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## Human/Non-Human Chimeras: Assessing the Issues

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Tonight I ask you to pass legislation to prohibit the most egregious abuses of medical research: human cloning in all its forms, creating or implanting embryos for experiments, creating human-animal hybrids, and buying, selling, or patenting human embryos. Human life is a gift from our Creator -- and that gift should never be discarded, devalued or put up for sale. (Applause.)

President George W. Bush, State of the Union Address, 2006<sup>1</sup>

It is mainly Irv Weissman's fault. In the 1980s Weissman, a Stanford University professor, was one of the first people to successfully identify and purify the human stem cells that form blood. In September 1988 Weismann and his colleague Mike McCune successfully created what they called the SCID-hu mouse, a mouse that lacked its own immune system but, through the transplantation of human bone marrow and other tissues,

had a functioning *human* immune system.<sup>2</sup> This mouse provoked special interest, as

HIV/AIDS, the most terrifying disease of the 1980s, was (and is) a disorder of the

immune system. The SCID-hu mouse permitted study of a human immune system in the

context of a living organism – an immune system that *could* become infected with HIV –

but in an organism that made a much better, easier, and cheaper experimental subject than

humans or chimpanzees, the other animal then known to be subject to HIV infection.

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The SCID-hu mouse became a useful tool for studying human immune systems: not as revolutionary as its creators hoped, but still in use more than 20 years later. It raised some controversy – “history may someday [sic] record the saga of this mouse as one of the greatest horror stories in the annals of medicine”<sup>3</sup> – but largely because some of the transplanted human tissue came from aborted fetuses.

In January 2000, Weissman and others announced that they had successfully isolated human brain stem cells, cells that form the neurons and glial cells that make up the human brain. From that initial announcement, Weissman talked of the SCID-hu mouse as a precedent for creating a “Human Neuron Mouse,” a mouse whose neurons, at least, were completely derived from human brain stem cells. Like the SCID-hu mouse, the Human Neuron Mouse could provide a way of examining human tissues inside a living organism that is much easier to study than Homo sapiens. Within a year, Weissman had asked me to organize an ad hoc working group to give him (and Stanford Medical School) advice on whether and how to proceed with experiments to create the Human Neuron Mouse. We did so, and then, several years later, published a paper about our recommendations.

In the meantime, media reports of Weissman’s plans sparked considerable public

interest and discussion. Eventually, in July 2005, then-Senator Sam Brownback from Kansas introduced the Human Chimera Prohibition Act, to classify as federal felonies a variety of activities that would mix genes, cells, or tissues from human and non-human animals. In what might be called “the Weissman clause,” the proposed legislation

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included in its prohibitions the creation or attempted creation of “a non-human life form engineered such that it contains a human brain or a brain derived wholly or predominantly from human neural tissues.”<sup>6</sup> And the next year, Weissman’s proposed

mouse seems to have made an oblique appearance in the President’s State of the Union

address – at least, it seems likely that President Bush meant “chimeras,” like Weissman’s,

when he said “hybrids,” as no one was proposing making human/non-human hybrids, crosses from mixing the sperm of one species with the eggs of another.

The last decade saw more accurate, analytical, and interesting discussions of human/non-chimeras, as well.<sup>7</sup> Some of the discussion was fairly abstract, but some if it

was quite practical or even political. Most of the discussion took off from Weissman’s Human Neuron Mouse and focused on non-human creatures with “humanized” brains, but some looked at other kinds of human/non-human chimeras as well. This chapter will

first describe briefly the arguments, and policies, that have been made about human/nonhuman chimeras. It will then discuss the three sensitive types of such chimeras, those involving brains, gametes, and outward appearance and one very sensitive use that could be made of human/non-human chimeras. And finally it will propose that we take a pragmatic stance toward most of the sensitive types and uses of

human/non-human chimeras, careful to create and employ them only for good reasons, and mindful of the possible negative social reactions.

## **I. Arguments and Policies**

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After defining the kinds of human/non-chimeras to be discussed in this chapter, this section goes on to look at both the ethical arguments made (or implied) about – generally against – human/non-human chimeras. Although some arguments may be partially or total rooted in religion, this chapter will not consider religious arguments against human/non-human chimeras. That is not to imply that those arguments may not be powerful, or determinative, for those who hold them, but that they are not arguments that will convince people who do not believe in that, or in any, religion. The chapter then looks at the rules made to govern research with human/non-human chimeras and the arguments they seem to embody.

## **A. Definition**

The term “chimera,” despite, or because of, its long history, is susceptible to many meanings.<sup>8</sup> This chapter will discuss living organisms that have, as an integrated part of their bodies, some living tissues, organs, or structures of human origin and some of non-human origin. Thus, Weissman’s Human Neuron Mouse would be a relevant human/non-human chimera if, in fact, the neurons in its brain were of human origin but the rest of its tissues were murine.

For this chapter’s purposes, those human components must be tissues, organs, or structures. The disaggregated human cells surviving (briefly) in the mouth of a man-eating tiger would not qualify it as a human/non-human chimera. Neither would the

human genes in the E. coli, yeast, or Chinese hamster ovary cells that the biotechnology

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industry uses to produce human therapeutic proteins – or the human proteins thus produced – make those cells into the kinds of chimeras this chapter discusses. The human tissues must be living and integrated into the creature. A chimpanzee with a wig made of human hair would not be a human/non-human chimera for these purposes.

Finally, this chapter deals with creatures that are, or are viewed as, non-human creatures to which human tissues are added. To some extent, this begs the question: is

the Human Neuron Mouse a mouse to which human brain tissue has been added or human brain tissue to which mouse tissues have been added? In that particular case, one

might make a temporal distinction – the human brain stem cells would have been literally added to the existing mouse fetuses shortly before their scheduled births – but one can imagine other cases, such as the mixing of human cells and non-human cells into a very

early embryo, where “what gets added to what” does not give a very clear answer. It is

perhaps clearer to say that this chapter *excludes* creatures that were recognized as human

beings (or human fetuses) who have acquired non-human tissues. It thus excludes the

hundreds of thousands of humans living because their faulty human heart valves were replaced with heart valves taken from pigs or valves fashioned from cattle cartilage, as well as those very few humans who have, so far unsuccessfully, received organ transplants from non-human animals.

Each of the choices made to limit the definition of human/non-human chimera could have been made in the other direction, or could have been avoided altogether. I have argued before that the existence, and often acceptance, of those other kinds of

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human/non-human chimeras is relevant for how we look at the more narrowly defined chimeras.<sup>10</sup> But it is the narrowly defined chimera that has dominated the debate so far – the non-human animal with some integrated human tissues or organs. And so that is what this chapter will discuss.

Many of the arguments, and almost all of the policies, have focused even more narrowly on human/non-human chimeras created from human embryonic stem cells. This has both a scientific and a political reason. Scientifically, embryonic stem cells offer a particularly plausible way for creating worrisome chimeras. These cells are much more versatile than whole organs, tissues, or more differentiated cells. Transplant a human kidney into a pig and it will remain a kidney; transplant human embryonic stem cells into a pig and they might take the form of any kind of cell – muscle, brain, skin, egg, or sperm.

Politically, the required destruction of human embryos made embryonic stem cell research became a focus for controversy, debate, politics, and regulation. No regulatory regime exists in the United States to govern the transplant of human tissues into non-human animals, beyond the concerns about animal welfare that been implemented through Institutional Animal Care and Use Committees (IACUCs), required by federal law for most research. But the controversies over embryonic stem cell research brought forth statutes, regulations, guidelines, and recommendations concerning such research,

policies that, although not primarily motivated by issues of chimeras, do address them.

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This chapter is not limited to a discussion of human/non-human chimeras created using human embryonic stem cells. It includes those created using other types of human stem cells, of human non-stem cells, of tissues, or organs. (The Human Neuron Mouse, for example, was to be created using human brain stem cells derived from fetal tissue and not less differentiated human embryonic stem cells.) Most of the examples, however, will involve embryonic stem cells, as they have generated the arguments and policies.

## **B. Arguments**

The report on (and subsequent article about) the Human Neuron Mouse discussed four ethical arguments about creation of the mouse: issues of cruelty to the mice, of the source of the human tissue, of the proper uses of human tissues in general, and of the possible creation of a mouse with some human cognitive abilities. We dismissed the first three arguments fairly quickly in the context of the Human Neuron Mouse,<sup>11</sup> and although aspects of them resurface from time to time in the discussions of human/non-human chimeras, they have not been subject to much attention. It is the last point, about “humanization,” that has been the center of the controversy. Our group refused to take a position on whether the creation of a mouse with some human cognitive abilities would be a good thing or a bad thing (and were criticized by some for that refusal). Instead, we

first laid out reasons to doubt that the Human Neuron Mouse would have any significant human cognitive abilities and then suggested guidelines to limit even further the very small possibility of such a result.

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The other authors, however, have not been as reluctant. Four main arguments have been raised, one implicitly and three expressly, against the creation of human/non-human chimeras: the impermissibility of mixing human/non-human species, the possibility of moral confusion, violation of human dignity, and inappropriate treatment of the resulting creatures.

Jason Robert and Françoise Baylis deserve credit for initiating the current serious discussion of human/non-human chimeras through their article in the American Journal of Bioethics in summer 2003, as well as by a workshop on chimeras they organized at Dalhousie University in April 2003.<sup>12</sup> Their article starts by teasing out an implicit, “folk” objection to chimeras that seems to account for much the unhappiness about human/non-human chimeras. On this view, species are real entities with fixed boundaries (for some, fixed by God at the time of their creation) and those boundaries should not be crossed. They particularly should not be crossed when they involve mixing humans, made in God’s image, with the non-human creatures over which they were given dominion.

The Human Chimera Prohibition Act, first introduced two years after the Robert and Baylis article, illustrates their point. This bill would have outlawed a variety of acts involving human chimeras – to create or to attempt to create, to transport or to receive in interstate commerce, any human chimera. The bill’s definition of human chimera,

however, differed importantly from this chapter's (as well as from any dictionary's). It defined a chimera as

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- (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.

Subsections (b) through (f) do not fall within this chapter's definition of human/non-human chimeras. Instead, they deal with hybrids or, perhaps, chimeras at the genetic or chromosomal level. And it is not at all clear what subsection (a) covers. Only subsections (g) and (h) seem clearly to involve the integration of human tissue or organs

(gonads or brains) into a non-human animal. But all the sections involve the mixture of human “things” – eggs, sperm, nuclei, cells, or tissues – into non-human animals.

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As Robert and Baylis point out, this perspective is incoherent. Species are not fixed entities. And, in fact, although their article does not stress this, humans have busily crossed species boundaries, not just with modern tools but, for 10,000 years or so, with the tools of agriculture. Many of our crops are human-created species mixtures, and some of our crops are literally chimeras (fruit trees and wine grapes are often grown on plants with the roots and trunk of one species but the limbs and fruits of another). Even some of our domestic animals are human-created hybrids. Consider the mule.

Robert and Baylis conclude that

despite scientists' and philosophers' inability to precisely define species, and thereby to demarcate species identities and boundaries, the putative fixity of putative species boundaries remains firmly lodged in popular consciousness and informs the view that there is an obligation to protect and preserve the integrity of human beings and the human genome. We have also shown that the arguments against crossing species boundaries and creating novel part-human beings (including interspecies hybrids or chimeras from human materials), though many and varied, are largely unsatisfactory.

This folk objection might be thought of as an argument based on human dignity,

not the dignity of any individual human but of the human species as a whole. The concept of human dignity has been a favorite of some conservative bioethicists and was

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the subject of a book published by the President's Council on Bioethics.<sup>13</sup> It has also

<sup>14</sup>been subject to scathing attack. The idea may be appealing as providing a secular way

to criticize “repugnant” actions that are undertaken voluntarily by competent adult

humans and that have no discrete harms to third parties. Thus, a voluntary decision by a

competent adult human to allow some of his (in this case, not adult) stem cells to be

incorporated into a mouse, with no negative consequences to any particular human, might

still be argued to violate the dignity (or “integrity”) of the human species. This version of the argument, however, seems no more satisfactory than the more specific argument about crossing fixed species lines.

Although they reject the folk objections, Robert and Baylis are not, however, willing to accept that the creation of such chimeras is appropriate. They disclaim any position on the ultimate propriety of such creatures, but they urge that “the most plausible objection to the creation of novel interspecies creatures rests on the notion of moral confusion.” Their article does not contend that moral confusion *is* a strong argument against such chimeras, but instead states that they put forth “the following musings as the beginnings of a plausible answer, the moral weight of which is yet to be assessed.”

They argue that it would not be clear what moral status human/non-human chimeras should enjoy. This could not only lead to confusion about how to treat those creatures, but might also open debates about the moral status of fully non-human

animals.

Forswearing part-human chimeras might be necessary “to protect the privileged place of human animals in the hierarchy of being”.

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[T]he creation of novel beings that are part human and part nonhuman animal is sufficiently threatening to the social order that for many this is sufficient reason to prohibit any crossing of species boundaries involving human beings. To do otherwise is to have to confront the possibility that humanness is neither necessary nor sufficient for personhood (the term typically used to denote a being with full moral standing, for which many—if not most—believe that humanness is at least a necessary condition).

. . .

Given the social significance of the transgression we contemplate embracing, it behooves us to do this conceptual work now, not when the issue is even more complex—that is, once novel part-human beings walk among us.

A third argument returns to “human dignity” but in another way – the human dignity of the chimeras, not of the “unmixed” human species. In several works, Cynthia Cohen and others have argued that some kinds of human/non-human chimeras might have some human traits that, because of their physical bodies, they would be unable to<sup>15</sup>exercise. Imagine, for example, a chimera with a fully human brain, capable of using

language, but without the vocal apparatus necessary for speech. This dignity argument is

not saying that the creation of the chimera itself undercuts human dignity, through a kind of pollution, but that the existence or use of human/non-human chimeras – creatures with

enough humanity to be entitled to “higher” moral treatment – would violate the human dignity of *the chimera*. Johnston and Eliot make a similar argument, contending that the

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creation and use of such chimeras as laboratory animals, or otherwise as means to  
16 someone else's ends, would violate the chimeras' human dignity.

Rob Streiffer has made a related but somewhat different argument. Rather than  
focusing on the implications of human/non-human chimeras for humans, he has looked  
at  
things from the chimeras' perspective – and what he sees is not pretty.

Streiffer has argued that some chimeras, at least, may deserve to be treated as  
persons, at least to some extent, but that humans are unlikely to grant them that  
status.<sup>17</sup>

As a result, sentient but only part-human organisms will be treated as laboratory  
animals,

or farm animals – as worse than slaves. It may be a benefit to a chimeric organism to  
be

sufficiently “human” as to merit a higher moral status – but only if that higher moral  
status is respected. His argument goes well beyond the concern about animal welfare  
in

the Human Neuron Mouse article. It encompasses not only with the unnecessary  
infliction of pain, but also with the denial of rights appropriate to “persons” even when  
that denial would not be inappropriate for what were truly “just” laboratory animals.

### **C. Policies**

Interestingly, in this field we have not only bioethical arguments, but bioethical  
*practices* to examine. Several guidance or regulatory regimes exist for some kinds of

stem cell research that deal expressly with human/non-human chimeras.

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In the United States, the most important action has been the 2005 Guidelines,<sup>18</sup> published by a committee of the U.S. National Academy of Sciences. These Guidelines cover a wide reach of policies about human embryonic stem cell research, from a requirement for ESCRO committees (“embryonic stem cell research oversight committees” – called “SCRO committees” in California, where their jurisdiction extends to some non-embryonic human stem cell research) to positions on informed consent and the extent of development permissible for *in vitro* human embryos. The Guidelines discuss issues around human/non-human chimeras<sup>19</sup> and focus particular attention on three aspects of such chimeras:

The hES cells may affect some animal organs rather than others, raising questions about the number of organs affected, how the animal’s functioning would be affected, and whether some valued human characteristics might be exhibited in the animal, including physical appearance.

Perhaps no organ that could be exposed to hES cells raises more sensitive questions than the animal brain, whose biochemistry or architecture might be affected by the presence of human cells. Human diseases, such as Parkinson’s disease, might be amenable to stem cell therapy, and it is conceivable, although unlikely, that an animal’s cognitive abilities could also be affected by such therapy. Similarly, care must be taken lest hES cells alter the animal’s germline. Protocols

should be reviewed to ensure that they take into account those sorts of possibilities and that they include ethically sensitive plans to manage them if they arise.

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Following from this discussion, the Guidelines propose several recommendations relevant to such creatures:

Recommendation 3(b)(ii) states

All research involving the introduction of hES cells into nonhuman animals at any stage of embryonic, fetal, or postnatal development should be reviewed by the ESCRO committee. Particular attention should be paid to the probable pattern and effects of differentiation and integration of the human cells into the nonhuman animal tissues.

Recommendation 3(c) states

c) Research that should not be permitted at this time:

...

(ii) Research in which hES cells are introduced into nonhuman primate blastocysts or in which any ES cells are introduced into human blastocysts.

In addition:

(iii) No animal into which hES cells have been introduced at any stage of development should be allowed to breed.

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Although they had no legal force in themselves, the NAS Guidelines have been quite influential. California has, in effect, adopted their main points in both its regulations for research funded by the California Institute for Regenerative Medicine (set up by California's 2004 Proposition 71) and its guidelines for non-CIRM funded stem cell research in California. Other states and universities have also adopted these guidelines.

The NAS Guidelines also heavily influenced the guidelines promulgated by the International Society for Stem Cell Research in December 2006.<sup>20</sup> Guideline 10(2)(e)

requires specialized oversight of human embryonic stem cell research, by an ESCRO committee or similar institution, for

Forms of research that generate chimeric animals using human cells. Examples of

such forms of research include, but are not limited to introducing totipotent or pluripotent human stem cells into non-human animals at any stage of post-fertilization, fetal, or postnatal development.

Guideline 10(3)© prohibits “Research in which animal chimeras incorporating human cells with the potential to form gametes are bred to each other.”

These are not the only policy recommendations that deal with human/non-human chimeras. Not all have adopted the same positions. Canada has taken a somewhat stricter position. The stem cell research guidelines of the Canadian Institutes for

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Research prohibit funding any research that would move human embryonic stem cells to

non-human embryos or fetuses (though they do not prohibit moving such cells to born non-human animals).

On the other hand, the regulations adopted by the U.S. National Institutes of Health in 2009 for human embryonic stem cell research it will fund are less restrictive than the NAS Guidelines. They do not require *any* ESCRO-type review at all, for human embryonic stem cells placed into non-human animals or for anything else. Even these regulations carry forward some of the human/non-human chimera prohibitions of the NAS Guidelines:

Although the cells may come from eligible sources, the following uses of these cells are nevertheless ineligible for NIH funding, as follows:

A. Research in which hESCs (even if derived from embryos donated in accordance with these Guidelines) or human induced pluripotent stem cells are introduced into non-human primate blastocysts.

B. Research involving the breeding of animals where the introduction of hESCs (even if derived from embryos donated in accordance with these Guidelines) or human induced pluripotent stem cells may contribute to the germ line.

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A narrower set of recommendations came from a multidisciplinary group convened by researchers at Johns Hopkins University. This group was formed in 2004 to consider issues of transplanting human neural cells or tissues to non-human primates. Because of the close relationship between non-human primates and human primates, and because of the large skull and brain size of some non-human primates, the group believed that the possibilities of, to some extent, “humanizing” their brains deserved special attention.

Its recommendations, published in July 2005, do not take a position on whether such research should be allowed – the group did not achieve consensus on that point – but it did propose “six factors that research oversight committees and other review groups should use as a starting framework. They are (i) proportion of engrafted human cells, (ii) neural development, (iii) NHP species, (iv) brain size, (v) site of integration, and (vi) brain pathology.” The SCRO, or other oversight body, would apply these factors to consider just how plausible some humanizing effect might be. Transplantation of a large number of human cells into an early embryo of a great ape would be of more concern than transplantation of a small number of human cells into the healthy adult brain of a small primate, such as a marmoset. The result in the first case might be a large brain made up largely or entirely of human cells; in the second case, it would likely be, at most, a few

scattered human cells in a very small brain.

## **II. Three Sensitive Kinds of Chimeras – and One Sensitive Use**

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The actual policies adopted with respect to human/non-human chimeras point us to an important reality, sometimes overlooked and rarely stressed in the debates about human/non-human chimeras: even as narrowly as this chapter defines them, not all chimeras are the same. We, at least in Western cultures, care about three kinds of chimeras: those with “humanized” brains (and hence behavior), those with human eggs or sperm, and those with a human outward appearance. The NAS Guidelines and the many policies that follow them speak to the first and third of these concerns by requiring consideration of the patterns of integration of the human cells in the non-human creatures, because of concerns about brains and physical appearance. Those policies address the second concern by banning the breeding of any chimeras that have received human embryonic stem cells, out of fear that the chimeras will have human eggs or sperm.

On the other hand, almost no one was worried when Weissman and McCune made mice with human immune systems. Except perhaps for concerns about animal welfare, no one seems to care about the possibility of a pig with a human kidney or a monkey with a human gall bladder – any more than we worry about humans with pig heart valves. Behaviors (generated by brains), reproduction, and outward appearance – it is not surprising that these are the features we care most about in human/non-human chimeras, as they are a good first approximation for what we care about in our fellow non-chimeric humans. (We also care about the mixing of these characteristics through ways other than human/non-human chimeras.) I believe that brains, gametes, and

looks

explain our concerns about human/non-human chimeras, with one exception concerning a

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particular use of human/non-human chimeras. This section of the chapter will therefore

look at each of three kinds of chimera in turn, before discussing the exceptional use.

## **A. Brains**

We clearly care about human behaviors and capacities and we therefore worry that “humanized” brains might create them.

Any kind of mixture between human and non-human animals is troubling to the folk objection to such chimeras. Brain-based chimeras, though, are the kind that most implicate the issues raised by Robert and Baylis, Cohen and Karpowicz, and Streiffer. (And, in that respect, the academic discussion of these issues may truly be said to be all

Irv Weissman’s fault, or, more neutrally, doing.) Both moral confusion and the concerns about the human dignity of the chimera require that the chimera have some human moral,

or plausible moral, status. It is most likely that we would locate that status in the brain, the source of our (we think) distinctly human consciousness and behaviors. A human/non-human chimera with a brain that functioned like a human’s would genuinely raise these ethical concerns.

Of course, what does it mean to say that the chimera’s brain “functioned like a human’s”? At one level, all mammalian brains function pretty much the same way – neurons are organized into a brain stem, a cerebellum, and a cerebrum and

communicate  
using the same repertory of neurotransmitters. We see, we hear, and we move our  
bodies

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using the same kinds of brain activity. Humans have large brains (although whales, porpoises, and elephants have larger brains, though not as a percentage of body size), very large cerebrums, and extremely large neo-cortexes compared with other mammals. No one has ever successfully identified a distinctly human brain location for consciousness, intelligence, conscience, or a soul.

And what behaviors are uniquely human? We used to cite tool use, but we now see more examples of tool use, not just from other primates but even from some kinds of birds. Speech still seems distinctly human, although symbol or hand-sign-based language abilities of some sort have been seen in chimpanzees and possibly gorillas.

The report on Weissman's Human Neuron Mouse project confronted these issues. We ended up telling the researchers to look at the mouse brains to see whether, for brain regions that differed between mice and men, the chimeras had human structures or murine structures. For behavior, though, we gave up. Certainly, if a mouse had stood on its hind legs and said, "Hi, I'm Mickey," that would have been evidence of a human-like behavior. But would a change in memory, for example, mean that the mouse had a more human-like brain? And, if so, in what direction? We do not know whether a human would perform most mouse memory tests better or worse than a mouse. Ultimately, we recommended watching any born chimeric mice for unusual behaviors, as we could not

predict what kinds of behaviors might show a human influence.

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Still, although defining a humanized brain or behaviors is difficult, at some hypothetical point it would become obvious, particularly if the chimera were able to communicate. How likely is such a result? It depends.

For a human/mouse chimera to be like Kafka's Gregor Samsa, but trapped in a mouse's body, is scientifically absurd. Researchers have shown that human neurons can live, grow, and divide in a mouse brain; mice have been made with several percent of their neurons of human origin. One researcher has even shown that a human neuron in a mouse brain will function, at least in the sense of "firing" (creating an action potential on the axon). Whether those cells really function, in the sense of playing a useful role in the working of the mouse brain, is still unknown. It may well be that subtle differences in the environment and the molecules surrounding the human neurons make them unable to contribute meaningfully in the mouse brain, and would, as a result, make a living, functioning Human Neuron Mouse impossible. Even if the Human Neuron Mouse did function, though, its brain would be about one one-thousandth the size of a human brain and the size of the mouse skull greatly limits its ability to expand. The absence of uniquely human areas associated with consciousness or intelligence makes it seem quite likely the sheer size of our brains is important to human functioning. Accordingly, the Human Neuron Mouse seems very unlikely to have a brain that is meaningfully human-like.

But that is much less clear for a human/great ape chimera. Human brains and the brains of the other great apes are much more similar to each other, in structure and in

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size, than human and mouse brains. Chimpanzee brains are about one third as large as

human brains; gorilla brains are about forty percent the size of ours. A brain from these

apes also has a large neocortex, although not as large as a human's. And, to the extent

that subtle differences in genes, proteins, and other molecules found in the brain may make a difference in functioning, because of recent (in evolutionary time) shared

ancestry, those are also more likely to be similar, or identical, between humans and other

apes than between humans and other mammals. As the Johns Hopkins group concluded,

it is not absurd to think that a gorilla with a brain derived from human embryonic stem cells or human brain stem cells would have a substantially "human-like" brain and possibly human-like behaviors.

It is important to note that, if our worry is the creation of something with a human consciousness or intelligence, human/non-human chimeras are not the only way to try to

achieve that goal, and may not be the most plausible. Computers can already beat chess

grandmasters; that level of intelligence seems a stretch for still hypothetical

human/gorilla chimeras. Artificial intelligence may be a more promising route for

anyone trying to create another human-like intelligence. If someone did want to use

biological materials, it might be more promising to try to make genetic modifications in

another great ape, making the genes suspected of being important in brain development

identical to their human equivalents. (These would be “genetic chimeras” according to the definition of chimera I proposed in 2003, but are not chimeras as defined for this chapter.) And, of course, we could end up confronting human-like but non-human intelligences in other ways, through communication with intelligent extraterrestrials or

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even through discovering an ability to communicate with existing non-human species, such as whales or porpoises.

But whatever the source of a non-human human-like intelligence, it would raise profound questions. Some of these were explored in a 1947 science fiction story by Robert Heinlein, “Jerry Was a Man.”<sup>23</sup> Heinlein’s story, set in an undefined future, features widespread genetic modification of animals, some as pets or follies (like a winged but flightless horse), but some as workers. Jerry was one of many genetically modified chimpanzees, given higher intelligence that included the ability to speak and used as field or domestic workers. These workers were treated as owned animals; the conflict in the story revolved around a court case seeking (successfully) to declare Jerry the holder of human rights.<sup>24</sup>

How would we react to a human-like but non-human intelligence? Would we greet it gladly, welcoming “someone else to talk to”? Would we, as Streiffer (and Heinlein) fear, treat it badly? How *should* we react? How would our societies have to change in reaction to these other intelligent creatures? How would we even recognize it<sup>25</sup>— through something like the Turing test for artificial intelligence? These questions are not easily answered.

## **B. Gametes**



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Worry about human/non-human chimeras carrying human eggs and sperm seems

obvious. One of the definitions of prohibited chimeras in the Brownback bill – “a non-human life form engineered such that human gametes develop within the body of a non-

human life form– spoke directly to this point. There are three possible bases for concern:

the presence of human gametes themselves in chimeras, the possibility of the fertilization

involving one human and one non-human gamete as a result of sex between two such chimeras (or a chimera and an animal), and the admittedly eerie chance that the mating of

two human/non-human chimeras with human gametes could produce a human embryo.

None of these, ultimately, is a strong argument against creating such chimeras.

Unless one sacralizes human gametes, there is no reason to be any more concerned about their mere presence in a human/non-human chimera than there is to be

concerned about the presence of human liver cells, kidney cells, or tumor cells – and far

less than for human neurons. The absence of gametes, which all human males experience

before puberty, or of functional gametes, which all human females experience before

puberty and after menopause, makes people infertile but has no other effect on their

functioning or personalities. Similarly, the mere presence of gametes should have no

consequences, either for humans or for chimeras.

Nor, in spite of a few religious efforts to the contrary, do we treat gametes as sacred. In the normal course of events, sperm and eggs are not cherished, protected, and treated with respect. In all humans' lives, their gametes live and die, in the billions for

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me and in the hundreds for women, almost always futilely and never mourned or subject to “proper” disposal.

The worry *must* be not about the gametes in themselves, but about the possibility that the gametes will be effectively used – that human sperm or eggs in chimeras will fertilize or be fertilized. The folk concerns about crossing species boundaries undoubtedly include worries about human sperm fertilizing non-human eggs or (perhaps viewed culturally as worse) non-human sperm fertilizing human eggs. The Brownback bill’s eight definitions of chimera contain two provisions speaking to this possibility: “(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 . . . .”

The idea that human sperm and rat eggs, or human eggs and mouse sperm, could form an embryo seems scientifically bizarre. The species are so different, down to the numbers of their chromosomes, that it seems impossible that they could make a hybrid that functioned, even at a prenatal stage. Nor are there any plausible reports of successful hybrids of humans with any other species. Controversy even continues as to whether modern humans could or did successfully with their very closely related Neanderthal cousins.

Of all existing species, it is least implausible that humans might be able to form hybrids that were viable, at least perhaps *in utero*, with chimpanzees, our closest living

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relatives. Would the existence of such a hybrid be a moral problem if it were terminated

well before birth? It would be quite likely that most, if not all, such hybrids would fail to develop successfully *in utero* for natural causes. Products of conception fail to develop

all the time; it is estimated that more than half of all human zygotes resulting from sexual intercourse do not develop into successful pregnancies; even in healthy young women, only about thirty percent of embryos transferred through *in vitro* fertilization develop. It is hard to see a serious ethical problem in the creation of transitory hybrid embryo that dies on its own, apart from a strict abhorrence of crossing species lines.

Even if such hybrid embryos could come into being and were not naturally unable to develop, the resulting pregnancies could be terminated. Aborting such a pregnancy seems unexceptional, even if the embryo or fetus were to be given, by the benefit of the

doubt, some human moral status. Many countries, and certainly the United States, allow

abortion of fully human fetuses for broad reasons, and others allow abortion for reasons

of fetal health. And, in the unlikely event such a hybrid were viable at all, any born human/chimpanzee hybrid would be highly likely to have major health problems and so could be legally aborted in most countries.

Thus far we have been discussing conceptions and embryos resulting from the conjunction of a human gamete, in a human/non-human chimera, with a non-human gamete. There is an odder possibility: two human/non-human chimeras, each with

complementary human gametes, mate. The product of a human sperm fertilizing a human egg, even if it occurred within a non-human reproductive tract, would presumably

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be some kind of human embryo. Whether or not it develops to be viable in an alien uterus, seems unlikely. (Certainly, depending on the non-human component of the chimera, a “human” pregnancy could be disastrous; no human fetus could develop successfully inside a mouse or a rat.) Using the same logic as before, though, termination of the pregnancy would be appropriate.

But there are more fundamental problems with these odd reproductive scenarios. First, scientists are not going to want to create such pregnancies. Usually they are not even going want to create chimeras with human gametes; an embryonic stem cell that was intended to be studied in the brain or heart or liver might, somehow, migrate to the host’s gonads and somehow produce gametes, but how often? And, in terms of intentional creation of gametes, what scientific question is answered by seeing if two mice with human gametes can “naturally” form a human embryo? Why would a scientist want to see if humans and chimpanzees could form even momentarily viable hybrids? Even a mad scientist intent on producing a creature with some characteristics of both species would be more likely to proceed through more targeted methods, such as transplanting particular organs, transplanting stem cells that would produce only those organs, or changing particular genes of interest. Any of these conceptions would be accidents, and unlikely accidents at that.

Accidents cannot always be avoided but they can be limited. Chimeras could be sterilized. They could be segregated by sex in different cages or different rooms.

Only  
immature chimeras could be used for research and they could be euthanized before  
they

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were reproductively mature. To avoid the Kafkaesque scenario of human sperm and human egg meeting as a result of the mating of two mice (or, more accurately, predominantly murine human/mouse chimeras), the chimeras could be made from only one sex. And accidents can be repaired – any pregnant chimeras could be euthanized as soon as the pregnancy was detected. These kinds of precautions are already being required by many SCROs in implementing the NAS guidelines or state rules. We may worry about human gametes, but we need not worry very much.

It is, however, again worth noting that similar issues could arise without any use of human/non-human chimeras. One could attempt fertilization between human and non-human gametes much more simply *in vitro* (or, in some cases, *in vivo*). In fact, one common test for whether human sperm to be used for artificial insemination or *in vitro* fertilization is properly functional is to see if it can penetrate hamster eggs. A scientist who, for some bizarre reason, wanted to see what would happen to a fertilized human egg in a non-human uterus could just transfer an *in vitro* human embryo to an animal. No chimeras would be necessary.

### **C. Outward Appearance**

The NAS Guidelines and other policies, as well as the Brownback bill, expressly discuss chimeras involving human cells in brains and, implicitly, chimeras with human gametes. Apart from under 25 words in the NAS Guidelines,<sup>26</sup> there is no

express

discussion of the possibilities of chimeras with any outwardly (and disturbingly) visible

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human features. Yet chimeras with some visible human characteristics could also be  
27profoundly unsettling.

To some extent, they already have been – and not just from mythological sphinxes, minotaurs, centaurs, and various human/non-human gods, from Anubis to Ganesha. In 1997 scientists in Massachusetts published a medical article with a photograph of what looked like a human ear, which they had grown on the back of a  
28mouse. The photograph became famous (or infamous) and the experiment became controversial, in part as a result of its use by a group campaigning against genetic engineering. Ironically, not only was the ear not the result of genetic engineering (except in the creation of the immune-deficient mouse used as a host), but the creature was not a human/non-human chimera. The ear was made of cartilage from the knees of cattle, molded into the form of a human ear.

One can imagine other chimeras with deeply unsettling human features, such as non-human primates with human faces or hands. These would, of course, break the folk requirement of a strict separation between humans and other animals. They could also create the kind of moral confusion that Robert and Baylis discuss: someone might, at least at first, be uncertain about how to treat a monkey with a human face. In a more extreme case, a non-human primate with a human outward appearance might lead to moral confusion about the status of a developmentally impaired human, one with less

cognitive ability than the non-human primate. Of course, these examples do point out an issue with the moral confusion idea. Is this moral confusion only bad if it leads people to

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treat other humans as having a lower moral status, more akin to that of the non-human animals they resemble? What if, instead, it were to lead to people treating non-human animals better, because their connections to humans have seemed closer as a result of human/non-human chimeras?

On the other hand, these kinds of chimeras do not seem to implicate the concerns

about the “human dignity” of the chimera that Streiffer and Cohen discuss as, understandably, they do not talk about outward appearance as something that would entitle the chimera to human moral status.

Are there other ethical issues here? It is hard to see any serious ones. But it is also hard to see much scientific interest in creating such chimeras. And, just as the chimera issues around brains and gametes could arise without actually involving chimeras, the creation of non-human living things that look, in part or whole, like humans would not necessarily require human/non-human chimeras. Realistic androids could present the same issues. So could animals made to resemble humans through cosmetic surgery or genetic engineering.

#### **D. An Exceptional Use**

One use of human/non-chimeras that does *not* involve brains, gametes, or outward appearance could still raise substantial public concerns: their consumption. Hannibal

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Lecter's meal of human liver would not lose much of its shock value if the human liver had been grown inside livestock.

For a human to eat tissue of human origin from a human/non-human chimera would likely be regarded as, at best, disgusting. The consumption of such tissue by non-human animals, either intended by humans or accidental, also seems likely to raise concerns. But *should* we be concerned? No human being was killed, or even died, to produce this meat. (In fact, if an adult stem cell or an induced pluripotent stem cell were used, not even a human embryo would have been destroyed.) And, after all, we are all, eventually, food for worms (or other small living organisms).

The taboo against cannibalism is broad and deep in the modern world (although, historically, it has not been universal). Similarly, human cultures generally require some special treatment of the dead. The dead, or, at least, "our" dead, are to be protected from the ravages of scavenging birds and animals. For large animals, burial serves this purpose, as does cremation. (Of course, these practices are also not universal. The Parsi custom of exposing their dead to scavenging by vultures is clearly contrary; so, less obviously, is the practice of burial at sea.)

Revulsion against eating human tissues, even if not from human beings, is not

necessarily specific to human/non-human chimeras. Consumable human meat might not

even require the death of any animal, human or human/non-human chimera. Research is ongoing to produce meat from stem cells grown *in vitro*. The current research focuses on

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pork, but, if it were successful, presumably there would be no technical barrier to growing “long pork” by tissue culture. (Similarly, if we were able to grow human tissues *in vitro* for medical purposes, that tissue might end up being eaten.)

Human/non-human

chimeras, however, might present a greater opportunity for human tissue, produced for a

non-food reason, to be consumed accidentally.

Taboos against cannibalism do not stem from crossing species barriers – in that case, the eater and the meat are from the same species. The idea that humans should eat

animals but not other humans does seem, though to be based in a concern about upsetting

a natural distinction between humans and non-human animals. Similarly, animals eating

human flesh reverse this normal order – that humans should eat animals and animals should not eat humans. As such these concerns seem to implicate both the folk concern

about the natural order and, possibly, the concern of Robert and Baylis about sowing moral confusion. They would not offend either Cohen’s or Streiffer’s slightly different concerns about human dignity, unless, of course, the particular human/non-human chimera was “sufficiently human” to deserve human moral standing.

Are there strong reasons to be alarmed by the consumption, by humans or other animals, of human tissue that was not taken from human persons? I find it repugnant

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the very thought is nauseating – but that is not a moral argument. The strongest argument

I see is that this very disrespectful use of human tissue might bleed over into immoral actions against human persons. The cannibal who has feasted on chimeric (or *in vitro*)

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human flesh might lose some reluctance to take flesh from actual humans, dead or (even worse) still living. Or someone who has seen chimeric human flesh sold as pet food might, as a result, devalue people. Treating human tissues, even when not produced directly from the bodies of humans, as meat could lead some people to treat people as morally equivalent to the non-human sources of our usual meat. This is, at heart, a speculative empirical argument about how people (or some people) would actually behave. It is necessarily speculative; both the existence and the extent of such an effect seem untestable without doing the experiment. One could argue, though, that the risks of such an effect are not worth taking.

None of the policies about human/non-human chimeras deal with this issue, for a good reason. They are policies about biomedical research. The chimeras they govern are research animals. When these animals – whether mice, rats, or monkeys – are dead, they will, in the normal course of events, be disposed of as biomedical waste. No one eats laboratory animals or feeds them to pets. There is, however, at least one example of non-human consumption of human/non-human chimeras.

In the early 2000s, Dr. Esmail Zanjani at the University of Nevada, Reno transplanted human stem cells, mainly human blood-forming stem cells, into pregnant sheep. According to Zanjani, these cells became a variety of different cell types in the

sheep and their offspring. In one sheep, he claimed that human cells made up 40 percent

of its liver.<sup>30</sup> The local press reported that the ewes that had received injections of the human cells were, after lambing, sent by the university to a ranch to be used in a weed

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control project. These naïve laboratory sheep were then allowed graze in the wild, leading to many dead sheep and some happy coyotes and mountain lions.<sup>31</sup> The newspaper story was part of a series about the misuse of animals at the university; it focused on the cruelty of intentionally allowing these animals to be killed by predators or chased by wild dogs to a drowning death in the river. Yet the fact that the article returned, several times, to the question whether there were human cells in the ewes suggests that there was at least some interest in the idea of human tissue being eaten by predators.

### **III. What Is To Be Done?**

The arguments about brain chimeras made by Robert and Baylis, Cohen and Karpowicz, and Streiffer all have real merit, but arguments for limiting the creation and use of other kinds of human/non-human chimeras are weak. The ethical arguments against human/non-human chimeras based on gametes, though, are almost wholly without merit, as are the arguments about human appearance. The ethical argument against eating human tissue is not, fundamentally, an argument against creating human/non-human chimeras and is, in any event, quite speculative.

The ethical arguments against such possible practices may be weak, but the public reaction against them seems likely to be strong. The delivery of President Bush's 2006

State of the Union Address and the multiple introductions of Senator Brownback's Human Chimera Prohibition Act both occurred when no clearly offensive human/non-

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human chimeras existed. Creating offensive chimeras could lead to a political backlash,

damaging to all of science.

At the same time, the benefits of most of the controversial work are at best, limited and, even where benefits are plausible, some precautions might usefully be taken to avoid giving offense. It could be scientifically useful to study the development of human gametes inside a laboratory animal, given how difficult it is to study them inside living humans. But there seems no reason to attempt to have human/non-human chimeras with human gametes breed, either with animals with non-human gametes or with other chimeras with human gametes, or even to allow the possibility. Measures can be taken to minimize those chances of fertilization or the highly unlikely prospect of any significant embryonic development.

Similarly, it might be useful to study the development of some aspects of human external appearance – the growth of the ear, the nose, or the thumb, for example – in non-human animals in order better to treat human diseases or deformities. One could imagine precautions to avoid using species where the result would look “too” human.

There seems no plausible justification, scientific or otherwise, for building or allowing a human meat industry.

Brain-based chimeras are the major exception to this line of argument. Some kinds of scientifically and medically useful experiments could certainly be done without

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risking the creation of a chimera with any potential for distinctly human cognitive functions. Weissman’s plans to use the Human Neuron Mouse to study the effects of pathogens, radiation, drugs, and other intervening forces on human neurons *in vivo* could, as our report argued, be done with minimal risk of creating a human-like brain. But if you wanted to study brain development, or, more broadly, the necessary brain prerequisites for some human abilities, human subjects cannot be extensively used because of the risks to them. Human/non-human chimeras might provide the only plausible approach.<sup>32</sup> One can at least imagine trying to grow human-like brains in chimeras to study, for example, the ability to use language.

So what should we do?

The issues, ethical and otherwise, around human-like intelligence in non-human creatures are profound. We should not attempt to create such an intelligence, and such potential carriers of “human” rights, without substantial prior public discussion. That discussion should take place in a factually rich context, with a realistic proposal at hand, and not only through abstract speculation. Until then, there should be a moratorium on any attempt to create such intelligences, whether through human/non-human chimeras, genetic engineering, or artificial intelligence. It is not clear whether that moratorium could be informal – a consensus of the relevant researchers – or whether it needs to be formal. (Ironically, situations where creators of human/non-human chimeras face

SCRO-

like oversight are the only times where there are formal limits on this effort, although, even there, without an express moratorium.)

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We should also be careful to avoid creating it accidentally. And, at least with respect to the creation of human/non-human chimeras human embryonic stem cell research, we do. The NAS Guidelines require SCROs carefully to assess the possible integration of the human cells into the central nervous system. (The processes suggested in our report on the Human Neuron Mouse and the factors set out in the article on neural grafting into non-human primates are two useful ways for SCROs to approach this task.)

But what should we do about other types or uses of human/non-human chimeras, where ethical concerns are weak but public concern is strong? Scientists, and those who believe, as I do, that this kind of research is scientifically important and, ultimately, morally positive, should be pragmatic. In this case that means acting prudently to avoid rousing public opposition unnecessarily. Scientists should not try to create human/non-human chimeras that are likely to provoke public controversy (or use less controversial chimeras in controversial ways) unless the potential scientific gains are large enough clearly to justify the controversy. Arguments about those gains should be made to some outside body and, if a decision to proceed follows, the public should be educated about the justification for the work. At the same time, researchers should take precautions to avoid uses of chimeras that give unnecessary offense.

This, in effect, is the regulatory regime proposed by the NAS and ISSCR and implemented by California. Research putting human embryonic stem cells into non-human animals must be approved by SCROs. The NAS tells the SCRO to pay "particular

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attention . . . to the probable pattern and effects of differentiation and integration of the human cells into the nonhuman animal tissues.” The chimeras may not be allowed to breed; in California SCROs, non-breeding plans are required for approval. There are no current specific requirements for proper disposal of human/non-human chimeras, but the disposition of dead laboratory animals is regulated. (It is not clear whether adding a provision on disposition of chimeric remains would add enough value to be worth the possible controversy caused by drawing attention to the possibility of their consumption.)

And the SCROs must decide whether, overall, the scientific merits of the research justify undertaking it. This weighing requirement was initially intended to assure those concerned about the moral status of the embryo that human embryos would not be destroyed (and the resulting stem cells would not be used) wastefully or for no good purpose. But it can also serve to prohibit, on a case-by-case and local basis, research with human/non-human chimeras where the costs – whether viewed as public unhappiness or outrage directly or through the negative effects of that reaction on science – outweigh the likely scientific benefits.

This kind of prudential regulatory scheme is likely to succeed, in part because there are few if any good scientific reasons to try to avoid or circumvent it. The spirit of provocation – the desire to *épater la bourgeoisie* – no doubt exists in some scientists, but scientists are usually quite constrained actors. They need jobs, they need tenure, and they

desperately need funding. Independently wealthy gentlemen-scientists might be able to annoy the non-scientific (and much of the scientific) world just for the pleasure of it, but

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almost all scientists will not be able to breed mice with human gonads or to create a monkey with a human face without a very convincing justification, to funders, department chairs, deans, and company CEOs. Even without regulatory oversight, science for the sake of provocation is unlikely. But in many countries today, this kind of research would almost always have to undergo some kind of regulatory oversight – occasionally by IRBs or their human experimentation equivalents in other countries, almost always by IACUCs or their equivalents, and in many jurisdictions by SCROs or their equivalents. The mad scientist may not be entirely extinct but it is safe to say that he is neither well-funded nor unregulated.

Of course, as noted above, the issues about brains, gametes, appearance, and even human meat could all arise outside the context of human/non-human chimeras. Even when chimeras were involved, those chimeras could be created outside the context of the regulatory scheme for human *embryonic* stem cells, through the use of induced pluripotent stem cells, of more differentiated stem cells, or just of tissue or organ transplants. The same kinds of pragmatic concerns about inflaming public opinion against science apply in those situations. It is not clear to me, though, that the risks of such actions, and, outside the politically charged world of stem cell research, justify a formal regulatory scheme.

Scientists ultimately do not worry me, but artists do. Many artists find skewering widely held sentiments particularly satisfying (and, for some of them, financially rewarding). Chimeras have already attracted the attention of modern sculptors and

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painters. More literal bioartists already exist. Edouard Kac famously asked a French laboratory to create a transgenic rabbit that had received a jellyfish gene, widely used in scientific research, for green fluorescent protein (GFP). The rabbit, which Kac named Alba, would glow at least somewhat green when viewed under a particular frequency of ultraviolet light. Kac was going to exhibit the rabbit and eventually take it home to his family as a pet. The laboratory eventually got cold feet and refused to turn the rabbit over to Kac; its fate (and that of the laboratory's other GFP rabbits) is unknown.

Other bioartists are also active. In 2008 the University of Alberta sponsored a fascinating exhibition of bioart and published a catalog of the exhibition with both photographs and descriptions of the art and essays by bioethicists and others.<sup>34</sup> Adam

Zaretsky, one of the contributors to that show, is particularly active, working himself in laboratories to create new life forms/art forms.<sup>35</sup> One artist, Steven Kurtz, was even prosecuted by the U.S. federal government for mail and wire fraud for obtaining microbes from a vendor inappropriately. (Charges were dismissed against Kurtz before trial; Robert Ferrell, the respected geneticist who had ordered the microbes for him, had pleaded guilty earlier to a misdemeanor charge.)

What should be done about bioartists creating controversial human/non-human chimeras or making provocative uses of them? Little or nothing. Whether regulating art

is more like a minefield or a quagmire is not clear to me (perhaps a minefield in a

quagmire?), but it is clear that it would be a contentious and difficult process. It is also the case that art's provocations might lead to useful discussion and insights into the

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science, for the public and for scientists. Even if it were plausible to regulate art, it would be a bad idea. On the other hand, it might be a good idea for science to dissociate itself

from provocative bioart. If the artists use facilities or collaborators from science, those should be subject to the regulation of SCROs and similar bodies. But we should not try

to stop artists, acting on their own (and within general health and safety regulations), from making bioart – though we may have to cross our fingers and hope they do not bring down the public's wrath on science.

## **Conclusion**

The ethics of creating and using human/non-human chimeras have led us down some strange paths. Where there are serious ethical issues, in the creation of other intelligences, the issues apply more broadly than just to such chimeras. Where the concerns focus directly on the chimeras, through the folk abhorrence of mingling human with non-human, this repugnance is not an ethical argument, but is a political reality that needs to be considered.

The Human Chimera Prohibition Act, though introduced a second time by Senator Brownback in 2007, has not passed. And, after all the controversy, Weissman still hasn't

made any fully human neuron mice. Early on, there were problems finding the mouse strain he needed to use to host the human cells. Then the post-doc interested in the project moved on from Weissman's lab. Weissman even began to refer to the Human

Neuron Mouse as a thought experiment. In early 2009, though, in response to the

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substantial stimulus funding from NIH for biomedical research, Weissman submitted a grant application, with Stanford stem cell researcher Marius Wernig and me as co-principal investigators, to create human neuron mice. This application proposed using not only human brain stem cells derived from fetal sources, but also induced pluripotent stem cells that had become differentiated into neural progenitor cells. That application

was denied – and the Human Neuron Mouse remains not yet born, but not yet dead. For

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better or for worse.

<sup>7</sup> George W. Bush, State of the Union 2006, <http://georgewbushwhitehouse.archives.gov/stateoftheunion/2006/>. <sup>2</sup> J.M. McCune, et al., “The SCID-hu Mouse: Murine Model for the Analysis of Human Hematolymphoid Differentiation and Function,” *Science* 241 (1988): 1632-39. <sup>3</sup> Terence P. Jeffrey, “NIH Mass Produces ‘Human Mouse’,” *Human Events*, Oct. 11, 2001, p. 1-9. <sup>4</sup> The discovery was announced in a press release by CytoTherapeutics, then the corporate parent of StemCells Inc., on January 20, 2000. “CytoTherapeutics Subsidiary Stemcells, Inc. Announces First Direct Isolation of Human Brain Stem Cells,” ~~BusinessWire (Jan. 20, 2000)~~. The press release can be found at <http://www.stemcellsinc.com/news/000120.html>. The first scientific publication of the result came in December 2000. Nobuka Uchida, et al., “Direct Isolation of Human Central Nervous System Stem Cells,” *Proceedings of the National Academy of Sciences* 97 (2000): 14720-14725. <sup>5</sup> Henry T. Greely, Mildred K. Cho, Linda F. Hogel, and Debra M. Satz, “Thinking About the Human Neuron Mouse,” *American Journal of Bioethics* 7(5) (2007): 27-40. <sup>6</sup> The Human Chimera Prohibition Act of 2005, SB . . . This discussion has recently been nicely captured in a short book, Andrea L. Bonnicksen, *Chimeras, Hybrids and Interspecies Research: Politics and Policymaking*, (Washington, D.C., Georgetown University Press, 2009). <sup>8</sup> I have discussed in earlier work quite a few of those meanings. Henry T. Greely, “Defining Chimeras . . . and Chimeric Concerns,” *American Journal of Bioethics* 3(3) (2003): 17-20. <sup>9</sup> It is unclear how many people have received such “xeno-transplants.” There are at least four famous examples. In 1984, a baboon heart was transplanted into a twelve-day-old baby born with fatal heart defects. The child, known as Baby Fae, survived for 21 days with the baboon heart. In 1992 and 1993 a team led by Dr. Thomas Starzl twice transplanted baboon livers into people dying of AIDS. One survived for 70 days; the other for 25. And in 1994 an AIDS patient named Jeff Getty received baboon

bone marrow, in the hopes that these cells, which are subject to infection by AIDS, would make white blood cells to keep him alive. The baboon cells quickly disappeared from Getty's body and did not successfully give him a baboon immune system, but Getty, at least, survived the procedure, eventually dying in 2006 from cancer. About twenty people received animal kidneys in the early 1960s from at least two different surgical programs, but to much less publicity. A few other experimental xenotransplants were tried over the years before 2000, but few if any have taken place since then. Still, an International Xenotransplantation Association still exists and its official journal, *Xenotransplantation*, has just completed its sixteenth volume. <sup>10</sup> Greely, *Defining Chimeras*. <sup>11</sup> We called for monitoring the any live mice for signs of pain but saw no reason to think that would be so likely as to prevent the experiment. We noted some ethicists and research institutions view the use of human fetal tissue as making the investigator unacceptably complicit in an abortion. The facts that abortion was been widely legal in the United States since January 1973; that the use of human fetal tissues, or cells derived from such tissues, is legal in the United States; and that research using them has, by Act of Congress, been eligible for federal funding since 1993 made their use, in general, ethically permissible. Finally, citing numerous other examples, we argued that whatever the limits of appropriate use of human tissues, its use in biomedical research was generally accepted as permissible. <sup>12</sup> Jason Scott Robert and Françoise Baylis, "Crossing Species Boundaries," *American Journal of Bioethics*, 3(3) (2003): 1-13. <sup>13</sup> President's Council on Bioethics, *Human Dignity and Bioethics: Essays Commissioned by the President's Council on Bioethics* (Washington, D.C., President's Council on Bioethics, 2008). <sup>14</sup> Ruth Macklin, "Dignity Is a Useless Concept," *BMJ* 327 (2003) 1419-20; Timothy Caulfield and Roger Brownsword, "Human Dignity: A Guide to Policy Making in the Biotechnology Era?" *Nature Reviews Genetics* 7 (2006) 72-76. <sup>15</sup> Cynthia Cohen, *Renewing the Stuff of Life: Stem Cells, Ethics, and Public Policy* (New York, Oxford University Press 2007); Phillip Karpowicz, Cynthia B. Cohen, and Derek van der Kooy, "Developing Human-Nonhuman Chimeras in Human Stem Cell Research: Ethical Issues and Boundaries," *Kennedy Institute of Ethics Journal* 15(2) (2005) 107-134; Cynthia Cohen, "Beyond the Human Neural Mouse to the NAS Guidelines," *American Journal of Bioethics* 7(5) (2007) 46-49. <sup>16</sup> Josephine Johnson and Christopher Eliot, "Chimeras and Human Dignity," *American Journal of Bioethics* 3(3) (2003) 6-7. <sup>17</sup> Robert Streiffer, "At the Edge of Humanity: Human Stem Cells, Chimeras, and Moral Status," *Kennedy Institute of Ethics Journal*, 15(4) (2005) 347-370. <sup>18</sup> Committee on Guidelines for Human Embryonic Stem Cell Research, *Guidelines for Human Embryonic Stem Cell Research* (Washington, D.C., National Academies Press 2005). <sup>19</sup> Guidelines at 38-41, 49-50. The discussion was based in part on presentations at a public workshop the Committee held on October 12 and 13, 2004. Cynthia Cohen and I both testified about chimeras at this workshop, as did several others.

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<sup>20</sup> International Society for Stem Cell Research, *Guidelines for the Conduct of Human Embryonic Stem Cell Research* (ISSCR 2006), available at <http://www.isscr.org/guidelines/>. <sup>21</sup> National Institutes of Health, “National Institutes of Health Guidelines for Human Stem Cell Research”, 74 *Fed. Register* 32170 (July 7, 2009). <sup>22</sup> Mark Greene, et al., “Moral Issues of Human–Non-human Primate Neural Grafting”, *Science* 309 (2005) 385-386. <sup>23</sup> Robert A. Heinlein, “Jerry Was a Man,” in *Assignment in Eternity* (New York, New American Library, 1953). <sup>24</sup> The court case, and the story, ends with what can only be called a cringe-inducing analogy between Jerry and African-American slaves. Jerry wins his court case by playing a harmonica and singing “Suwannee River.” <sup>25</sup> The Turing test refers to a proposal by Alan Turing that a computer could be considered to have attained artificial intelligences when an observer could not tell from its responses whether it was a computer or a human being. See the fascinating discussion of the Turing test in Graham Oppy and David Dowe, “The Turing Test”, *The Stanford Encyclopedia of Philosophy (Fall 2008 Edition)*, Edward N. Zalta (ed.), URL = <<http://plato.stanford.edu/archives/fall2008/entries/turing-test/>>. <sup>26</sup> The NAS Guidelines mention this possibility twice on page 50. First, the report says “The hES cells may affect some animal organs rather than others, raising questions about the number of organs affected, how the animal’s functioning would be affected, and whether some valued human characteristics might be exhibited in the animal, **including physical appearance.**” (emphasis added). Then, two paragraphs below, it lists five questions an ESCRO should consider in reviewing protocols for transfer of human embryonic stem cells into non-human animals. The fifth is “If visible human-like characteristics might arise, have all those involved in these experiments, including animal care staff, been informed and educated about this?” <sup>27</sup> The characteristics need not necessarily be “visible.” A human/monkey chimera with a human voice would be upsetting. Or the disturbing trait might be visible but not a matter of appearance *per se*. An ape that walked like a human could be distressing. The most plausible examples, though, involve physical appearance and so the chapter will focus on them. <sup>28</sup> Yilin Cao, Joseph P. Vacanti, Keith T. Paige, Joseph Upton, and Charles A. Vacanti, “Transplantation of Chondrocytes Utilizing a Polymer-Cell Construct to Produce Tissue-Engineered Cartilage in the Shape of a Human Ear,” *Plastic and Reconstructive Surgery* 100(2) (1997) 297-302. <sup>29</sup> It is at least interesting that a central ritual of Christianity, communion or the Eucharist, is an example of the cannibalistic consumption of the body and blood of Christ, either symbolically in many sects or, in Catholic doctrine, literally, through the Miracle of Transubstantiation. “And as they were eating, Jesus took bread, and blessed it, and brake it, and gave it to the disciples, and said, Take, eat; this is my body.” Matthew 26:26 (King James Version). <sup>30</sup> Jamie Shreeve, “The Other Stem Cell Debate,” *The New York Times Magazine* (April 10, 2005).

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<sup>31</sup> Francis X. Mullen, “From Research to Waste,” *Reno Gazette-Journal*, 1A (Mar. 30, 2005). There appears to be some dispute as to whether the ewes, which had been injected with the human cells, retained human cells at the time of their disposal to the ranch. The reporter notes that the ranchers and neighbors were warned that they did have human cells and were told not to eat them. <sup>32</sup> One might try to reach a similar result through a genetic chimera, starting with, say, a baboon and gradually knocking out baboon genes and adding parallel human genes. Although I view such transgenic creatures as one kind of chimera, see Greely, “Defining Chimeras,” they are not within the scope of this chapter. <sup>33</sup> The full story of Kac and Alba is unclear. See Christopher Dickey, “I Love My Glow Bunny,” *Wired* 9(4) (April 2001). The French laboratory seems to have been producing GFP rabbits for several years before Kac requested one. The rabbits did not glow very green. The eyes were green and the skin had some green glow, but the skin was obscured by the (white) fur. <sup>34</sup> Sean Caulfield and Timothy Caulfield, editors, *Imagining Science: Art, Science, and Social Change* (Edmonton, University of Alberta Press, 2008). See my contribution, Henry T. Greely, “Within You, Without You.” <sup>35</sup> See Zaretsky’s website, Emutagen.com, <http://emutagen.com/index.html>.