Background Submissions

1. An Argument for Transplanting Human Stem Cells into Non-Human Embryos
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2. Stem Cell Research and Interspecies Fusion: Some Philosophical Issues
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AN ARGUMENT FOR TRANSPLANTING HUMAN STEM CELLS INTO NON-HUMAN EMBRYOS

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Characteristics of Embryonic Stem Cells

The defining characteristic of an embryonic stem cell is that it is "*pluripotent*"—capable of differentiating into every cell type present within the foetus.

This unique property of embryonic stem cells has ignited aspirations that one day, embryonic stem cells will be able to ameliorate diverse human diseases. Why? Many human diseases (e.g. diabetes, deafness) are due to the deficiency of a specific cell type from the patient's body—such as the pancreatic β-cell or the inner hair cell, respectively[1]. Such diseases should be curable by restoration of normal or near-normal numbers of the missing cell type.

Given the pluripotentiality of embryonic stem cells to differentiate into any cell type within the body, one could differentiate embryonic stem cells into the "missing" cell type, and then transplant these stem cell-derived cells into the patient's body, thus renewing near-normal numbers of the missing cell and ameliorating the disease. Indeed, such an embryonic stem cell-based approach shows great therapeutic promise, as embryonic stem cells have been successfully used to ameliorate a spectrum of conditions within animal models, such as blindness, cardiac infarction, diabetes, immunodeficiency, Parkinson's Disease, and spinal cord injury[2-8].

Limitations of Human Embryonic Stem Cells

Nevertheless, our exploitation of human embryonic stem cells for clinical and scientific applications remains restrained by certain present-day limitations.

Above, we have stated that embryonic stem cells are pluripotent—capable of differentiating into any cell type. However, we note that this is only true for mouse embryonic stem cells and may not apply for human embryonic stem cells (hESCs). Thus, the question remains whether or not hESCs can indeed differentiate into any cell type that is desired by a patient or a researcher. Although hESCs have a capacity to differentiate into specific clinically-relevant cell types (such as pancreatic β-cells[9]), it remains uncertain whether or not hESCs can differentiate into all cell types within the human body. Disturbingly, certain hESC cell lines differentiate into certain lineages thousands of times more inefficiently than other hESC lines[10]. Furthermore, hESCs display gene expression patterns and molecular characteristics unbecoming of

pluripotent cells—for example, hESCs exhibit X chromosome inactivation[11], which is diagnostic of differentiated cells[12]. Such observations have elicited allegations that hESCs indeed are not entirely pluripotent[13,14] and that they may be incapable of differentiating into all human cell types; if this were to be true, this might invalidate the utility of hESCs for therapeutic and academic applications.

In contrast, mouse embryonic stem cells are unequivocally pluripotent and have been shown to be able to differentiate into every cell type present within the mouse foetus[15,16]. Within the early embryo (the "blastocyst"), pluripotent embryonic cells (known as "epiblast" cells) are responsible for constructing the entire foetus proper[17]. When mouse embryonic stem cells are transplanted into blastocyst-stage embryos, they synergize with the native epiblast cells and contribute to normal foetal development, generating many foetal cell types[18]. Thus, transplantation of embryonic stem cells to early embryos undergoing foetal development serves as a test of whether or not these embryonic stem cells are truly pluripotent and are competent to generate many different foetal lineages.

Rationale For A Physiological Test to Assess hESC Pluripotency

Thus, it is imperative to resolve whether or not hESCs are authentic pluripotent cells. Validation or invalidation of such a statement will be necessary to determine the extent of the clinical and academic utility of hESCs. Our current assessments thus far of the pluripotentiality of hESCs have largely been restricted to: (1) trying to differentiate hESCs into specific lineages of interest and seeing whether or not it is possible for hESCs to differentiate into that lineage or (2) subjecting hESCs to conditions that favour promiscuous differentiation into multiple lineages simultaneously, thus allowing for the assessment of whether or not hESCs can differentiate into those lineages. However, as one could imagine, such *in vitro* approaches are unsatisfactory in determining the pluripotency of hESCs, for the following reason: *in vitro* differentiation of hESCs is an imperfect recreation of *in vivo* differentiation of human epiblast cells during foetal development. hESCs differentiated *in vitro* are not subject to the complex organisation of cells in a developing embryo and all *in vitro* culture methods essentially are differentiation and embryonic development progressing under an unnatural environment[19,20]. Therefore what we can learn from *in vitro* hESC differentiation is limited and may even be misleading.

Ultimately, we conclude that verification of the pluripotentiality of hESCs to differentiate into every human cell type can only be attained through testing whether or not hESCs can contribute to foetal development within the early embryo[21]. Here, we argue for the development of an assay whereby hESCs are transplanted into non-human embryos to determine the capacity of hESCs to respond to developmental signals and to differentiate into the entire repertoire of cells present within the body. The resultant embryos would be "chimeras" —embryos comprised of human cells generated from the hESCs as well as non-human cells from the host embryo.

Background to Chimerism

The word chimera means different things in different disciplines:

1. Molecular biologist: Chimeric DNA sequences (genetic material) from 2 sources (i.e. cells from 2 individuals) are combined into one.

2. Cell biologist: Somatic nuclear transfer into oocyte cytoplasm, intra-species or inter-species (i.e. transferring a nucleus from a body cell into an egg, replacing the egg nucleus; the egg can be from the same or a different species).

3. Embryologist: Prenatal combinations of cells with zygotes (fertilized eggs) or early embryos, intra-species or inter-species.

4. Stem cell biologist: Grafting tissue into a prenatal host of a different species (a xenograft).

In this paper, "chimerism" refers to the embryos resultant after the transplantation of hESCs into early non-human embryos—such embryos would be comprised of both human and non-human cells.

Why Studies With Such Chimeras Are Useful

We reify again the decisive benefits that can be attained by transplanting hESCs into non-human embryos—

1. *In vivo* experiments (literally, 'in life'; experiments with live organisms) are more physiological and yield more accurate data than *in vitro* studies (literally 'in glass'; experiments with artificially maintained tissues). *In vitro* studies with hESCs are an unsatisfactory surrogate for *in vivo* studies[19-21].

2. hESCs cannot be proven to be authentic pluripotent cells without testing whether or not they can contribute to foetal development[21].

3. To regenerate human tissue for cell replacement therapies, we first need proof of human cell contribution in corresponding animal models.

4. Examination of how hESCs differentiate into the early embryonic lineages within the nascent foetus is key to understanding how we can control hESC differentiation *in vitro*. Present attempts to recreate developmental differentiation signals *in vitro* to control hESC differentiation thus far have been largely unsatisfactory[19,20] and the resultant cells may be aberrant and partially non-functional[2,9,22].

We highlight a recent landmark publication wherein rat pluripotent stem cells (the rat equivalent of hESCs) were transplanted into mouse embryos that were unable to

generate a pancreas (due to a genetic mutation; *Pdx1*$^{-/-}$)[23]. The transplanted rat stem cells were capable of developing into an entire pancreas within the resultant mice, generating rat-mouse chimeras which were mostly mouse but had entirely rat-derived pancreata[23]. Such a striking example of chimerism unequivocally demonstrated the competence of rat pluripotent stem cells to generate an entire pancreas—repetition of this experiment utilising hESCs (but pausing it at an earlier developmental stage) could test whether or not hESCs are capable of generating other tissues of therapeutic interest. Such a demonstration would be an *avant garde* advance in the utilisation of hESCs for cell replacement therapies.

Human-Animal Chimera Experiments

Many studies involving the transplant of human cells (besides hESCs) have demonstrated the utility of inter-species chimeras to illuminate the developmental potential and curative value of various human cell populations:

1. Human hematopoietic stem cells (stem cells that are precursors to the different kinds of blood cells, HSCs) transplanted into mice have been used to detect pluripotent stem cells.[i]

2. Human skin grafts in xenografted mice are useful for studying skin disease.[ii]

3. Human mesenchymal stem cells injected into rat embryos have been shown to give rise to organ tissue.[iii] Mesenchymal stem cells are usually bone marrow stem cells.

4. hESCs injected into chick embryos showed that they can proliferate and contribute to neural cells.[iv]

5. hESCs injected into foetal mouse brains showed that they can generate functional human neurons within the adult mouse brain.[v]

6. Transplants of human retinal stem cells into the eye and brain of foetal animals can address questions such as:

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[i] Guenechea G. et al. Distinct classes of human stem cells that differ in proliferative and self-renewal potential. *Nature Immunology* **2**(1), 75-82 (2001).

[ii] Raychaudhuri S.P. et al. Severe combined immunodeficiency mouse-human skin chimeras: a unique animal model for the study of psoriasis and cutaneous inflammation. *British Journal of Dermatology* **144**, 931-9 (2001).

[iii] Yokoo T. and Kawamura T. Ex vivo regeneration of the murine kidney from human mesenchymal stem cells. *Kidney International* **68**, 1967 (2005).

[iv] Goldstein R.A. et al. Integration and differentiation of human embryonic stem cells transplanted to the chick embryo. Developmental Dynamics **225**, 80-6 (2002).

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i) Can human stem cells integrate into a developing eye?

ii) What is the potential of adult stem cells to form tumours in an immune suppressed environment?

iii) Can human retinal stem cells form non-retinal tissues in a mammalian host?

7. Transplantation of hESC-derived β-cells into diabetic mouse models has demonstrated that such β-cells are capable of ameliorating hypoglycemia within diabetic organisms, and thus, they are likely to ameliorate diabetes within human patients[2].

Proof-of-Principle For hESC Transplantation Into Mouse Blastocysts

Most recently, experiments have been performed using hESCs transplanted into mouse blastocysts[24].

What were the important findings?

1. hESCs injected into mouse blastocysts multiply, intermingle and differentiate along with host cells.

2. hESCs tended to gravitate to the inner cell mass of the blastocysts (the physiological residence of pluripotent stem cells such as hESCs and their murine counterparts).

3. hESCs persisted in a few embryos that were transiently implanted into mice.

This study demonstrated the feasibility of human-animal chimera experiments with hESCs. This approach can be extended to using large collections of variant mice as hosts. Genetically modified or diseased hESCs can also be used in these experiments. This will then allow us to better understand the developmental capacity and pluripotentiality of hESCs and assess the capacity of hESCs to differentiate into clinically-relevant cell types suitable for cell replacement therapies for human patients.

Degree of Chimerism

A major concern about chimeric studies relates to the generation of chimeric animals that might have a high proportion of human cells that could confer them with human behaviours or characteristics.

This is largely restricted to the direct or indirect introduction of human neurons into animals, which might "humanise" them and potentially attribute them with self-awareness or other human cognitive properties. However, the transplantation of even large numbers of human neurons into non-human brains is unlikely to impart any degree of human consciousness[25]. It should also be noted that given the radically different gestational times of mice and humans (a mouse foetus' uterine development

time is one-fifteenth of a human foetus')[25], so it is extraordinarily unlikely that any kind of advanced human tissue could form from the transplanted hESCs.
This is substantiated by findings over decades of chimera research that chimeras between distantly related species have been found to be often nonviable and developmentally compromised. Although chimeras between related mouse strains (*Mus musculus* and *Mus caroli*) are viable[26], as are sheep-goat chimeras[27,28] and rat-mouse chimeras[23,29], it has been shown that mouse-vole chimeras and other chimeras of distant species are nonviable and rarely progress to an advanced stage *in utero*. Such studies strongly suggest that chimeras resultant from hESC transplantation into mouse blastocysts would be nonviable, thus abrogating most ethical concerns about developing an advanced being with contributions from both human and mouse cells. This assertion was affirmed by a recent study with hESC-mouse chimeras[12], where the majority of embryonic chimeras that implanted successfully and retained hESC-derived cells were developmentally abnormal and delayed—indeed, it appears that hESCs rarely persisted in embryos of normal form. Thus, it indeed appears therefore that rare mouse-human chimeras can be generated in which hESCs have limited contributions; nevertheless, such mouse-human chimeras are likely to be developmentally compromised and unable to fully develop.

Guidelines For Human-Animal Chimeric Studies

Two questions that would be important to address as part of the consideration to set guidelines for human-animal chimeric studies are:

1. The extent to which human cells can contribute to viable mouse–human chimera

2. The extent to which progression to later developmental stage can be followed

The intent of our studies is not to confer human attributes upon an animal. Rather, it is to assess the developmental potential of hESCs and potentially other human stem cell populations, thus testing whether or not these stem cells can make limited contributions to foetal development. Installation of appropriate safeguards is necessary to ensure limited total contribution of human cells to the chimera, to ensure limited specific contribution of human cells to the nervous system, and to ensure that human-animal chimeras do not become too advanced and progress beyond a developmental stage.

To this end, we suggest adoption of the following guidelines:

1. Distinguishing between human cells and animal cells within the nascent chimera. The transplanted hESCs can be labelled (with a fluorescent marker) such that they and all their progeny within the chimera are easily identifiable at all times[24]. Such a system will allow for determination of the extent of human cell contribution to the chimera and for determination of the chimeric tissues in which there are human cells.

2. Limiting the number of human cells transferred. Fewer human cells transplanted into the animal blastocysts would reduce the degree of human cell contribution since host cells will outnumber and overwhelm the human cells, thus minimising the risk of "humanising" non-human embryos. Previously, it has been demonstrated that the approximate number of donor cells transplanted into the host blastocyst determines the amount of contribution that the donor cells will have to the resultant chimera[27,28].

3. Choice of host animal for experiments involving early animal embryos. Experiments with hESCs on early animal embryos should only use evolutionarily distant animals such as mice that will likely yield nonviable embryos that will not develop to an advanced stage.

Conclusion

Human embryonic stem cells have significant therapeutic potential, and have already been used to ameliorate diseases, such as diabetes and spinal cord injury, within animal models[2,5]. Nevertheless, the extent of their therapeutic utility is dependent on the resolution of the extent of their pluripotency. Formal proof of the capacity of hESCs to differentiate into any cell type that a patient might require is still lacking, and indeed, there have been multiple allegations that hESCs indeed may not be pluripotent or may represent a "corrupted" cell type with minimal clinical or research relevance[14]. The complete exploitation of hESCs for therapeutic or research purposes will require determination of whether or not hESCs are authentically pluripotent—such a demonstration can only be made by testing whether or not hESCs can contribute differentiated progeny to foetal development[21]. To this end, here we propose the creation of limited animal-hESC chimeras wherein small numbers of hESCs are transplanted into non-human blastocysts to assess whether or not hESCs can respond to developmental signals and differentiate into therapeutically-relevant cell types. Preliminary tests performed elsewhere have shown that hESCs and their progeny often persist minimally within the mouse conceptus[24], suggesting that few human cells will ultimately remain within the chimera, thus reducing the chance of "humanisation" of the chimera.

We conclude that development of the proposed animal-hESC chimeras will extend the reach of regenerative medicine and stem cell research by validating or invalidating the pluripotency of hESCs, and such assays are unlikely to generate animal chimeras with human characteristics.

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STEM CELL RESEARCH AND INTERSPECIES FUSION: SOME PHILOSOPHICAL ISSUES

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In 1988, Harvard scientists patented the "OncoMouse" after successfully transferring a human cancer gene into a mouse. Since then, human neural stem cells have been transferred into the fetal brains of monkeys, chick embryos, fetal sheep, mouse brains and so on.[1] These are examples of biological research that creates, or is capable of creating, interspecies transgenics, chimeras, hybrids and xenografts. The aim of this paper is to discuss the main ethical issues arising from this kind of research.

1. What and Why

As the examples above show, it is now possible to transplant genetic or cellular material of one organism into another. If the host is prenatal, what results is a chimera. Chimeras can be intraspecies (when the organisms are of the same species) or interspecies (when the organisms are of different species). An interspecies chimera can be a combination of DNA sequences from different species, or a mixture of cells from different species (through somatic cell nuclear transfers), or a combination of cells from zygotes of different species. The term "transgenics" is sometimes used to refer to the results of gene transfer to distinguish them from chimeras. Chimeras are usually distinguished from hybrids (such as mules, "ligers," "geep," and hybridized plants) and xenografts (the products of grafting tissues from one species onto postnatal hosts of another species). Hybridization and xenografting occur naturally but also have been going on experimentally for some time. However, chimera research has only just begun, spurred on by advances in stem cell research. Most recent chimera research efforts involve transplanting human stem cells into prenatal nonhuman animals. The chimeras that result from these efforts allow scientists to study the development of certain human cells, such as bone-marrow stem cells, without involving human embryos or human patients. Stem cells, like drugs, need to be tested on nonhuman subjects first. In the case of many stem cells, tests can be done *in vitro*, but the results will be more accurate if their development can be observed in living animals. In the case of some stem cells, their development can take place and be observed only *in vivo*. This does not mean that chimeras must be used, as certain tests can be conducted on postnatal animals by xenografting. However, certain stem cells can only be successfully assayed in prenatal hosts. So far at least, scientists have been able to study human retinal stem cells only by transplanting them into preanatomic hosts such as embryonic mouse blastocysts, or postanatomic hosts such as the eyes and brains of

fetal monkeys. Other attempts at transplanting stem cells into postnatal hosts have only produced tumours.

2. The Issues

2.1 Health and Safety Risks

There are risks involved in the creation of chimeras. The crossing of species boundaries may allow diseases to transfer between humans and nonhumans. Zoonosis may be a big problem given threats such as avian influenza. Dangerous new strains of viruses and bacteria may pose new health and safety risks. (In 2001, Imperial College, London, was found guilty of breaching health and safety rules in a study that involved the creation of a chimera of the hepatitis C and dengue fever viruses.) In the longer terms, there is the risk of creating uncontrollable chimeric monsters.

2.2 Against Nature-Playing God

A cluster of issues comes under this heading. One is that a chimera is a life form artificially created and any such creation may be wrong, as it may be thought that the creation of life should be left to God or nature. Another is that, left alone, human and nonhuman tissues have their own, natural, ways of developing, which will be frustrated when they are merged together in chimeras. Also, it is often said that each species has it own natural integrity (and some say, dignity as well), and it is wrong to destroy it through chimera research.

2.3 The Repugnance Argument or the "Yuk" Factor

Some people find the idea of crossing species repugnant (although probably the majority have in mind hybrids and xenografts rather than chimeras). In the context of bioethics, the term "repugnance" was first used by Leon Kass against cloning.[2] He claims that there is "wisdom in repugnance" and if people find cloning repugnant then it is likely to be wrong. Many critics of stem cell research contend that Kass' claim applies especially to chimeras (as well as hybrids and xenografts).

2.4 The Imago Dei Argument

Related to the repugnance argument is the argument that since humans are created in (the Christian) God's image, any tempering with the human form is a tampering and an offence to God's image. One reason for the offence is that since animals are lower in the chain of being, to mix animal tissues with human tissues is to degrade the human form. John Paul II uses the term "original solitude" to describe the uniqueness and superiority of humans vis-à-vis the rest of nature.[3] Chimera research disturbs our "original solitude."

2.5 Moral and Social Confusion

Current social institutions and practices are based on long established and fairly entrenched views about humans and animals, and demarcation lines between the two groups. Chimeras can blur the demarcation lines and thus cause confusion. There will be new rights and obligations but it will be difficult to recognize them. Questions that may be asked include: What will happen to our meat-eating practice in a world in which many animals have human tissues in them? How are we to treat, say, monkeys that have human blood running through their veins?

2.6 Identity Problem and the Moral Status of Chimeras

The issues in 2.5 above are grounded in more deep-seated issues about the identity and the moral status of chimeras. On the assumption that the moral status of something can only be determined if we know what kind of a thing it is, i.e. its identity, we need to settle questions such as: What kind of a thing is a human-animal chimera? Is it human or nonhuman? When is a chimera human enough for certain moral standards to apply (such as being respected, not being used solely as a means to an end, etc.)? In particular, some people find the prospect of transferring cognitive capacities to nonhumans alarming.

The above are the main ethical issues arising from chimera research. There are other issues, such as the use of animals in research generally, the use and destruction of human embryos and so on, which are ignored in this paper either because they are no longer controversial, or because the ethical safeguards are well enough established, or because they relate to a larger research context and should be discussed in such context.

3. Discussion

Issue 2.1

The issue of health and safety risks can be addressed from the utilitarian point of view, which focuses on consequences. From this point of view, whether something ought to be permitted depends on the balance of benefits over harms. Whether the health and safety risks of doing something constitute an ethical barrier depends on what we stand to lose without doing it. Looking at the harms, or risks of harms, alone is not sufficient. The taking of any kind of drug has risks and the sensible thing to do is to weigh the risks against the benefits. It would be irresponsible, and perhaps morally wrong, not to immunize one’s children against deadly childhood diseases on the grounds that the vaccines are not risk-free. If chimera research promises to do no better than curing skin acnes then perhaps it is not worth the risks (not to mention the financial costs). What benefits can we expect from chimera research is largely a scientific question. The evidence so far indicates that the benefits are likely to be substantial, more than enough to justify the known risks. Naturally, there is an ethical responsibility on the part of scientists to discover as much as possible about health and safety risks and to minimize

them (just as there is an ethical – as well as legal – responsibility to produce safer vaccines and other drugs). The greater the threat of harm, the greater care scientists will have to exercise in conducting research. The threat can be estimated by estimating the actual harm and the probability of it occurring, and taking the product of the two. The harm of chimeric monsters being unleashed may be great, but the probability of this occurring is low enough for the threat to be regarded as minimal. One worrying kind of "monster" is a nonhuman animal with human cognitive functions. However, there is little likelihood of one being created if only dissociated human neural cells are used, and none if nonneural cells, such as human retinal stem cells, are used. Indeed, as long as the number of cells transferred is small enough, the host will retain its own characteristics. Even if the number is large, the anatomical constraints of the host are such that the development of human characteristics is unlikely. Still, in general, it is wise for the society to work with the scientific community to keep the probability of great harms occurring as low as possible through stringent rules regulating the number and kind of human cells transferred and the selection of host animals.

Issue 2.2

The "Playing-God" objection applies to a whole range of biomedical issues, ranging from IVF to gene therapy. In nonreligious terms, the claim is that anything "unnatural" is wrong. A number of things can be said about this claim. One is that nothing can be unnatural in the sense of going against the laws of nature. Scientific experiments, like everything else, must conform to the laws of nature. If "unnatural" is taken in this sense then there is no objection. If on the other hand by "unnatural" is meant "not how things turn out in nature" then the objection can be reduced to an absurdity, namely we should not take any medication for any illness (as this is not how a body heals itself in nature). Another point to make is that it is at least problematic to translate from what is the case to what ought to be the case. Whether something is right or wrong ethically must be based on ethical considerations (which, to be sure, have to be factually informed), rather than purely factual considerations.

In the case of chimera research, the objection is that scientists should not be playing God in harming species integrity and dignity and in creating new life forms. Species integrity and dignity will be discussed below, in relation to Issue 2.6. As for creating new life forms and other ways of "playing God," a number of things can be said:

- To some extent, this objection amounts to a misunderstanding of what scientists do. They do not create life as such; they just "rearrange" the ways life manifests itself. If this is also considered wrong then the reductio ad absurdum point above applies: many standard medical procedures are just "rearranging" how life manifests itself, typically from a diseased state to a healthy state and it is absurd to suggest that such medical intervention is wrong.

- How do we know what God's plans are when it comes to scientific knowledge and practice? Is it not possible that stem cell research is part of those plans?

- The "playing God" argument cuts both ways. In the euthanasia debate, many opponents of euthanasia claim that doctors should not be playing God in deciding who should die and when. If this claim is sound and if chimera research can save life then to stop it is to play God with respect to those whose lives can be saved.
- At least one scientist has claimed that Judaism permits us to "play God" as long as we play according to His rules.4 Indeed, we are encouraged to "play God" if "playing God" means to heal and to provide effective medical relief. What is forbidden in Judaism is stem cell research, or any kind of research, conducted for eugenic purposes: this would be playing against His rules.

Making the points above does not mean that the religious aspect of the "playing God" argument can simply be ignored. The underlying religious convictions may still be sincerely and strongly held, and a society, particularly a multi-religious one, has the responsibility to engage all of its members in a dialogue to ensure that good science can be done without violating anyone's fundamental rights, or offending anyone's dignity or religious sensibility.

Issue 2.3

Concerning the repugnance argument or the "yuk" factor, the obvious point to make is that repugnance is an emotional response. What role it plays in moral judgments is not clear. It may be argued that it should play no role at all. Leon Kass admits that the "repugnance argument" is not really an argument in the logical sense, but insists that repugnance cannot be ignored because there is "wisdom" in it. It is not clear what this claim amounts to. One possibility is that we are made by nature to feel repugnant against something so as to avoid it for our own good. For instance, we find that incest is repugnant and it turns out that there are good reasons to say that it is a bad thing and should be avoided. However, the case of incest shows that we should not object to something just because it is a taboo but because there are good reasons to say that it is a bad thing. On this interpretation, all that the "repugnance argument" shows is that we should find out whether there really are good reasons for objecting to chimera research other than the feeling of repugnance. Kass does not offer any. Repugnance is at best a symptom of what is wrong and there is no substitute for a proper diagnosis of what is wrong. Incidentally, while anthropologists have found that incest is near enough to being universally repugnant, a taboo in nearly all cultures, the idea of a biological chimera is not so. Repugnance against chimeras, if any, is not even a reliable symptom of something wrong. Kass is right in insisting that we should not become "souls that have forgotten how to shudder," but having shuddered, we should take a close look at what we are shuddering at before taking a swipe at it: it could well be a harmless crawling insect on the back or worse still a prized specimen!

Another way of cashing out Kass' "repugnance argument" is to put it in terms of Midgley's argument about emotions.[5] She claims that feelings and reasons are complementary: judgments of right and wrong are accompanied by feelings of approval and disapproval (and in the case of a serious wrong, a strong feeling such as

disgust, or repugnance). She concludes that strong emotional reaction should be taken seriously, for there may be good reasons for it, and even if there are no obvious good reasons, it should still be respected rather than summarily dismissed as "emotional." However, once again, all that the argument establishes is that we need to find out whether there are good reasons for reacting negatively to something and that, even if no good reasons are found, we should still respect the negative reaction. The practical question now is how to show respect for the negative reaction when there are no good reasons for it. Clearly, it is unreasonable to suggest that an activity should be stopped just because some people strongly object to it (without being able to offer good reasons for the objection). After all, many people did, and some still do, strongly object to interracial relations, kissing or holding hands in public and so on. Still, it may be said that just because a large number of people feel that something is repugnant, it is at least morally problematic. The problem is how to deal ethically with members of the community who react negatively to certain things for no apparent good reasons. There may be social and ethical costs to bear in allowing something like chimera research. The costs can be minimized through public dialogues, consultations and discussions. Whatever costs that remain, bearing in mind that not all people can be pleased all the times, will have to be weighed against the expected benefits. On available evidence, the benefits of chimera research seem substantial enough to absorb the ethical costs of going against the preferences of those who object on non-rational grounds, particularly if it can be ensured that such research does not violate anyone's fundamental rights.

Issue 2.4

In nonreligious terms, the "Imago Dei" argument inveighs against crossing species boundaries, typically on the grounds of preserving the dignity and integrity of the human species. This aspect of the argument will be discussed later in relation to Issue 2.6. In religious terms, the objection is directed at the crossing into the human form, which is regarded as holy insofar as it is the image of God. The point to notice straightaway is that this objection is rooted in the Judeo-Christian tradition (which does not mean that all followers of this tradition raise it). Other religious traditions do not seem to give rise to the same objection. Indeed, in some religions, the worshipped images often combine human and animal features, such as a human body with an elephant head. The "Monkey God," it seems, is human, monkey and God rolled into one.

Another point to make is that the argument does not make a distinction between the human form and tokens, or manifestations of that form. Chimera research does not alter and is not aimed at altering the human form as such even though it may alter the form of some token humans. Indeed, it may be said that chimera research aims at preserving the human form against diseases that threaten that form. Failing to make this distinction could well be an offense to all those humans unfortunate enough not to con*form* to the human form for whatever reason (does an amputee offend Imago Dei?). There is a danger of altering the human form if the human germline is systematically affected by chimera research but the risk of this is low. Naturally, there is a responsibility to keep it low. Also, a society has the responsibility to engage those

members of the society who take the Imago Dei argument seriously, through public dialogues, consultations and discussions.

Issue 2.5

In general, just because something causes confusion, it does not follow that it is a bad thing or that it should not be permitted. The emancipation of black slaves caused a great deal of economic and social confusion for the United States, but that is not a reason to say that it should not have happened. Many people complain that the women's liberation movement has caused a great deal of social confusion, but this not a reason not to emancipate women. When fundamental rights are concerned, the costs in terms of moral and social confusion may have to be born. It may be argued that those whose lives would be better off as a result of chimera research has a right to its benefits that may outweigh the costs in terms of moral and social confusion. However, the issue is more likely to be settled on the basis of the likelihood and the extent of social and moral confusion. It will be at least a concern if the confusion is so great as to outweigh any benefits to be had, but there is no evidence to show that this is the case with chimera research. We are already familiar with images of human-animal mixtures, in various religions, in folklores, in story books, in films and art works and so on. Many of us growing up with Sesame Street stories of Miss Piggy do not seem to have any trouble with eating pork. To be sure, we may think differently if some pigs do act like Miss Piggy, but the evidence so far indicates that they will fly before they do so. It is of course possible that those who raise this objection have in mind a confusion at a deeper level, having to do with the integrity and dignity of species, which would be threatened if species boundaries are breached. The thought is that there would be a moral confusion as the established moral order based on existing species boundaries would no longer apply. This aspect of the objection will be discussed below.

Issue 2.6

Many different ethical concerns arise from the fear that stem cell research, in creating interspecies organisms, will undermine the boundaries that now separate the species. As pointed out above, in one aspect, the "playing God" argument says that crossing species boundaries will harm the integrity and dignity of species. Another concern is that blurring the species boundaries will cause moral confusion insofar as there is an established moral order based on the hierarchy of species. Many writers have dismissed both concerns, arguing that they are based on a mistake, namely that there are rigidly fixed species boundaries.[6] They point out that biologists themselves do not believe in them: "The biological categorization of species is empirical and pragmatic," which means that "species categories are never real, ontological entities or natural kinds."[7] Indeed, there are many different concepts of species.[8] However, dismissing the idea of fixed species boundaries goes some way toward addressing the first concern, but does not settle the moral issue underlying the second, which can simply be shifted to the talk about kinds of things that we are perfectly familiar with. In our ordinary conceptual scheme, there is such a thing as the human kind, members of which we can easily identify and pick out, and distinguish from members of other

kinds. Mapped onto this conceptual scheme is a moral hierarchy of kinds on which the human kind occupies the top rung and the other kinds occupy the lower rungs according to how close they are to us in terms of anatomical and psychological development. For instance, we typically regard killing an insect not as serious as killing a cat, which in turn is not as serious as killing a monkey, a chimpanzee and a human being, in that order. The complaint against stem cell research is really based on this ordinary conceptual and moral framework.

There are two types of complaint. One is that chimeras, hybrids and so on invalidate our conceptual scheme concerning kinds and as a result causes moral confusion. Differently put, they will provide a metaphysical test that our conceptual scheme could well fail. We may no longer be sure about what we have taken to be the criteria for being a member of a certain kind. This type of complaint can be fairly easily dismissed. The introduction of interspecies entities, such as the "OncoMouse," does not lead to the elimination of kinds of beings as we know them anymore than the creation of "ligers" and "geep" leads to the elimination of lions and tigers and goat and sheep. Our ordinary conceptual scheme still applies to ordinary human beings and ordinary lions, tigers, goat and sheep. To be sure, the new entities could overwhelm the existing ones in a battle for survival. However, the likelihood of this occurring is so remote as to constitute no threat at all. Even if it ever came to pass, there would be no moral issue, as there would no longer be the human kind as we know it, for which it is a moral issue. What is not so remote is that there would be more and more entities that do not fit in any existing kind. However, conceptually, if we could cope with mules as a kind, there is no reason why we cannot cope with ligers and geep, or for that matter, onco-mice or humice, as new kinds of entities. That leads to the second type of worry, namely how we are to treat the individual new entities, or what moral status they possess.

To facilitate the discussion, it is useful to distinguish three possible varieties of chimeras and hybrids: (1) Those that can be said to belong to different kinds, that is, wholly of kind X *and* wholly of kind Y (and Z …), (2) Those that are wholly of one kind only but possess features of another kind and (3) Those that do not belong to any existing kind, neither fish nor fowl. It may be thought that (1) is logically impossible. However, DiSilvestro has argued that it is logically possible for one entity to be wholly of one kind and wholly of another kind.[9] He cites a theological view of the doctrine of Incarnation on which the entity Jesus is wholly human and wholly God. DiSilvestro then suggests what he calls the "Maximum Respect Principle" to determine the moral status of any such entity: it has the status of the kind that deserves the most respect. Thus, since God has a greater status than humans, the human Jesus who is also God deserves the moral status of God, which includes our worshipping Him. If this suggestion is right then any entity that is both wholly human and wholly animal has the higher moral status of a human, insofar as humans are ranked higher than animals on the moral scale. The only alternative to the Maximum Respect Principle is one that calls for recognizing the minimum status (the Minimum Respect Principle), or somehow adding the two (the Additive Principle), or subtracting the lower from the higher (the Substractive Principle), or averaging the two (the Averaging Principle).

None of the latter would work in the case of Jesus who cannot be respected just as a human being (as required by the Minimum Principle), or as more or less than God (as required by any of the other three principles). It looks like we have a reasonable principle to settle the question of the moral status of interspecies entities.

As it turns out, the ethical issue is much simpler than DiSilvestro has envisaged. This is so because even if he is right in his claim that (1) is logically possible, there is no evidence to suggest that it is biologically possible. Biological properties characteristic of a biological kind tend to preclude the development of biological properties characteristic of another kind. For instance, it has been pointed out that it is "highly unlikely that even a monkey chimera whose entire thalamocortical system was human-derived could possess human consciousness, as its neurons would lie in anatomically different networks."[10] This means that even if we take the capacity for human consciousness as sufficient for being a member of the human kind, it is still "highly unlikely" that there can be an entity that is wholly human and wholly simian or wholly something else. Stem cell research is likely to lead to entities of type (2) or (3). A type (2) entity is wholly of one kind but possesses characteristics of another kind. A monkey with human blood flowing through its vein remains wholly monkey, and only monkey, even though it is not an ordinary monkey. Likewise, a human being with a baboon heart remains wholly human, and only human, even though he or she is not an ordinary human. As such, the question of moral status does not arise: the monkey with human blood has the moral status of a monkey, no more and no less, and Baby Fae, had she survived and grown up with the baboon heart beating in her chest, would have retained the moral status of a human being, no more and no less. Entities of type (3) are somewhat more troublesome but still, as a minimum, we can say that if something is neither human nor simian then it does not have the status of a human being nor that of a monkey. What it has depends on our decision concerning where we would fit that kind of entities in our existing moral order. There is little problem if the new animal comes from different kinds of animals of the same moral status. (Thus, insofar as the goat and the sheep have the same moral status, the hybrid geep takes on that same moral status.) As for other entities, decisions need to be made. We might decide to place the "humouse" kind higher than the mouse kind, in which case we would give a "humouse" a greater moral status than we would a mouse. However, it will be a very long time, if ever, before there are enough entities of this type for us to have to start thinking of new kinds and their moral status, particularly if they remain laboratory specimens rather than proliferating as naturally living entities.

4. Conclusion

The ethical concerns about stem cell research are extensive and not unreasonable. It has major implications for our fundamental values, beliefs and practices. However, there does not seem to be any ethical barrier against it. Nevertheless, there is a continuing need for public dialogues and debates in order to gain as much consensus and support for the new science as possible. Ethical and other safeguards should also be in place to ensure public trust. There is little doubt that the health benefits will be substantial. But perhaps the greatest benefit is not something related to human health

and welfare. It has to do with the way we think of ourselves. Human-animal chimeras will confirm once and for all our continuity with the rest of nature, or as Barash puts it, our "glorious connection with the rest of life."[11]

NOTES

1. See *Science*, Vol.293 (2001), pp.1820-1824, *Developmental Dynamics*, Vol.225 (2002), pp.80-86, *British Journal of Haematology*, Vol.130 (2005), pp.276-283, and *Proceedings of the National Academy of Sciences*, Vol.102 (2005), pp.18644-18648.

2. Leon R. Kass, "The Wisdom of Repugnance," in Leon R. Kass and James Q. Wilson, *The Ethics of Human Cloning* (Washington D.C.: AEI Press, 1998), pp.3-59.

3. John Paul II, *Theology of the Body: Human Love in the Divine Plan* (Boston: Pauline Books and Media, 1979).

4. Yoel Jakobovits, "Judaism and Stem Cell Research," *Jewish Action*, Vol.62 (No.4, Summer 2002).

5. Mary Midgley, "Biotechnology and Monstrosity: Why Should We Pay Attention to the 'Yuk Factor'," *Hastings Center Report*, Vol.30 (2000), pp. 7-15.

6. Françoise Baylis and Jason Scott Robert, "Primer on Ethics and Crossing Species Boundaries," *http://www.actionbioscience.org/biotech/baylis_robert.html*, May 2006.

7. Phillip Karpowicz, Cynthia B. Cohen and Derek van der Kooy, "It Is Ethical to Transplant Hman Stem Cells into Nonhuman Embryos," *Nature Medicine*, Vol.10 (No.4, 2004), pp.331-335, at p.333.

8. R. Mayden, "A Hierarchy of Species Concepts: The Denouement in the Saga of the Species Problem," in M. Claridge, H. Dawah and M. Wilson (eds.), *Species: The Units of Biodiversity* (London: Chapman and Hall, 1997), pp.381-424.

9. Russell DiSilvestro, "A Neglected Solution to the Problem of the Metaphysical and Moral Status of the Human-Animal Chimera," *Ethics and Medicine*, Vol.20 (No.2, 2004).

10. Karpowicz et.al, *op.cit.*, p.334.

11. David P. Barash, "Humans Don't Stand Outside Nature," *Commentary, Seattle Post Intelligencer*, Wednesday, May 25, 2005.