The concerns are evident in the "findings" each bill contains.[161] The findings are:

> (1) Advances in research and technology have made possible the creation of chimeras, which are beings with diverse human and non-human tissue.
> (2) Serious ethical objections are raised to some types of chimeras because they blur the lines between human and animal, male and female, parent and child, and one individual and another individual.
> (3) Respect for human dignity and the integrity of the human species may be threatened by chimeras.
> (4) The uniqueness of individual human beings is manifested in a particular way through their brain and their reproductive organs/cells.
> (5) With an increase in emerging zoonotic infection threatening the public health, both domestically and abroad, chimeras present a particularly optimal means of genetic transfers that could increase the efficiency or virulence of diseases threatening both humans and animals.[162]

> ual" — describes a blastocyst that has been created to produce stem cells. Thus, the bill bans somatic cell nuclear transfer (one of Brownback's longtime goals). But this language also enters the realm of the bizarre: as written, it also bans creation of embryos produced the traditional way; after all, an embryo produced by human sexual reproduction contains cells derived from more than one "born individual." Thus, babies are "chimeras" under Brownback's definition of the term.

Press Release, Am. Soc'y for Biochem. & Molecular Biol., Public Affairs News, Views, and Links — April, 2005 (Apr. 27, 2005), http://www.asbmb.org/ASBMB/site.nsf/web/AF98278139BC60FB85256FE1006784A6?OpenDocument.

159. S. 659 § 3; S. 1373 § 3.

160. S. 659 § 3; S. 1373 § 3.

161. S. 659 § 2(1)–(5); S. 1373 § 2(1)–(5).

162. S. 659 § 2(1)–(5); S. 1373 § 2(1)–(5). Sen. Brownback's term "chimera" is basically equivalent to the term "human-nonhuman chimera" used in this Article.

The concerns expressed in the bills, while compelling to many observers, differ in some respects from mine. Although Part III of this Article identifies manifold ethical concerns pertaining to human-nonhuman chimeras, none relates specifically to blurring the lines between humans and other species, between males and females, between parents and children, or between individuals. The Kantian strand in my moral framework makes human dignity central. However, I do not think that the existence of human-nonhuman chimeras would threaten "the integrity of the human species." Some religious and creationist views hold that chimeras could undercut a unique place for humans in the world order,[163] but analysis of such views lies outside the scope of this Article. With some minor qualifications about conjoined twins who share brain matter or one set of reproductive organs, I agree that "the uniqueness of individual human beings" has something to do with human beings' brains and reproductive organs and cells. Still, many other factors besides those organs and cells, such as human beings' histories, memories, and plans, contribute to that uniqueness. Furthermore, it is not clear from the proposed statutes how this uniqueness is directly pertinent to human-nonhuman chimeras. Sen. Brownback and I agree, though, that cross-species diseases pose a risk relevant to the creation and use of human-nonhuman chimeras, as the earlier moral discussion in this Article makes plain.[164]

I now consider the particulars of the definition of the term "human chimera" in S. 1373. In contrast to the definition of "chimera" in the findings of the bill, Section 3 of the proposed legislation contains a much more detailed definition of "human chimera":

> (1) HUMAN CHIMERA. — The term "human chimera" means —

163. Christian views of this sort fall into two broadly different categories. The first, adopted by some evangelical Christians, emphasizes the creation narrative of *Genesis*, where species and sexes are created separately and are distinct. *Genesis* 1:1–2:4a (New Jerusalem). Those who see this narrative as historical and inerrant oppose creation of chimeras as contrary to God's plan. *See, e.g.*, Don Batten, Human-Animal Hybrids?, Answersingenesis.org (Aug. 29, 2001), http://www.answersingenesis.org/news/010829 hybrid.asp. The second category, associated especially with the Roman Catholic Church, employs bioethics and moral theology to oppose creation of chimeras, particularly human-nonhuman chimeras. This theology sometimes holds that if human-nonhuman chimeras are created, they ought not to be destroyed. *See, e.g.*, Simon Caldwell, *Embryos Injected with Animal Cells Should Be Given Human Status, UK Bishops Urge*, CATHOLIC NEWS SERV., June 26, 2007, *available at* http://www.catholic.org/international/international_story.php?id=24515 (opposing injection of animal cells into human embryos but favoring the nurture of any chimeras so created). For a more scientific discussion embracing a somewhat similar view, see Tara Seyfer, *The Science of Chimeras and Hybrids: Combining Humans and Nonhumans*, LIFEISSUES.NET, Jun. 26, 2007, http://www.lifeissues.net/writers/sey/sey_03overview1.html.

164. *See supra* text accompanying notes 84–86.

> (A) a human embryo into which a non-human cell or cells (or the component parts thereof) have been introduced to render its membership in the species Homo sapiens uncertain through germline or other changes;
> (B) a hybrid human/animal embryo produced by fertilizing a human egg with non-human sperm;
> (C) a hybrid human/animal embryo produced by fertilizing a non-human egg with human sperm;
> (D) an embryo produced by introducing a non-human nucleus into a human egg;
> (E) an embryo produced by introducing a human nucleus into a non-human egg;
> (F) an embryo containing haploid sets of chromosomes from both a human and a non-human life form;
> (G) a non-human life form engineered such that human gametes develop within the body of a non-human life form; or
> (H) a non-human life form engineered such that it contains a human brain or a brain derived wholly or predominantly from human neural tissues.
>
> (2) HUMAN EMBRYO. — The term "human embryo" means an organism of the species Homo sapiens during the earliest stages of development, from 1 cell up to 8 weeks.[165]

The careful categorization of S. 1373 is superior to the less detailed efforts found in other existing legislation, such as in the Swiss Federal Act on Research Involving Embryonic Stem Cells[166] and the Canadian Assisted Human Reproduction Act.[167] The Swiss statute prohibits the creation of clones, hybrids, and chimeras but does not define any of these terms.[168] The Canadian statute recognizes only two categories of human-nonhuman chimeras: nonhuman cells in human embryos and human embryonic, fetal, or adult cells in a nonhuman embryo.[169] It prohibits both.[170]

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165. S. 1373 § 3. For an even more reticulated account of "chimeric embryos and animals containing human cells," see U.S. Patent App. No. 2003/0079240 (filed Dec. 3, 2002).

166. Stammzellforschungsgesetz [StFG] [Federal Act on Research Involving Embryonic Stem Cells], Dec. 19, 2003, SR 101 (Switz.), *available at* http://www.bag.admin.ch/suchen/index.html?keywords=Stem+cell&go_search=search&lang=en; *see also* Monika Bobbert, *Ethical Questions Concerning Research on Human Embryos, Embryonic Stem Cells and Chimeras,* 1 BIOTECH. J. 1352, 1366 (2006) (analyzing the statute).

167. The Assisted Human Reproduction Act, 2004 S.C., ch. 2 (Can.); *see also* Kopinski, *supra* note 10, at 641–66 (providing a useful analysis of the statute).

168. *See* S.R. 101, arts. 3(1)(a), 24(1)(a) (decreeing imprisonment for willful violations of the act).

169. 2004 S.C., ch. 2, § 3.

170. 2004 S.C., ch. 2, § 5(1)(i). Initially, the United Kingdom deferred a decision on such matters. Tom Blass, *U.K. Agency that Overseas Embryology Postpones Decision on Hybrid Research*, 6 MED. RES. L. & POL'Y REP. 38 (2007). But, in September 2007, the relevant

A few possible criticisms of the S. 1373 definition of chimeras seem unfair. For example, one could take issue with the definition because the first six of the eight categories have little to do with contemporary hESC research.[171] This criticism is misguided for three reasons. First, the first six categories map out possibilities in an organized manner. Just because few scientists are exploring these possibilities now, it hardly follows that scientists will refrain from doing experiments in the future that fall in these categories. Second, these six categories reflect Sen. Brownback's concerns. The fact that not everyone shares all the same concerns fails to make the proposal illegitimate. Third, definitional clarity is worthwhile, even if achieving it requires describing some possibilities that verge on science fiction or strike scientists as hypothetical. Just as hypothetical cases can sometimes tease out our moral intuitions and help to construct moral principles, so can hypothetical cases spur us to think more carefully about what the law should require, prohibit, permit, or encourage.

The bill's first seven categories are mostly irrelevant to the framework. Because of this Article's focus on stem cell research and its applications, I concentrate on human-nonhuman chimeras created by hESCs or their derivatives. The bill's first seven categories concentrate on germ cells and human embryos rather than hESCs and their differentiated derivatives. There is, however, one case where my analysis implicates the seventh category. Recall that the human-primate chimeras in Case (4) are allowed to breed, which raises the theoretical possibility that some of the offspring might, quite troublingly, be fully human. The Case (4) hypothetical evokes the concerns of Categories B, C, and F in S. 1373. In some cases, mating could result in (B) a human egg being fertilized by a nonhuman sperm, (C) a nonhuman egg fertilized by a human sperm, or (F) a human or nonhuman egg with haploid chromosomes derived from a human and a primate. Both the proposed legislation and I conclude that such breeding should be prohibited. The legislation does so by definition. I do so by looking at the consequences of the chimeras' condition contemplated by Case (4).

The last two categories (G and H) in S. 1373 reflect the same concerns as those expressed by the NRC/IOM report on hESC re-

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British agency decided in principle to permit the creation and use of human-nonhuman embryos, provided that they are destroyed within 14 days. *"Human-Animal" Embryo Green Light*, BBC NEWS, Sept. 5, 2007, http://news.bbc.co.uk/1/hi/health/6978384.stm.

171. Scientists at Advanced Cell Technology claimed to have introduced a human nucleus into a bovine egg in 1998, which meet the criteria of Category E. *See* Nicholas Wade, *Researchers Claim Embryonic Cell Mix of Human and Cow*, N.Y. TIMES, Nov. 12, 1998, at A1 (describing the experiment and its results).

search.[172] In fact, the bill's phrasing does not stray far from the guidelines. Like the NRC/IOM report, the proposed legislation would not prevent scientists from carrying out the types of experiments performed thus far, so long as the gametes and the brain function of the chimeric creature are closely monitored.

A drawback of S. 1373 and, to a lesser extent, of the Council report and the NRC/IOM report is the failure to focus adequately on the contexts in which human-nonhuman chimeras are created. Part III makes plain that we have to look at what organism created, the reasons for creating the chimera, the uses to which the chimera will be put, the ways in which the chimera will be treated, the risks the chimera faces, and the safeguards against such risks. S. 1373 is not adequate because it simply defines human chimeras and then prohibits their creation. No statute or administrative regulations can anticipate or provide for all of the variables that our moral analysis has shown to be relevant. Thus, statutes and regulations should allow for and empower more flexible and fact-based decision making by lower-level administrative bodies, IRBs, and Independent Ethics Committees.

A more far-reaching drawback of S. 1373 is its underinclusiveness. This drawback stems from its neglecting to take into account the use of hESCs to produce human-nonhuman chimeras. The six cases examined in Part III, for example, represent ways of creating human-nonhuman chimeras that the bill does not consider.

3. A Different Approach. I would approach the drafting of a statute differently. A statute should distinguish between the *creation* and *use* of human-nonhuman chimeras and, in the case of the former, between cellular and anatomic creation. The statute should place no restrictions on chimeric embryos that never leave the laboratory dish and are not implanted. A statute should, however, prohibit the knowing or reckless cellular or anatomic creation of dramatically enhanced chimeras. Such a prohibition should cover all transfer techniques that are applied before and during embryonic development (that is, up to eight weeks after fertilization) and that simultaneously use totipotent or pluripotent stem cells from either human or nonhuman species.[173] Any dramatically enhanced chimeras created in violation of the statute ought to be afforded roughly the same moral status as human beings. The statute should also specify that enhanced chimeras be subject to

172. *Compare* S. 1373, § 3(1)(G)–(H), *with* NRC/IOM Guidelines, *supra* note 25, at 99, 106 (restricting research based on the type of cells into which hES cells are introduced and on the brain function of the resulting chimeras).

173. This recommendation follows Bobbert, *supra* note 166, at 1367.

the same statutory provisions and administrative regulations that currently govern the treatment of chimpanzees.[174]

As to the use of human-nonhuman chimeras, the statute should not allow them to be bred and should require scientists who do research on chimeras to take steps to keep the chimeras from breeding. The statute should, moreover, restrict the use of enhanced chimeras to important research that cannot be performed without them. Any research on dramatically enhanced chimeras (whose creation should be forbidden by statute) should be legally permissible only if their voluntary informed consent is secured and the same statutory provisions that apply to human research subjects govern these chimeras.[175] Even for basic chimeras, it should be legally permissible to use them in research only if the risk-adjusted benefits exceed the costs. For legal matters, risk assessment ought to be consequentialist. To make the legislative framework easier to administer, the statute should not address risk distribution along nonconsequentialist lines.[176]

No sensible statute should try to solve all problems relating to human-nonhuman chimeras. Some problems of application ought to be left to administrative regulations authorized under the statute. Relevant federal agencies include FDA, NIH, EPA, and USDA. Agency administrators are likely to be more knowledgeable than Congress when dealing with the specifics of real-world problems. Applications to create and use enhanced chimeras should be handled by one of these agencies, which would be in a better position to assess the attainability and quality of the applications. Agencies should also retain sufficient flexibility under the statute to adjust the means for reaching the statute's goals.

It would be an oversimplification to say that administrative rules are usually easier to change than statutory provisions if they prove to be unwise. However, it is true that enacting a new statute relating to human-nonhuman chimeras would be visible to a broader segment of the public than the rulemaking process for administrative agencies. Of course, anyone familiar with Washington, D.C., law practice also knows that entities having a stake in the outcome of administrative rule-making will not cede an inch without a fight.

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174. *See, e.g.*, Chimpanzee Health Improvement, Maintenance, and Protection Act of 2000, 42 U.S.C. § 287a-3a (2000); Animal Welfare Act, 7 U.S.C. §§ 2131–59 (2000); 9 C.F.R. § 3.81 (2006); *see also* Symposium, *The Evolving Legal Status of Chimpanzees*, 9 ANIMAL L. 1 (2003).

175. *See* 45 C.F.R. § 46.101–.409 (2006) (detailing guidelines for research on human subjects).

176. Even a consequentialist analysis would be complicated. *See, e.g.*, Matthew D. Adler & Chris William Sanchirico, *Inequality and Uncertainty: Theory and Legal Applications*, 155 U. PA. L. REV. 279 (2006) (identifying problems arising from uncertainty and a social preference for equality).

Furthermore, other problems of application should be the province of social policy. Commission reports, such as those considered in Part IV,[177] are apt to be better guides than statutory provisions and administrative regulations to solving some problems on the ground.[178] The use of local mechanisms, such as IRBs, for implementing these policies also makes practical sense.

I close with three comments on the drafting of legislation governing human-nonhuman chimeras. First, both of Sen. Brownback's bills overlook some egregious morally impermissible hESC-derived human-nonhuman chimeras. Such chimeras are plausible candidates for legal prohibition, though their creation should not incur the severe punishment that the bills propose. Second, the costs of any legislative prohibition should be weighed carefully. These include the costs of enforcement and of overcoming legislative inertia should it turn out that some research on statutorily prohibited chimeras can be conducted ethically, safely, and in a socially responsible manner. Some advantages of prohibiting and regulating research on certain chimeras through social means, such as the NRC/IOM guidelines, are that some social means rest on informed scientific and bioethical thinking. Social means can also be implemented sensitively by IRBs and do not require an act of Congress to undo them if later developments make it wise to withdraw such regulation. Third, a comprehensive statute should indicate which sorts of chimeric research are permitted, which sorts (if any) merit government encouragement or funding, and how FDA, NIH, and USDA are to regulate and oversee such research. This statute should explicitly authorize FDA and USDA regulation and oversight.

B. Should Human-Nonhuman Chimeras Ever Be Patentable?

As part of omnibus appropriations bills in 2004,[179] 2005,[180] and 2006,[181] Congress enacted the Weldon Amendment, which bans the use of federal funds "to issue patents on claims directed to or encompassing a human organism."[182] The Amendment has no effect on previously issued patents. Its most likely application, at least in the near

177. *See supra* pp. 28–35.

178. *Compare, e.g.*, COUNCIL REPORT, *supra* note 24, *and* NRC/IOM Guidelines, *supra* note 25, *with* S. 1373.

179. Consolidated Appropriations Act, 2004, Pub. L. No. 108–199, § 634, 118 Stat. 3, 101 (2004).

180. Consolidated Appropriations Act, 2005, Pub. L. No. 108–447, § 626, 118 Stat. 2809, 2920 (2005).

181. Consolidated Appropriations Act, 2006, Pub. L. No. 109–149, § 509, 119 Stat. 2833, 2880 (2006).

182. Consolidated Appropriations Act, 2004, § 634 ("None of the funds appropriated or otherwise made available under this Act may be used to issue patents on claims directed to or encompassing a human organism.").

future, is to patent applications concerning human-nonhuman chimeras. In 1997, Stuart Newman, a developmental biologist at New York Medical College, and Jeremy Rifkin, a Washington, D.C., activist who often works to curb biotechnology research, filed an application to patent a human-chimpanzee ("humanzee") chimera and various methods of creating it.[183] The humanzee was purely theoretical. Newman and Rifkin did not file the application with the intention of making the humanzee or of reaping any financial benefits. On the contrary, they sought to make the public aware of the potential dangers of this type of research and stimulate public debate. The application specified the percentage of human DNA in the chimeric animal to be "up to 50%" to force the United States Patent and Trademark Office ("USPTO") to grapple not only with whether human beings can be patentable subject matter but also with how much human genetic material it takes to make a living organism human.[184]

The USPTO initially rejected the application in 1999[185] and, after an appeal, issued its last rejection letter in early 2005.[186] The USPTO believed that the humanzee would be too closely related to a human to be patentable under the Weldon Amendment.[187] USPTO officials stated that reaching this decision was not difficult, for Newman's proposed technique was too crude to be able to fine-tune the percentage of human cells in the chimera and therefore could have easily produced a creature that was more human than chimpanzee.[188] Because laboratory techniques now make such fine-tuning more feasible,[189] the USPTO will likely have to face the question of what is "human" again. The prospect makes USPTO officials somewhat uneasy. "I don't think anyone knows in terms of crude percentages how to differentiate between humans and nonhumans," said John J. Doll, the Commissioner of Patents. He added that the USPTO is also not comfortable with a "we'll know when we see it" approach, commenting,

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183. Thomas A. Magnani, *The Patentability of Human-Animal Chimeras*, 14 BERKELEY TECH. L.J. 443, 443 (1999); Valerie J. Phillips, *Half-Human Creatures, Plants & Indigenous Peoples: Musings on Ramifications of Western Notions of Intellectual Property and the Newman-Rifkin Attempt to Patent a Theoretical Half-Human Creature*, 21 SANTA CLARA COMPUTER & HIGH TECH. L.J. 383, 385 (2005).

184. *See* Magnani, *supra* note 183, at 443.

185. Jagels, *supra* note 7, at 133.

186. Transaction History, U.S. Patent App. No. 08/993,564 (filed Dec. 18, 1997), *available at* http://portal.uspto.gov/external/portal/pair (enter application number 08/993,564, click "submit", then click "Transaction History" to view the list of office actions). The USPTO issued a final notice of abandonment for failure to respond to office action on Mar. 1, 2005.

187. *See* Aaron Zitner, *Patently Provoking a Debate*, L.A. TIMES, May 12, 2002, at 1 (reporting that the humanzee patent was rejected because it "embraces a human being"); *see also* Consolidated Appropriations Act, 2004, § 634.

188. *See* Rick Weiss, *U.S. Denies Patent for a Too-Human Hybrid*, WASH. POST, Feb. 13, 2005, at A3.

189. *Id.*; *see also* Carolyn Y. Johnson, *From Myth to Reality*, BOSTON GLOBE, Apr. 19, 2005, at D1 (describing potential therapeutic uses for chimeras).

"It would be very helpful . . . to have some guidance from Congress or the courts."[190]

The moral framework and social policy developed in this Article help give Commissioner Doll the guidance he seeks. First, instead of considering crude percentages or failing to adopt a standard, the USPTO should consider the distinction among basic, enhanced, and dramatically enhanced human-nonhuman chimeras. Provided that basic and enhanced chimeras meet the usual requirements for patentability, there is little reason to rule out either process patents for creating them or composition of matter patents on them.[191] If Dr. Chakrabarty can patent genetically modified bacteria that do not exist in nature,[192] in principle Congress should allow scientists to patent basic and enhanced chimeras that do not exist in nature.[193]

Congress will not necessarily follow the approach taken by foreign legislatures regarding these issues. For example, the European Patent Convention has a "morality" or "ordre public" clause that injects ethical considerations into European patent law.[194] Legislatures of members of the European Community might have to limit the patentability of chimeras if a patent would run afoul of morality. In contrast, the analogous U.S. doctrine of "moral utility" or "beneficial utility" announced in *Lowell v. Lewis*[195] in the early nineteenth century was moribund for years. Its death was finally pronounced in 1999 by *Juicy Whip, Inc. v. Orange Bang, Inc.*[196] Of course, Congress could inject morality into U.S. patent law through an amendment to the Patent Act. However, there is no sign that it is ready to do so for basic or enhanced chimeras, and the courts have generally treated the law of patents as ethically neutral.[197]

Unlike in Europe, in the United States patents are generally granted without regard for moral concerns. However, the situation should be quite different with regard to dramatically enhanced chime-

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190. Weiss, *supra* note 188, at A3.

191. A process patent (also called a "method" patent) issues on an invention that gives a series of steps for using or making something. A composition of matter patent, which is a subset of "product" patents, issues on an invention relating to a material thing such as alloys, chemicals, and biological creations. *See* 35 U.S.C. § 101 (2000). For a further explanation of the distinction, with specific reference to biotechnology, see ROGER E. SCHECHTER & JOHN R. THOMAS, PRINCIPLES OF PATENT LAW 25–38 (2d ed. 2004).

192. Diamond v. Chakrabarty, 447 U.S. 303, 309–10 (1980).

193. No patent should issue if it is obvious how to create such creatures, as it might seem to be with cross-breeding (consider such "hybrids" as mules, ligers, and wolphins). *See* 35 U.S.C. § 103(a) (2000); *supra* note 5 and accompanying text. Further, the use of hESCs in creating basic and enhanced chimeras raises additional questions having to do with stem cell patents. *See* KOROBKIN, *supra* note 92, at 92–125 (discussing patents relating to stem cells).

194. Convention on the Grant of European Patents, art. 53(a), *concluded on* Oct. 5, 1973, 1065 U.N.T.S. 254.

195. 15 F.Cas. 1018, 1019 (C.C.D. Mass. 1817) (No. 8,568).

196. *See* 185 F.3d 1364, 1366–67 (Fed. Cir. 1999).

197. *See* Magnani, *supra* note 183, at 451–54 (discussing the history of the moral utility doctrine).

ras. If Congress follows this Article's earlier recommendation and makes it illegal to create or use such chimeras, this would probably provide ample notice to the USPTO that it should grant no process or composition of matter patents on such chimeras. Were dramatically enhanced chimeras to become a genuine possibility, Congress ought to exercise its authority to make them unpatentable.[198]

Other questions of patentability are more difficult to analyze. From Part I, it is clear that the chimeras in question have cells from more than one species but are not transgenic.[199] But suppose that the use of stem cells to create a basic chimera in this sense has the unintended and unexpected consequence that the resulting organism is also transgenic. Exactly this scenario occurred in a well-known study of human hematopoietic stem cell engraftment in swine.[200] In that case, the researchers injected human stem cells into fetal pigs *in utero*. As expected, the piglets had some human cells and some porcine cells. But, unexpectedly, 95 percent of the piglets' cells contained both human and porcine DNA and expressed proteins.[201] Cellular fusion occurred spontaneously. In the language used here, the "piglets" were both chimeric and transgenic.

Should the chimeric-transgenic piglets be patentable? Patentable subject matter must be nonobvious and useful. The piglets do not exist in nature but are rather the result of human intervention. Bioethicist Monika Bobbert apparently finds the outcome of the piglet experiment troubling.[202] Bobbert opposes patents on any and all human-nonhuman chimeras.[203] Still, she offers no argument for this blanket opposition. Neither does she offer any argument for opposing patents only on chimeric-transgenic piglets.

Claiming that the chimeric-transgenic piglets are not useful is not defensible. In fact, they could be useful for studying developmental plasticity across different cell lineages ("transdifferentiation") and for studying the formation of synkaryons to explain viral transfer across species (here, porcine endogenous retrovirus in human cells).[204] As a matter of U.S. patent law, one cannot say that chimeric-transgenic creatures fail the utility requirement because of the risk of viral transmission outside the laboratory; the Federal Circuit's reasoning in *Juicy Whip v. Orange Bang* expressly eliminated "moral utility"[205] as

198. *See* U.S. CONST. art. I, § 8, cl. 8.

199. *See supra* text accompanying notes 3–4.

200. Brenda M. Ogle et al., *Spontaneous Fusion of Cells Between Species Yields Transdifferentiation and Retroviral Transfer In Vivo*, 18 FASEB J. 548, 548 (2004).

201. *Id.* at 548.

202. *See* Bobbert, *supra* note 166, at 1363–64 (discussing the Ogle experiment).

203. *See id*. at 1366 (stating that the law should "check any grand hopes that human-animal chimeras might become patentable").

204. *See* Ogle et al., *supra* note 200, at 549–50 (describing these uses).

205. *See* 185 F.3d 1364, 1368 (Fed. Cir. 1999).

a basis for declining to grant a patent for an otherwise patentable invention. It is up to administrative agencies, rather than the USPTO, to regulate such risk.

A better justification for those who think that the chimeric-transgenic piglets should be unpatentable lies in the linked requirements of written description and enablement.[206] A successful patent application must enable a person of ordinary skill in the relevant art to make the invention. However, in the swine experiment, there was "spontaneous" fusion of human hematopoietic stem cells and porcine parenchymal cells.[207] Because the fusion was unpredictable and unprompted, another scientist following the procedure might not be able to control the stability or percentage of fused cells. If the outcome is uncontrolled, a patent examiner could question whether the applicant's written description of the invention enables others to reproduce it.[208] If the examiner found that the patent did not teach how to replicate the claimed invention, a patent should not issue. Yet even this possible limitation on patentability may ultimately disappear. Subsequent technological developments may give stem cell scientists substantial control over the results of such experiments. If so, and if the application describes "in . . . full, clear, concise, and exact terms"[209] how to make and use the invention, a patent should issue so long as the other requirements of patentability are met.

As this discussion suggests, it is too early to tell if a patent on chimeric-transgenic creatures would be appropriate. By using the case of chimeric-transgenic piglets, this discussion has uncovered some of the relevant considerations that would be likely to arise during the prosecution of patent applications on chimeric-transgenic creatures.

VI. CONCLUSION

This Article has constructed and justified a moral framework for assessing the permissibility of creating and using human-nonhuman chimeras and has applied this framework to six cases. The moral analysis, in turn, enabled us to think more insightfully and rigorously about social policy affecting chimeras. The weightiest social policies, as evaluated by their impact, are those that find their way into the reports of commissions set up by the government or medical and scientific organizations. I hope that the social policies developed here will contribute to future policy discussions and committee reports.

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206. *See* 35 U.S.C. § 112 (2000) (stating these requirements).

207. Ogle et al., *supra* note 200, at 550.

208. *See* Christopher A. Harkins, *Fending Off Paper Patents and Patent Trolls: A Novel "Cold Fusion" Defense Because Changing Times Demand It*, 17 ALB. L.J. SCI. & TECH. 407, 470–72 (2007) (linking reproducibility and enablement).

209. 35 U.S.C. § 112.

Finally, this Article considered the law. There is precious little law on human-nonhuman chimeras and their use in embryonic stem cell research. This Article has suggested how to change that. It has critiqued legislation proposed by Sen. Brownback. It has recommended that future legislation prohibit the creation and use of dramatically enhanced chimeras while carefully regulating the creation and use of basic and enhanced chimeras. In principle, basic and enhanced chimeras are eligible for both process and composition of matter patents. However, the Article has argued that it would be a grave mistake to permit patents to issue on dramatically enhanced chimeras.