At Humanity's Boundary: Ethical Issues in the Creation of Human-Animal Chimeras

by

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Class of 2007

Bowdoin Prize for Undergraduates for Essays in the Natural Sciences

Epitome: This essay explores scientific and ethical issues raised by society's newfound ability to create human-animal chimeras and proposes a general principle to govern ethical decision-making in this area.

Acknowledgements

This essay is a significantly abridged version of my senior thesis. There are several people to whom I owe much gratitude in helping me in that endeavor.

I would like to thank my thesis advisor Doug Melton for teaching me how to think big. He taught me stem cell biology when I worked in his lab; he taught me bioethics when I was in his classroom; and he taught me humility when I was on the tennis court. Most of all, he taught me that being a great scientist means more than just doing experiments; it means thinking beyond them. He has been a great teacher, a greater mentor, and an even greater inspiration.

I would like to thank my "unofficial" mentor David Grewal for teaching me how to think sharply. Without his encouragement, I would not have written this thesis. He is undoubtedly the best teaching fellow I have had during my time at Harvard. He is indeed one of the best teachers I will have ever had. I thank him most for teaching me that arguing about ethics and arguing about what you believe need not be so different.

And lastly, I would like to thank my family. Sometimes gratitude can only be given, not explained.

Chapter I: Introduction

The word "chimera" originally referred to a creature from Greek mythology that was part lion, part snake, and part goat. Today, biologists are able to create chimeras in the laboratory that once existed only in the human imagination. The term "chimera" may be used relatively loosely across different branches of biology. In genetics, a "chimera" refers to the result of cross-fertilizing two genetically dissimilar and normally reproductively isolated individuals (for example, a sheep and a goat). In cell biology, the term "chimera" refers to the result of nuclear transfer from a member of one species to another. In embryology, "chimeras" describe the result of prenatal combinations of cells derived from members of different species. In the field of transplantation, "chimeras" describe the result of moving a discrete organ from a member of one species to a member of another (Karpowicz 2005). In this essay, we focus on the possibility of creating human-animal chimeras by transplanting cells from humans to animals. We take "animal" to mean "nonhuman animal".

The academic literature on the topic is sparse. However, scholars have already noted that as researchers cross species boundaries between humans and animals, scientists and ethicists must similarly cross the disciplinary boundaries between science and ethics.[1] It is with this goal in mind that we embark upon our exploration here.

The central focus of this manuscript regards the conditions, if any, under which it is ethical to create human-animal chimeras in this way. We in this manuscript propose the following simple principle as a guide for ethical decision-making: *one should treat transferred humanity with the same level of respect as one treats inherited humanity*. Importantly, our conception of normative "humanity" in this manuscript is independent of any biological definition of "humanness," a distinction that this essay explores at length. We focus in particular

[1] See Karpowicz (2005); Kobayashi (2003); "Avoiding a chimaera quagmire," *Nature* (2007).

on applying our principle to assess the ethicality of two types of human-animal chimeras that scientists have recently produced: neural chimeras and embryonic chimeras.

The core of this essay rests in its ethical argument. Yet these ethical considerations are inextricably linked to a firm understanding of biology. The following broad outline may therefore be helpful in grasping the relationship between the scientific details and the ethical discourse in this essay. In Chapter II, we discuss the scientific benefits offered by creating human-animal embryonic and neural chimeras. In Chapter III, we formulate our general principle for ethical decision-making in this area. In Chapters IV and V, we apply this principle to assess the ethicality of creating human-animal embryonic and neural chimeras, respectively.

Chapter II: Benefits of Creating Chimeras

Embryonic Chimeras

One of the main forces driving current interest in human-animal chimeras is the medical promise offered by human embryonic stem cell research. Human embryonic stem cells are widely regarded as pluripotent – that is, as having the ability to differentiate into any cell type in the body – based largely on *in vitro* experiments. However, scientists do not as yet know whether human embryonic stem cells would retain their pluripotency *in vivo* – that is, within an actual human body. Scientists almost universally agree that ethical considerations preclude the possibility of performing the necessary experiments on humans because these experiments would require the destruction of a developing human being beyond the point at which most of society is willing to accept human destruction (DeWitt 2002).

However, the creation of a human-animal embryonic chimera presents a potential solution to this hurdle. For example, Brivanlou (2006) created an embryonic chimera by engrafting human embryonic stem cells into a mouse blastocyst and subsequently implanting the resultant embryo into a live mouse uterus. Experiments of this type offer the opportunity to study the behavior of human embryonic stem cells in a living system and offer the opportunity to confirm the hypothesis that these cells are pluripotent *in vivo*.

<u>Neural Chimeras</u>

The creation of human-animal neural chimeras – that is, organisms bearing neural cells from both animals and humans – offers even more significant scientific benefits. Scientists can create neural chimeras in order to acquire a better understanding of diseases afflicting the brain and to create *in vivo* models of potential treatments for these diseases. For example, researchers have recently investigated the use of neural precursor cells to recover cells lost during strokes. Kelly (2004) transplanted human neural cells into rats following stroke, and noted that the transplanted neurospheres were able to survive and were influenced by their environment within the recipient brains. In another study, scientists identified a specific human neural cell line that – if transplanted into rat brains following injury – will not only survive in the host brain, but will also influence the behavior of host cells in their vicinity (Zhang 2005).

Scientists have also begun to employ monkeys as recipients of human neural tissue. Monkeys are more useful than rodents because of their closer evolutionary relationship to humans. For example, scientists have recently used human-monkey neural chimeras in exploring cell-based cures for Parkinson's disease. Bjugstad (2005) implanted human neural stem cells into the brains of chemically impaired monkeys recapitulating Parkinson's disease. The results were provocative: not only did the human stem cells migrate toward the site of damage and replace lost brain cells, but also interacted with the endogenous monkey cell populations. The human neural cells transplanted into the brains of monkeys (as contrasted with rodents) thus appear to behave in more advanced ways that more closely approximate the behavior of these neural cells in the human brain.

Beyond these examples, much of the research involving human-animal neural chimeras reflects a shift toward basic scientific research and even away from research involving immediate medical applications. For example, Irving Weissman and his colleagues at Stanford have successfully created live mice whose brains were 1% composed of human neurons (Uchida 2000). Weissman has further announced his intent to create a mouse with a brain composed entirely of human neurons. Weissman's proposed experimental chimera differs from the earlier examples because it does not involve any immediate medical applications. More recently, Ourednik (2001) transplanted human neural stem cells into the forebrains of developing monkeys merely for the purpose of observing the "segregation" of these cells, with no imminent or stated medical goal for this research. These kinds of experiments offer not only a general experimental model by which scientists can investigate potential treatments for human diseases, but also a useful tool to fundamentally understand human brain function.

Although none of the following experiments have been performed to date, it is worth reflecting on the types of experiments that could be performed in the future, especially in light of the recent trend toward using neural chimeras to understand basic human brain function. For example, scientists often ascertain the functionality of a physiological "unit" by performing loss-of-function experiments: the physiological unit is removed, and scientists deduce the function of that unit by observing the resultant abnormal phenotype in the organism. Ethical considerations preclude the possibility of performing useful loss-of-function experiments directly on the brains of live humans. However, the creation of human-animal neural chimeras may offer an ideal substitute for humans in these loss-of-function experiments. Hypothetically, let us suppose that

Ourednik (2001) now actively performs further experiments on the human-monkey neural chimeras that he created, instead of merely using them to observe the migration and differentiation of transplanted human neural cells. The investigators in this case could physically damage specific regions of the chimera's brain thought to be associated with specific functions, and then compare the phenotype of this experimental chimera with a control chimera that had not been subjected to any such damage. For example, cognitive processing in mammals is thought to occur in the cerebral cortex, but may also rely upon midbrain and limbic functions in ways that are currently not fully understood. To test whether or not cognitive processing depends on these regions, researchers could use a human-monkey chimera (such as an adult version of the one created by Ourednik) to discern whether loss of midbrain or limbic function significantly correlates with a loss of cognitive function.

Likewise, gain-of-function experiments could be used to assess what distinguishes human brain function from that in other species. For example, scientists could create human-monkey chimeras whose brains are identical to monkey brains, except some discrete part of the chimera's brain is constituted by human brain cells. This would allow scientists to identify (and perhaps isolate) the functionality of specific parts of the human brain. For example, the amygdala is thought to be at least one site of the brain governing human memory and emotion, but scientists still lack a robust understanding of this relationship (NIMH 2001). Human-monkey chimeras could thus be used in the following way: a human amygdala (or neural precursors destined to contribute to the amygdala) could be transplanted from a human to a monkey. The modulation of memory and emotion in this monkey could then be assayed in comparison to that in a monkey that had not received a human transplant. One might object that such an experiment would not be informative because complex brain functions such as memory and emotion depend upon not only the amygdala, but also upon the effects of the amygdala upon its surrounding regions. However, when considering this objection in the context of Bjugstad's conclusion that transplanted human neurons can interact with brain cells in an animal recipient and can exert a significant influence on the endogenous cell populations, the following is at least a conceptual possibility: the transplant of an amygdala to a monkey brain *could* conceivably transfer the capacity for human memory and emotion in the resultant chimera. In this way, experiments involving human-animal neural chimeras could contribute to revolutionary advances in understanding the relationship between the human brain and higher-order capabilities that are unique to human beings.

Chapter III: A General Principle

"Humanness" versus "Humanity"

Before formally presenting our general principle, we must first explain a distinction between biological "humanness" and normative "humanity." We take "humanness" to refer to the empirically observable, scientific criteria by which an organism may be identified as *Homo sapiens*. Although such criteria may be useful in establishing species identity, they are not the relevant basis for morally respecting human beings. "Humanness" defined by the possession of 23 chromosomes or the presence of a specific genetic polymorphism does not, in itself, imply a moral obligation to treat an organism exhibiting these qualities in a particular way.

By contrast, we take "humanity" to refer to a set of *capabilities* that distinguish humans from all other living beings. Philosophers throughout history have sought to identify a foundationally distinguishing feature of humanity. For example, Kant identifies the human quality of autonomy grounded in rationality. As Kant compellingly argues, the human capacity for autonomy – that is, the ability to give oneself the law through reason – is what uniquely renders human beings worthy of respect.[2] Aristotle too attributes a special moral status to human reason. Aristotle argues that the existence of human reason – or "logos" – is the grounding for the unique moral status of human beings.[3] Drawing from these philosophical traditions, Oxford bioethicist Savulescu (2003) has more recently proposed the following list of candidate properties as those which morally differentiate humans from all other species: the capacities to (i) reason, (ii) act from normative reasons, (iii) act autonomously, (iv) engage in complex social relationships, (v) display empathy and sympathy, and (vi) to have faith. Importantly, we in this manuscript need not take sides in the debate among philosophers over which precise capabilities distinguish humans because all of these philosophical accounts are united by a common belief: humans should be treated with dignity because of some quintessentially human *capability*, and not because of a biological definition of humanness.

The following figure aims to illustrate the distinction between "humanity" and "humanness" in relation to our discussion of human-animal chimeras. Circles labeled by "A" represent the set of organisms possessing humanity, while circles labeled by "B" represent the set of organisms exhibiting humanness. Before researchers' ability to create human-animal chimeras, organisms possessing humanity ("A") were a subset of organisms exhibiting humanness ("B"). Organisms in "A" include the vast majority of human beings, whereas organisms in "B" but not "A" include organisms possessing biological characteristics of humanness but not quintessential characteristics of humanity; subject to debate, fetal life may fall in this category. However, this relationship is radically altered by the advent of human-animal chimeras. As reflected in figure 6.2b, organisms possessing humanity are no longer necessarily a subset of organisms exhibiting biological humanness. An entirely new category of organisms is

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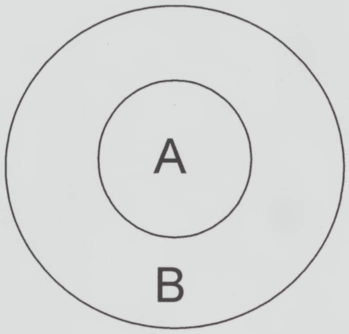
[2] For a fuller explanation, see Kant's *Groundwork for the Metaphysics of Morals*.
[3] For a fuller explanation, see Aristotle's *Nichomachean Ethics*.

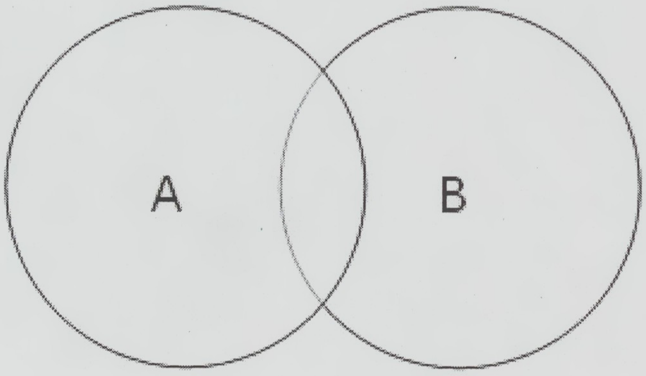
created, which may possess humanity without possessing biological humanness (represented in 6.2b by the portion of circle A that is not included in circle B).

Figure 6.2: Relationship between "Humanity" and "Humanness"

6.2a: Before Human-Animal Chimeras



6.2b: After Human-Animal Chimeras



A = "humanity"
B= "humanness"

Because the precise capabilities that define humanity remain the subject of ongoing debate, we in this manuscript take an expansive view of what these capabilities encompass.

General Principle

We now offer the following simple principle as our guide in answering ethical questions raised by the creation of human-animal chimeras: *one should treat transferred humanity with the same level of respect as inherited humanity.* That is, one should treat a *recipient* of transferred humanity with the same level of respect as a being with inherited humanity – namely, a human being. An important corollary of this principle follows: one should not do to transferred humanity what one would not do to inherited humanity. This principle seems to be an obvious consequence of our definition of "humanity," but it has been overlooked in its application to bioethics – and specifically, to the question of creating human-animal chimeras.

Drawing on our distinction between "humanness" and "humanity," we note that our principle is applicable even in cases where the recipient of transferred humanity is significantly different (in biological ways) from a human being. Even if quintessentially human capabilities are transferred from a human to a nonhuman being, the nonhuman being would still bear significant biological differences compared to the human being from whom the relevant capabilities were transferred. However, the most important implication of our principle is the following: although these resultant beings may not possess biological "humanness," they are still identical to human beings in the ways that are ethically relevant – because they possess *humanity*. The task of determining humanity-defining qualities is ethically complex and has been debated for centuries. One need not resolve the challenge of defining specific humanity-defining qualities – a question that has been debated for centuries – in order to accept the principle that one should accord a recipient of transferred humanity with the same level of respect as a human being.

What about cases in which only some characteristics of humanity but not others are transferred to a human-animal chimera?[4] These cases would seem to challenge our presumed duality between beings that possess humanity and beings that do not. Yet we need not accept this duality at all, recognizing that there is quite possibly a spectrum of organisms in between those that fully possess humanity and those that do not. In determining whether or not it is ethically acceptable to create beings that partially possess humanity, we are required to make absolute judgments about whether or not we should accord these beings with the same inviolable rights that we grant to human beings. Indeed, our understanding of this situation is not as unfamiliar as it may first seem. We are in fact deeply familiar with cases in which fully functional human beings lose some of their quintessentially human capacities to disease or physical accidents. We are also familiar with instances in which humans born with disabilities fail to ever possess these capacities.[5] Yet we grant these individuals the same fundamental rights as all other humans. The same intuition which guides one to treat these individuals as though they possess humanity should also guide one to treat human-animal chimeras possessing at least some humanity-defining qualities with the same level of respect – even though we recognize that some human and human-like beings possess these qualities to a lesser degree than others.

<u>Uncertainty</u>

The simplicity of our general principle belies the complexity of applying it to the difficult moral questions raised by the creation of human-animal chimeras. One difficulty arises from

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[4] For example: if we took rationality and capacity for language to represent the set of quintessentially human capabilities that capture the notion of "humanity," how would we apply ethical judgment to a case in which only one of these two qualities is transferred to a chimera?

[5] For example: if we take capacity for language to be at least one defining characteristic of humanity, then we can easily think of instances in which human beings lack this capacity – either due to an inherited disability or due to a handicapping accident following birth.

uncertainty: we do not know whether specific types of human-animal chimeras possess humanity. If we are certain that they possess humanity, our principle undoubtedly applies; if we are certain that they do not possess humanity, our principle does not apply. However, the main ethical challenge lies in the uncertainty about whether or not humanity is actually transferred from a human to an animal when creating a chimera.

In applying our principle to these more nuanced cases, we recall the intuition underlying our original principle: both the chimera and the human being possess certain qualities that are inviolable and worthy of intrinsic respect. Because this respect is foundational, it is necessarily wrong to violate those beings. Yet if it is wrong to violate those beings, it must also be wrong to take the risk of violating those beings. This leads us to the following conclusion: *we cannot tolerate uncertainty about violating humanity.* Scientists and ethicists must therefore examine on a case-by-case basis whether a particular chimera has some chance of possessing humanity, and if so, must refrain from creating it. We now turn to applying our general principle to the specific cases of creating embryonic and neural human-animal chimeras, both of which involve significant uncertainty about whether or not the chimera actually possesses humanity.

Chapter IV: Ethicality of Creating Human-Animal Embryonic Chimeras

Under our general principle, the creation of human-animal embryonic chimeras raises a moral contradiction. By engaging in the practice, researchers seek to accord animal embryos with human characteristics precisely in order to avoid performing those same scientific tests on human embryos. However, in according animal embryos with human qualities, researchers may endow the developing animals with precisely those qualities that create ethical problems with performing such tests on humans in the first place. If this were not the case, then there would be little or no scientific utility to engaging in the practice. Stated differently, it is the very "humanization" of the animal embryo that makes it a useful tool to study the pluripotency of human embryonic stem cells. Our ethical analysis aims to determine whether this "humanization" involves merely the transplantation of biological humanness or a more fundamental transfer of normative humanity.

One may claim that the creation of human-animal embryonic chimeras is no different than transplanting non-brain human organs into adult animals. However, an embryonic chimera is accorded with humanity in a way that a recipient of fully differentiated human organ is not. As elaborated earlier, humanity (in contrast to "humanness") is not defined by possession of a single organ or biological characteristic, but instead by possession of certain capabilities that distinguish human beings from all other creatures. These capabilities are not ordinarily acquired through possessing a single non-brain organ.[6] By contrast, the ability of human embryonic stem cells to contribute to every part of the chimera's body, *including* the brain, raises a real possibility of transferring humanity to that chimera.

One might reply that although the transplantation of human embryonic stem cells to animal embryos accords those embryos with some human qualities, these are not the same human qualities which make experimentation on human embryos morally objectionable. Perhaps the transplantation of human stem cells to an animal embryo involves a transfer of humanness but not humanity. To investigate the validity of this claim, we must first examine which human qualities create the ethical problems associated with using human embryos to study the pluripotency of human embryonic stem cells. We must then examine whether or not human-animal embryonic chimeras possess these qualities as well.

Building upon the framework offered by the philosophers cited earlier (Kant, Aristotle, Savulescu), we find that some of the salient qualities distinguishing humans from animals are the

[6] The human brain takes exception because – based on current scientific understanding – it is thought to be responsible for generating a wide range of uniquely human capabilities. For this reason, we separately consider the ethicality of creating human-animal neural chimeras in the next chapter.

capacities for reasoning, consciousness, and language. In examining the ethicality of experimenting on a developing chimeric embryo, let us engage in a thought experiment: suppose a scientist performed a whole brain transplant from a human to an animal. One would broadly agree that this animal has acquired – or at least runs a significant risk of acquiring – some of the human qualities that make exploitative experimentation on humans morally objectionable.

Yet there is no morally significant difference between the case of an animal that receives a brain transplant from a human and an embryonic chimera whose brain is partially constituted with human brain cells arising from *in vivo* differentiation of embryonic stem cells. Notably, our thought experiment would not have yielded a different result if scientists had merely transplanted three-fourths or one-half of a brain instead of a whole one: the animal recipient would still possess some human quality that would make its exploitation morally objectionable. With the knowledge that human embryonic stem cells could constitute a nontrivial portion of the chimera's brain, it is at least conceptually possible that this chimera would also come to possess some humanity-defining capacities. And our general principle demands that we do not tolerate uncertainty about violating humanity.

One might counter that human embryonic stem cells grafted into a mouse embryo may not contribute to the brain cells of the chimera, but only to other organs – so a human-animal embryonic chimera need not be considered on the same moral plane as a human brain transplant to an animal. However, a brief venture from the theoretical to the empirical level is particularly instructive here: the contribution of human embryonic stem cells to the brain of the chimera is not only an ethically risky "side effect" of creating human-animal embryos, but also one of the main aims of research on chimeras in general, as discussed in chapter II. Furthermore, the experiments which have been performed to date have demonstrated that human embryonic stem cells do indeed contribute to the brain of the adult chimera: Wichterle (2002) experimentally established the differentiation of transplanted embryonic stem cells into neurons "through a pathway recapitulating that used *in vivo*"; indeed, these neurons extended axons and formed synapses with their target organs. The essential purpose of an experiment investigating the pluripotency of human embryonic stem cells is to examine their capacity to contribute to all parts of the body. The fact that scientists' null hypothesis presumes that embryonic stem cells will contribute to the brain, taken with recent experimental observations indicating that this is the case, demands that scientists act on the assumption that human stem cells will indeed contribute to the brain.[7] Caution demands that – at least in our ethical analysis – we too assume that human embryonic stem cells will contribute to the brain.[8]

RNA Interference Technology: A Potential Solution

Our central ethical claim is that human-animal embryonic chimeras in such a way that allows them to possess humanity. This possibility is a consequence of the fact that human embryonic stem cells are thought to be pluripotent, suggesting that these cells contribute to all parts of the developing chimera, including the brain.

However, what if it were possible to transfer human stem cells to an animal embryo with the knowledge that the human cells would *not* contribute to the brain? This type of embryonic chimera would not be morally objectionable under our general principle because there would be no risk that it could possess humanity. From an ethical perspective, the hypothetical creation of this type of embryonic chimera more closely resembles the ethically benign practice of transplanting a fully differentiated non-brain human organ to an animal, and would thus be ethically unproblematic.

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[7] By "null hypothesis" we mean the following: if experiments demonstrated that human embryonic stem cells do not contribute to the brain of the adult chimera, this would contradict, not confirm, scientists' expectations.

[8] Karpowicz (2005) attempts to ethically distinguish the transplantation of "undissociated" human cells (as in the case of a whole or partial brain transplant from human to animal) and the transplantation of "dissociated" human cells. If this holds, then the creation of human-animal embryonic chimeras may be vindicated on ethical grounds. We address this claim in the next section during our discussion of neural chimeras.

Although scientists currently lack the technical sophistication required to perform such an experiment, advances in “RNA interference” technology may eventually offer a solution. RNA interference enables researchers to artificially suppress the expression of specific target genes by inhibiting messenger RNA that is transcribed from those genes. RNA interference technology bears relevance in the ethical issues surrounding human-animal embryos because it could be used to selectively suppress the expression of a chimera’s genes implicated in brain development. Researchers have already successfully used this technology to selectively suppress genes in developing mice (Wianny and Zernicka-Goetz 2000). It is reasonable to expect that researchers in the future could do the same thing when developing human-animal embryonic chimeras too, in a way that would prevent that chimera from ever possessing humanity.

This possibility is highly theoretical and perhaps even speculative. But our conjecture is nonetheless significant because it offers a potential solution to the ethical dilemmas raised by the creation of human-animal chimeras. If this possibility is eventually realized, it would represent an instance of scientific advances offering a solution to the ethical problems raised by science itself – contravening the popular viewpoint that scientific progress and ethical awareness must necessarily be in tension with one another.

Chapter V: Ethicality of Creating Human-Animal Neural Chimeras

We now argue against the creation human-animal neural chimeras on similar grounds: this practice raises an explicit risk of transferring humanity to animal recipients and thus contravenes our general principle which demands that one treat transferred humanity with the same level of respect as inherited humanity. Although the risk of transferring humanity to neural chimeras may be mitigated by a range of empirical factors – differences in brain size, cell cycle control, or cell dissociation state – the current lack of knowledge about the physiological basis for humanity-defining capacities prevents scientists from being certain that neural chimeras will not possess humanity.

The focus of ethical discussion surrounding neural chimeras has been primarily concerned with instances in which nonhuman primates (such as monkeys) come to possess human brain material (*New Scientist* 2005). However, the creation of human-primate neural chimeras should not cause us to overlook the potential ethical concerns raised by the creation of neural chimeras between humans and other species, such as mice – on which research will proceed more quickly without gaining as much public attention. Given that these experiments involve the insertion of human brain cells into a mouse, there is at least a basis for raising the following question: could the recipient mouse acquire any human brain function?

As discussed in chapter II, Stanford investigators have already created human-mouse neural chimeras in this way. Researchers generally remain skeptical of the possibility that the resultant chimera could acquire any human brain function, pointing to physiological differences between mouse and human. They claim that the mouse brain "lacks the size, organizational structure, and complexity" to exhibit human mental function (Cohen 2003). Neurobiologist Nao Kobayashi (2003) claims that the transfer of human stem cells into the mouse brain "does not imply the essence of traits such as reasoning or account for 'a man' in the mouse." Karpowicz (2005) adds that "xenografted human stem cells would not be able to achieve human brain size…needed to give rise to human neural functions and behaviors." As a result, even ethicists such as Cynthia Cohen (2003) – who express ethical concern about creating human-monkey neural chimeras – defer to the claims of scientists regarding human-mouse neural chimeras and do not offer ethical objections.

Yet we now more closely question the claims of those who readily permit the creation of human-mouse neural chimeras based on the claim that a mouse's cranium is too small to accommodate a brain exhibiting human function. While it is factually true that a mouse cranium is smaller than a human one, it does not necessarily follow that a mouse cranium is too small for a brain entirely constituted with human brain cells to exhibit human brain function. To those who claim that a human-mouse neural chimera could not exhibit human brain function, we appropriately ask the question: how is this known?

There are two conceivable ways that one could support this claim. The most reliable way would be to test it empirically – that is, by actually creating the neural chimera. However, this approach involves a significant ethical risk of exploiting the resultant chimera. The experimental aim itself acknowledges the possibility of discovering that the chimera actually possesses human brain function, thereby violating our categorical unwillingness to harbor uncertainty about the violation of humanity.

The only other way to claim that a human-mouse neural chimera will not exhibit human mental function would necessarily be *a priori* – that is, based on prior knowledge before ever performing the actual experiment. Yet contemporary understanding of neuroscience is too rudimentary to support such a claim. The range of human capacities that define humanity is in its own right the subject of debate. Further, scientists have little or no understanding of the physiological basis for even those capacities that are thought to be associated with humanity. Current scientific understanding is not nearly advanced enough to make the decisive claim that a difference in brain size between human and mouse would necessarily preclude the emergence of human brain function. Indeed, the desire to acquire a fuller understanding of the physiological basis for human capacities lies at the core of why scientists seek to create neural chimeras in the first place. Karpowicz (2005) readily admits that the "reasons why human [neural] networks differ from those of nonhuman primates are not known." It is therefore puzzling that he and other scientists assert with such certitude that a human-mouse chimera possessing a brain constituted with human brain cells would not exhibit any human mental function.

Considering these ethical difficulties associated with human-mouse neural chimeras, our concern regarding the creation of human-primate neural chimeras is necessarily heightened. The ethical difficulties associated with human-mouse neural chimeras are *scalable* to cases in which the physiological features (such as cranium size) of the recipient animal more closely resemble those of humans, as in the case of a human-primate chimera. The likelihood of a human-primate chimera fully realizing human cerebral capacities is even higher than the case of the human-mouse chimera, so our ethical considerations are necessarily more significant. Importantly, ethical concerns regarding human-primate neural chimeras are not merely hypothetical or speculative in nature. These concerns are directly applicable to the already-cited experiments performed by Ourednik (2001) involving the injection of human neural stem cells into the forebrains of developing monkeys.

Cell Dissociation State: Relevant Ethical Distinction?

Karpowicz (2005) views the injection of human neural stem cells into the brains of primates as ethically unproblematic so long as the transplanted human stem cells are "dissociated." On this basis, Karpowicz attempts to distinguish the sort of experiments performed by Ourednik (2001) from hypothetical experiments involving a whole or partial brain transplant: "It is likely that dissociation weakens the organization already present in a mass of cells prior to their transplantation and forces the human cells to reorganize themselves in response to the host environment."

Yet the distinction drawn by Karpowicz fails to absolve from ethical difficulty the practice of transferring human neural cells into the brains of animals. Two empirical examples highlight this concern. First, Polzin (1987) created an embryonic sheep-goat chimera and demonstrated that the chimera exhibited many qualities specific to the goat (the donor) but not the sheep (the recipient) – indicating that transplantation of cells had the ability to also transfer quintessential donor species characteristics to the recipient. Second, Balaban (1988) transplanted quail neural cells into the brain of a chick, and observed "the transfer of certain aspects of species-typical behavior" from the donor to the recipient, yielding a chimera resembling a chick that possessed certain quail-like brain regions.

Karpowicz dismisses these examples as dissimilar from those involving human-animal neural chimeras because they involved the transfer of a cell mass that was "undissociated." Yet neither of those two experiments contained any indication that interactions within the undissociated cell mass were responsible for the transfer of characteristics from donor to recipient. Rather, it is plausible that characteristics of the donor were transferred to the recipient simply because of the transfer of certain donor cells, irrespective of their state of dissociation. Further, it is at least conceptually possible that even "dissociated" human brain cells would *re-associate* with one another following transplantation into the host animal's brain. Neurons are indeed exceptional among cells in their disposition to uniquely associate with one another via synapses and direct intercellular signaling; one may rightly say that neurons have the "telos" (or "end") of associating with one another. Given that cell-to-cell adhesion proteins bind more favorably intraspecifically than interspecifically, one could easily hypothesize that dissociated human neural cells would associate more favorably with one another than with surrounding host brain cells. Additionally, it is possible that the transplanted human brain cells would interact with their host environment in a way that imparts human cell behavior to the surrounding host cells – in a manner that recapitulates the result of the chick-quail chimera experiments. The results of some initial experiments involving human-animal neural chimeras support this possibility. Englund (2002) transplanted human neural progenitors to a rat brain and found the human progenitors gave rise to brain cells in various parts of the rat brain, including parts of the brain into which the human cells were not originally transplanted. There was no indication that the host environment governed this migration. Likewise, Bjugstad (2005) implanted human neural stem cells into monkeys and observed not only migration of the human stem cells, but also their exertion of control over the behavior of host monkey cells in their vicinity. This finding is significant: the human donor cells affected the behavior of the brain cells in the host environment, contravening the assumption that the host environment would govern donor cell behavior – and strengthening the possibility that transferred human cells may impart human characteristics to the resultant chimera. While Karpowicz's attempt to find a concrete standard for distinguishing which types of neural chimeras are ethically acceptable is laudable, we ultimately fail to find his proposed standard compelling because the dissociation of transplanted human cells does not preclude the emergence of "humanity" in the resultant chimera.

Neural Chimeras, Mind and Vagueness

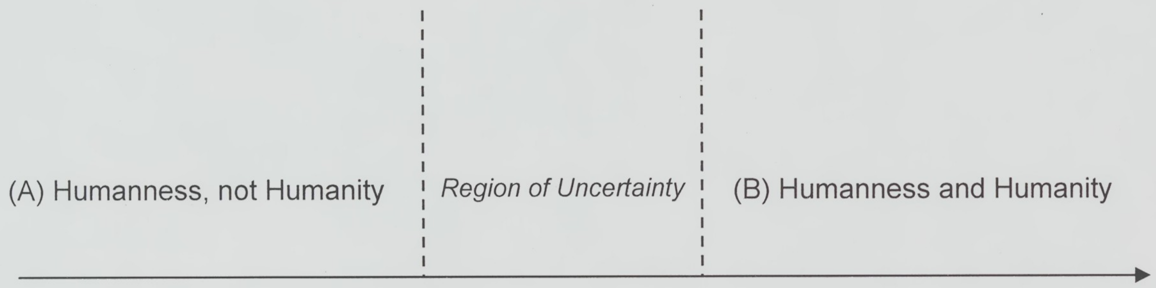
Nearly all philosophers and scientists accept a fundamental connection between the human mind and human brain function. The creation of human-animal neural chimeras thus raises a special ethical concern because it involves a risk of transferring emergent human mental capacities to an animal recipient along with the transplantation of human brain matter. Conceptually, there are at least some instances in which the creation of human-animal neural chimeras would clearly be ethically permissible in this framework – for example, the transfer of a single human neural cell to an animal brain. Although scientists have little knowledge regarding how interactions between human neurons give rise to advanced human brain function underlying humanity-defining capacities, they affirmatively know that advanced human brain function relies on interactions *among* different neurons, as opposed to merely intracellular function. While it is difficult to conceive of any scientific utility in performing this experiment, it nonetheless represents a case of creating a human-animal neural chimera that is clearly acceptable from our ethical perspective. But the central question persists: at what point does the transfer of biological "humanness" (namely, the transplanted brain cells) also constitute the transfer of normative "humanity" (namely, higher-order human mental functions)? Once identified, this is the point at which an experiment involving chimeras becomes ethically unacceptable.

Yet identifying the point at which the transfer of humanness results in the transfer of humanity seems vulnerable to a problem of vagueness known as the Sorites paradox.[9] The hypothetical transplantation of one human neuron at a time to an animal brain is analogous to the quintessential Sorites case of adding individual grains of wheat to eventually build a heap: in both cases, there exists an important but indiscernible boundary beyond which the addition of one more unit fundamentally alters the resultant creation. Between the cases of transferring a

[9] The Sorites paradox is the name given to a class of paradoxical arguments which arise as a result of the ambiguity surrounding certain empirically observed predicates. One simple example is the following: no one grain of wheat can be identified as making the difference between being a heap of wheat and not being a heap of wheat. Given then that one grain of wheat does not make a heap, it would seem to follow that two do not, thus three do not, and so on. In the end it would appear that no amount of wheat can make a heap. We are faced with a paradox since from apparently true premises we arrive at an apparently false conclusion (Hyde 2005).

single human neuron (which we deem ethically acceptable) and transplanting an entire human brain (which we deem ethically unacceptable), there exists an entire spectrum of cases in which our ethical judgment seems less clear – involving the partial transfer of human neurons, the transfer of dissociated versus undissociated cell masses, the transplantation of human neurons into animals with smaller cranium sizes, and so forth. This intuition is captured by the "region of uncertainty" depicted below in figure 8.6. The emergence of mind from brain (which we take to represent the emergence of "humanity" from "humanness") occurs somewhere in this region:

Figure 8.5: Vague Boundary: "Humanness" and "Humanity"



The earlier-cited experiments performed by Ourednik (2001), Englund (2002), and Bjugstad (2005) most certainly fall within this "region of uncertainty." In the absence of a concrete and empirically observable standard such as that presented by Karpowicz (2005), how can we distinguish the ethically acceptable cases from the unacceptable ones?

We escape this vagueness dilemma by recognizing that the hypothetical cases in which a single neuron is transferred and in which an entire human brain is transferred are qualitatively different from one another in an ethically significant way. Just because one cannot precisely identify the point at which that ethically significant change takes place does not imply that no such point exists; one's inability to discern a boundary does not preclude the existence of that boundary.[10] With the presently rudimentary understanding of the biological basis for human brain function, it is highly unlikely that ethicists will be able to arrive at any empirically grounded benchmark (such as Karpowicz's benchmark based on cell dissociation state) in deeming a general class of experiments involving neural chimeras to be ethically permissible or impermissible. Rather, we in this manuscript suggest assessing on a case-by-base basis whether there is any possibility that humanity could be transferred to the resultant chimera. In reference to figure 8.6, our unwillingness to tolerate uncertainty about violating humanity demands that we treat organisms in the "region of uncertainty" as though they fall in category B, not A – and a particular experiment is ethically permissible if and only if it passes this strict uncertainty standard. Scientists lack a sufficiently robust neurological understanding to identify the point at which a quantitative change in the number of transferred neurons give rise to qualitative shifts in the emergence of "humanity." Our strict uncertainty standard therefore militates against most experiments in the area and in favor of ethical caution.

At least until contemporary understanding of neurobiology progresses, our strict standard of permissibility most likely represents a prohibitive ethical obstacle for experiments involving human-animal neural chimeras because the range of conceptual possibilities for transferring humanity to an animal is greater when our knowledge regarding the physiological basis for humanity is sparse. That is, one can more easily *conceive* of ways in which humanity can be transferred to a chimera (in ways that stop us from experimenting on those chimeras) when less is known about the physiological basis for humanity. As a result, the less we know about the science, the more ethically cautious we must be.

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[10] For further discussion, see Williamson (1994): "Although we cannot know whether the term [knowledge] applies in a borderline case, we can know that it applies in many cases that are not borderline."

As we conclude our discussion of the ethicality of creating human-animal chimeras, we note that there exists a sharp tradeoff between scientific utility and ethical precariousness: as these experiments become more scientifically useful, they are also subject to more serious ethical objections. Taken to the extreme, the most scientifically and medically useful studies would directly experiment on the brains of other live human beings. Of course, this proposal is clearly unacceptable under contemporary ethical standards. Yet the tradeoff is no different when researchers use chimeras instead of humans. Researchers would fundamentally learn the most about human nature by creating human-animal chimeras possessing quintessentially human capabilities. Yet in so doing, these researchers also raise the likelihood of violating the normative respect that such a chimera deserves. If we accept the principle that one should not do to transferred humanity what one would not do to inherited humanity itself, then the most scientifically useful experiments are precisely the ones that should not be performed.

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