Governing future science: human/animal chimeras and bioethical ambition

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Introduction

When biologist Irving Weissman dreamt up the idea of creating a 'human neuron mouse' – a mouse in which the brain neurons were replace with human neural stem cells – he turned to his colleague at Stanford University, Henry Greely, a lawyer and bioethicist, for advice on whether such an experiment should proceed. Although the experiment remains undone, Greely and the panel he convened concluded that the research 'could be performed ethically, subject to some guidelines' (Greely et al., 2007: 27). That bioethical input on this 'thought experiment' was asked for, and given, before the research actually took place is suggestive of a new phase in the burgeoning relationship between bioethics and science, manifest though the proactive anticipation of the potential governance issues emerging from new scientific developments.

In this paper, we use the production of animals containing human biological material in bioscience research as a case study to examine the new role that bioethics may be taking in the governance of this emerging field. Of itself, the demand for the 'co-production' of new forms of governance in parallel to novel forms of scientific research is a recognised feature of the political landscape (Jasanoff, 2004). Science continually generates new activities that have the potential to become contentious as they enter the public domain. The potentiality lies in the tension between the proposed science and prevailing cultural values that 'may be more or less sympathetic to the new science and may or may not resonate positively with values supportive of the science such as those of "scientific progress" and "population health gain"' (Salter & Salter, 2007: 554-555). Examples where such tension has led to public conflict are research using human embryos to produce stem cells, which has clashed with religious values that accord a high moral status to the embryo, notably Catholicism, and the development of genetically modified crops, which provoked considerable opposition on the grounds of its 'tampering with nature' in the UK and much of Europe, where 'nature' is highly valued. Whether or not the tension between new science and prevailing cultural values results in containment, consensus or open conflict will depend on the skill of those epistemic actors involved in the production of governance knowledge.

With increasing frequency, the production of such governance knowledge has relied on bioethical expertise as an authoritative source capable of legitimating the regulation of contentious issues in bioscience and, through its political operation, acting as 'a device for bridging potentially troublesome divides: among disciplines, professions, and institutions; and increasingly also among science, state and society' (Jasanoff, 2005: 188). Bioethics is considered 'an appropriate strategy for engaging public disputes about science in pluralist

democracies in that it provides a predominantly secular, rational, and "neutral" discourse, not unlike the law or science itself, for negotiating the competing value complexes of various public interests' (Kelly, 2003: 342). As such, there is an increasing demand from national and international policymakers for the visible demonstration that 'bioethics' has engaged with science, as 'a kind of assurance that potential or actual ethical problems have been identified, attended to and resolved. Thereby, no matter how ambitious or controversial, biomedical research is then able to progress' (Hoeyer & Tutton, 2005: 386).

Until recently, the production of governance knowledge has generally lagged slightly behind the production of scientific knowledge: science makes an advance and governance responds. Where the lag has been substantial, as with GM crops, the political inefficiency of the co-production process has been thrown into sharp relief by the accompanying public controversy. What we examine in this paper is the extent to which the political costs of this *responsive* mode of co-production are encouraging a shift towards an *anticipatory* mode of co-production capable of pre-empting potential conflict through a more proactive role for bioethics.

If this is the case, then we can expect that the engagement between bioethics and science will move 'upstream' in the co-production process and that bioethics may take the initiative to problematise aspects of emerging science as 'ethical issues' in order to facilitate their anticipatory governance by bioethical expertise. Greely suggests that the role his committee took in considering Weissman's 'human neuron mouse' was that of providing a '"benchside consult", an effort to provide ethics-based advice on research in progress' (Greely *et al.*, 2007: 27). This model suggests a possible role for ethical engagement with science to ensure that science emerges from the lab pre-authorised with the legitimating stamp of bioethical approval, a kind of 'embedded' Research Ethics Committee or Institutional Review Board function to deal with proposed science that raises novel ethical problems (rather than to ensure that planned science conforms to pre-established procedures that define what is ethical). Elsewhere, there have been calls for a 'closer collaboration between scientists and philosophers' (O'Malley & Dupre, 2005: 1271) in the form of 'socio-ethical' research that 'does not merely follow scientific transitions but accompanies and interacts with them' and as such 'helps anticipate (and to some extent shape) the emerging social issues' (O'Malley, Calvert, & Dupre, 2007: 67, 74). The 'socio-ethical' model suggests something deeper than a 'benchside consult', a symbiotic co-production of ethical and scientific knowledge that ensures that only "good" (ethical) science gets done. It is the co-production of such 'good science' that we investigate in the case of human/animal chimera research.

As social scientists, we are therefore following the ethicists upstream in their engagement with the science of human-to-animal chimera production to analyse the changing relationship between the epistemic communities of bioethics and bioscience: a relationship that may be acting as a vehicle for the 'anticipatory governance' necessary for the production of 'good science'. Our approach, to adopt another idea from science studies, is to follow this 'good science'-in-the-making, rather than to wait until it has been produced and then study it as 'ready made science' (Latour, 1987). Our focus is on developing an understanding of what constitutes bioethical expertise in this arena and how that expertise operates as a form of power, a topic that has received little empirical attention (Haimes, 2002: 110; Salter & Jones, 2005: 715). We examine the extent to which there may be a mutual reinforcement between the epistemic communities of bioethics and bioscience, so that science that is considered good (sound) science (as opposed to poor, unsound, science) by science is simultaneously configured as good (ethical) science (as opposed to bad, immoral, science) by bioethics: a mutually pleasing form of co-production.[1] If this is the case, then does it mean that the successful bioethical legitimation of the science of human/animal mixing automatically increases the authority of bioethics: a virtuous circle of mutual power enhancement? Finally, is there a political price to be paid by bioethics for this acquisition of new governance territory? Like journalists embedded in military campaigns, bioethicists embedded in scientific knowledge production may find themselves obliged to exchange independence for access.

Scientific demand and governance supply

From one perspective, the production of animals containing human biological material is not a new scientific or governance domain (Behringer, 2007: 262). For example, cancer research uses chimeric mice produced by xenografting human tumours and transgenic mice containing human oncogenes both to develop new understandings of disease processes and as tools to screen new therapies. These technologies have become an accepted, and for scientists essential, part of scientific practice with very little in the way of open controversy or ethical debate. This unproblematic acceptance is in contrast to much of the science that uses the converse approach, putting animal material into humans, where the development of xenotransplantation of animal organs into humans as a potential therapeutic tool has received a good deal of scrutiny (NCoB, 1996).[2] Such technologies are considered to raise ethical issues around human identity, challenging the way we intuitively think about what it means to be human (Birke & Michael, 1998: 247) and potentially violating the sanctity of human entities (Robert & Baylis, 2003: 7).

[1] The notion of good vs. poor and good vs. bad is derived from Hurwitz (2002).

[2] However, the use of some animal tissues in humans has become accepted practice unproblematically, in the case of the use of pig heart valves as replacements for defective human ones.

In the UK, the recent debate over the ethical permissibility of producing inter-species embryos through Somatic Cell Nuclear Transfer of the nucleus from a human cell into an enucleated animal oocyte as the first step in the generation of stem cells for research opened a Pandora's Box of human-to-animal biological mixing. For example, in its report on inter-species embryos, the Academy of Medical Sciences (AMS) notes:

> Whilst much of the current debate focuses on *human* embryos incorporating animal material, we consider that discussion of the converse situation – already an active and productive field of research – is helpful for a full appreciation of the issues involved. We think it possible that this area of research will generate more active discussion as the science progresses over the coming years. (AMS, 2007: 33)

Furthermore, is not just mixing of human material into animal *embryos* that is becoming an issue. The AMS is, as we write, undertaking a project to examine the 'scientific, social, ethical, safety and regulatory aspects of the creation and use of non-human animals and embryos incorporating human material', noting in its press release announcing the project that this is a 'burgeoning area of research' (AMS, 2009).

What is significant from an ethical and political perspective, is not that the area of research is expanding, but that it is moving to produce forms of animal containing human material that are seen to be potentially problematic through the raising of new ethical issues and the stimulation of disquiet among the public. According to Greely, when Irving Weissman approached him with his 'thought experiment' for producing a 'human neuron mouse', he was 'aware of the sensitivity of these planned experiments, both ethically and in terms of public reaction' (Greely *et al.*, 2007: 32). Weissman's hesitancy suggests a concern with mixing of neural material between human and animal – although such mixing had been performed prior to his proposal in 2000, and has continued and expanded since. Why the concern? The expansion of the field of stem cell science, particularly the opening up of the field of human embryonic stem cell (hESC) science following the passing of the Human Fertilisation and Embryology Act 2008 in the UK, and Obama's rescinding of Bush's ban on federal funding of hESC research in the USA in 2009, seems to have been a significant motivating factor encouraging ethicists and policy makers to consider human-to-animal mixing a potential issue, and much of the current ethical debate on human/animal chimeras focuses exclusively on those chimeras produced using human pluripotent stem cells (see for example the Stanford Encyclopaedia of Philosophy entry on 'human/non-human chimeras' (Streiffer, 2009)).

A second factor contributing to the emerging political profile of this governance domain is the use of non-human primates (NHPs) in scientific research. In the UK, use of NHPs has been considered to raise particular ethical concerns (Boyd Group, 2002; Wetherall, 2006), and at the EU level, the European Parliament has adopted a declaration (0040/2007) urging the Commission to establish a timetable for replacing all NHPs in scientific experiments with alternatives. However, the demands of science, particularly neuroscience, for an efficient supply chain of research materials fit for scientific purpose militate against the aspiration to reduce NHP use. Driven by the increasing burden of neurodegenerative disease in Western populations for which it is striving to find treatments, and spurred by new techniques for modelling these diseases in NHPs and new possibilities for therapies which, it is argued, can only be properly evaluated in primate systems, the suggestion from science is that use of NHPs, and specifically use of NHPs with brains containing human neural material, can only increase. Thus for neuroscience researchers, while *in vitro* studies are useful, 'animal models are necessary to study and intervene in the dynamic process of the disease' and

> researchers emphasised that, while initial studies of the genetic, molecular and cellular factors involved [in Parkinson's Disease] can be performed in vitro and in rodents the development of effective stem cell therapies will need to ensure that the cells differentiate into specific neural cell phenotypes and generate appropriate synaptic connections. This can only be carried out in a living system of neural complexity comparable to humans. (Wetherall, 2006: 75)

The demand from science for the essential use of NHPs in research is backed by an associated political interest: the pharmaceutical industry:

> The [pharmaceutical] industry's view is that its future lies in developing entirely new classes of neuroactive drugs to combat the increasingly important neurological diseases of old age. [...] The existence and availability of an effective non-human model with similar neuroanatomical and biochemical properties to humans, both for basic research in the neurosciences and subsequent pharmaceutical development, is considered by the pharmaceutical industry to be paramount to the success of this endeavour. [...] It is industry's view that this may well mean that primates will become the *only* species, rather than merely the *preferred* option, both for fundamental research into these conditions and for the regulatory toxicology associated with product development. (APC, 2002: 29)

With two such powerful players insisting that the enhanced production of animals, specifically NHPs, is a necessary condition of scientific and industrial advance in important new fields of medical research, it naturally behoves a body such as the Academy of Medical Sciences (AMS) to reflect and respond. This they have done with the view that: 'The increasing power and sophistication of methods for introducing human material into animals, including new stem cell technologies, is likely to present new opportunities and significant regulatory and ethical challenges in the future' (AMS, 2009).

The AMS brackets together the 'regulatory and ethical' as challenges emanating from new scientific 'opportunities'. These are challenges that the epistemic community of bioethics is keen to address with, as noted earlier, the AMS itself hosting a current project addressing the topic. Elsewhere, the production of governance knowledge is beginning to accelerate as bodies formally responsible for ethics management respond to the governance opportunity. In Denmark, the Council of Ethics and the Ethical Council for Animals have already produced a report: *Man or Mouse? Ethical Aspects of Chimaera Research* (Danish Council of Ethics, 2008). In Germany, the National Ethics Council, which can choose its own topics, has listed 'Research on genetic chimeras' as one of the areas it will be examining (German Ethics Council, 2008). The Swedish National Council on Medical Ethics, which requires a remit from its government to undertake projects, 'requests that the Government addresses ethical and legal aspects of research with human-animal mixtures' (Swedish National Council on Medical Ethics, 2008). In addition, the EU, under its Sixth Framework Programme of Research for Structuring the European Research Area by Research on Ethics, commissioned research into 'fundamental problems in research with mixing creatures between human beings and animals in Europe and abroad' (Chimbrids (Chimeras and Hybrids in Comparative European and International Research: scientific, ethical, philosophical and legal aspects)) (http://www.chimbrids.org/).

Meanwhile, the ethical issues raised by human-to-animal chimeras has already received considerable attention in the wider bioethics community in articles and debates in bioethics journals, articles on ethical issues in scientific journals, and in reports such as that by the 'Ethics and Public Policy Committee' of the International Society for Stem Cell Research (ISSCR) (Hyun et al., 2007). These discussions are setting the agenda for the global debate. It is this material that we use here to analyse the engagement between the epistemic communities of bioethics and bioscience in our exploration of the extent to which 'good' science is guaranteed through 'anticipatory governance'. But first we need to consider how and why bioethics has achieved its elevated position as science's 'first choice' on the mode of governance most appropriate for new and emerging forms of medical science. What

does bioethics bring to the political table that gives it a competitive advantage when compared to other possible forms of science governance?

Bioethics, governance and the construction of legitimacy

The emergence of bioethics as an epistemic community with a legitimating function in the governance of science forms part of the political response to the inadequacies of the technocratic mode of science policy formation with its heavy reliance on the input of expert advisory committees and limited public scrutiny (Irwin & Michael, 2003: 44). Rising in parallel to bioethics have been participatory modes of governance. A more inclusive approach to science policy making was spurred, in the UK case, by a spate of very public controversies over science in the 1980s and 90s, such as the crisis over bovine spongiform encephalopathy (BSE) (where there was a conflicting scientific advice was withheld from the public, prompting a questioning of the validity of scientific knowledge claims) and the reaction to genetically modified (GM) crops (where there has been widespread opposition to their proposed development). The initial response from scientists and policy makers was to consider such reactions as a dispute over facts, with the public, in a 'deficit model', seen as lacking requisite understanding of the science, such that disputes could be alleviated through education (The Royal Society, 1985: 10). This public deficit model has been challenged by sociologists of science, who have argued that all knowledge is situated, perspectival and contingent (e.g Irwin, 1995; Irwin & Wynne, 1996; Jasanoff, 2005). Such claims for the symmetry of knowledge are used to support arguments that 'lay expertise' be brought into the decision-making process on an equal footing with the expertise of scientific authorities. The means to resolve tensions, in this case, is considered to be not education of the (deficient) public, but engaging the (expert) public in dialogue with other experts so that a consensus can be achieved. The 'dialogic turn' (Irwin & Michael, 2003: x) in public understanding of science resonates positively with the wider 'deliberative turn' in democratic modes of governance. As such, it is unsurprising that engagement of the public in dialogue over science was readily taken up by governments, in the form of initiatives such as citizens' juries, consensus conferences and public debates (for example the *GM Nation?* debate in the UK).[3] However, while such initiatives might be attractive in principle to governments searching for new ways to engender trust in their activities through 'openness' and 'transparency', in terms of political practice they have proved rather less appealing,

[3] Such initiatives have been much criticized by social scientists for their failure to be fully inclusive, engaging only a limited number of viewpoints, and so undermining any claims that the consensus reached is properly democratic (Irwin, 2001, 2006; Rowe et al., 2005; Horlick-Jones et al., 2006) and for holding on to the privileging of to scientific/rational forms of knowledge, so that disputes are reduced to technical problems with technical solutions (Levidow, 1998; Wynne, 2001; Irwin & Michael, 2003: ch. 2; Macnaghten, 2004; Goven, 2006; Stirling, 2008).

being ‘difficult to operationalize with any consistency and regarded with suspicion and hostility by the established culture of the UK’s scientific and advisory system’ as well as having the potential to politicize previously uninvolved constituencies therefore generating controversy where there was none before (Salter & Jones, 2005: 713). From the perspective of the pragmatic policy maker, ‘power to the people’ constitutes a cumbersome and unpredictable form of science governance.

As an alternative to understanding scientific controversies as disputes over facts, the more recent ‘ethical turn’ in science governance frames tensions as due to a conflict of values between science and ‘the public’. It is in this context that bioethics has developed as an epistemic community with the power to legitimate the governance of science. Scientific expertise in policy making is replaced with a new form of expertise – bioethical expertise – that ostensibly provides ‘a formalized procedure to define public values for policy purposes’ (Tallacchini, 2009: 283). At the same time, from the point of view of functional politics, bioethics ‘offers interpretations of political reality which provide policy-makers with a means for defining and codifying their interests, providing orientation and dealing with conflict’ (Salter & Jones, 2005: 712).].

It is important to note that the epistemic community of bioethics here is distinct from academic ethics, as a form of moral philosophy. It is ‘public’ (Kelly, 2003) or ‘official’ (Jasanoff, 2005: 173-188) bioethics. While both forms of ethics might be interested in the question of ‘what should we do?’, for academic ethics the aspiration is to arrive at a position of substantive moral agreement, whereas ‘public bioethics’ is interested in achieving a workable compromise, a consensus in the ‘characteristically liberal sense of agreement on the legitimacy of certain procedures in the face of substantive disagreement’ (Moore, 2010: 200), so allowing both science and policy making to proceed. This is not to say that public bioethics does not have an academic identity. As an epistemic community, bioethics establishes its international identity, like any discipline, through the creation of ‘common professional standards and conceptual frameworks, transnational disciplinary societies and networks, and the international mobility of its workforce’ (Salter, 2007: 273), evidenced in the production of journals, courses, conferences, professional associations, websites and the other familiar tools of the academic trade (De Vries, Dingwall, & Orfali, 2009: 562). The epistemic identity of bioethics may not yet be fully formed, certainly as a truly transnational community (Salter & Jones, 2005: 715; Holm & Williams-Jones, 2006), but it has nonetheless become a key player in legitimating science policy to elites and civil society alike.

In terms of political process, in the course of policy debates 'public bioethics' acts as a proxy for 'the public' (Kelly, 2003), but has the advantage for policy makers that it purifies the ethical discourses existent in society, reframing them in 'proper' language and addressing them using 'proper' techniques of evaluation (Moore, 2010). Notably, it reconfigures value disputes in ways that are amenable to *formally rational* debate and decision making. This does not mean that such bioethics ignores emotional responses to scientific developments among the public. Rather, it works to distinguish between public opinions with 'latent ethical potential', which can be worked up into formally rational arguments that can then play a part in the debate, and those founded on 'prejudice', which do not deserve consideration (Moore, 2010: 207).' Such criteria for inclusion naturally mean that entrenched positions do not gain a place within the deliberations. For example, pro-life interests were not represented on the US Human Embryo Research Panel (Kelly, 2003). Similarly, in the UK, the NCoB working group on the ethics of research involving animals made a clear statement that extremist organisations such as the Animal Liberation Front had placed themselves and their views beyond the bounds of consideration by their tactics of violence and intimidation (NCoB, 2005: xxvii).[4] There is no place for such entrenched positions because they are deemed incapable of participation in the process of bioethical deliberation. They are not amenable to compromise through *reasoned debate* and, if included, would thus prevent bioethics reaching the consensus that is its *raison d'être*. In excluding such interests, bioethics starts from the desired output of governance – workable consensus and policy relevance – and ensures the inputs are such that this end will be achieved: an eminently attractive political quality particularly when compared to the uncertainties of the 'public dialogue' option.

Bioethics, then, privileges rational debate as a means for achieving a workable agreement on what to do when values are in conflict. Such debate is not conceived of as a Habermasian ideal speech situation, from which a consensual communicative rationality can emerge. Rather, it is a 'formal rationality' in a Weberian sense. Formal rationality is calculative: 'an action is formally rational if it is calculated to be the most efficacious means for achieving predetermined or assumed ends' (Evans, 2002: 13). For bioethics, the ends are specific predetermined or assumed *principles*. It is 'through the enunciation and application of a set of principles, [that] standardized rules are established that enable the translation of different moral positions to a common metric capable of facilitating, usually on a cost-benefit basis, choices and decisions' (Salter & Salter, 2007: 560).

[4] The working group did contain a representative from the British Union for the Abolition of Vivisection (BUAV). However the majority membership was from science. The anti-vivisectionist stance was effectively neutralised, included as part of the debate but, as a minority voice, never allowed to gain ground.

A major attraction of bioethics as a mode of science governance is that its method of rule creation provides it with a *modus operandi* that is highly adaptable. As each new territory of bioscience emerges, so bioethics works to maintain its reputation for cutting edge governance by negotiating the particular way forward that will provide legitimacy for the new development of the new science. In so doing bioethics absorbs, and is absorbed by, the new science in an effortless communion of self-interest. As an ambitious epistemic community, bioethics has a natural interest in expanding its authority into new territories and over time has refined the strategies it uses to achieve this political end. Appearing in the 1960s and 1970s as a replacement for 'medical ethics' which had been discredited through its paternalist approach, bioethics was initially concerned with issues in biomedicine. Now, as a mature and increasingly self-confident epistemic community, it considers itself to have the authority to pronounce on any aspect of the biosciences whatever their application. The fortieth anniversary issue of the influential bioethics publication *The Hastings Center Report* contains articles on ethics of 'bioprospecting' and of biological weapons, for example. The editor notes: 'both topics are unusual enough for bioethics that when we first received the manuscripts, we wondered a little whether they quite fit within our scope. [But] it's always good to be stretched' (Kaebnick, 2010). Certainly, from a disciplinary perspective, it is 'good' to be stretched if this means expanding ones epistemic territory to encompass new bodies of knowledge over which authority can be asserted.

In adapting to meet the governance demands of science, bioethics has constantly to evolve fresh principles to deal with novel research developments. One concept that has become particularly prevalent in the policy discourse of bioscience and which, associated as it is with the established discourse on human rights, has great rhetorical power is that of 'human dignity' (Andorno, 2009; Jordan, 2010). Human dignity is the foundation of much human rights policy and legislation and is enshrined in the 1948 United Nations' *Universal Declaration of Human Rights* (1948) which is founded on 'recognition of the inherent dignity and of the equal and inalienable rights of all members of the human family'. Over the last two decades, the principle of human dignity 'has emerged as a key point of reference for the regulation of modern science and technology' (Caulfield & Brownsword, 2006: 72). The Council of Europe *Convention on Human Rights and Biomedicine* (1997) resolved 'to take such measures as are necessary to safeguard human dignity and the fundamental rights and freedoms of the individual with regard to the application of biology and medicine'. Similarly, the UNESCO *Universal Declaration on Bioethics and Human Rights* (2005) recognises that 'ethical issues raised by the rapid advances in science and their technological applications should be examined with due respect to the dignity of the human person and universal respect for, and observance of, human rights and fundamental freedoms'. Human dignity has also begun to feature prominently in bioethics discourse in

the USA; for example the first report of the President's Council on Bioethics (2002) was entitled *Human Cloning and Human Dignity.*

The rise of 'human dignity' as a principle is not undisputed. For academic ethicists, it is a 'useless concept' (Macklin, 2003) that is 'notoriously slippery, [...] confounding and contentious, and, as such, its utility as an action-guiding tool' is limited (Harmon, 2009: 946; see also Caulfield & Brownsword, 2006). However, while its ill-defined character might restrict its appeal to academic ethicists seeking an absolute philosophical resolution of its conceptual ambiguities, in governance arenas the criteria of worth are different and here the very vagueness of human dignity is undoubtedly viewed as an asset — at least from a political perspective. Human dignity, 'precisely because it is understood in so many ways, facilitates the drafting of international aspirational statements' (Caulfield & Brownsword, 2006: 75).

Taking 'human dignity' as a core principle allows bioethics to expand its global ambition by extending its own epistemic and cultural boundaries. First, it facilitates a move beyond the boundaries of its original terrain of bio*medicine* to deal with issues in wider bio*science* where the established and much-used bioethical principle of patient autonomy, so central in the medical domain, is of limited use. The majority of the ethically contentious issues in bioscience do not involve 'patients' and actions cannot be evaluated on the extent to which individual choice is upheld. Second, the principle of human dignity allows bioethics to cross cultural boundaries more easily. While 'autonomy' as a principle has proved much more mobile than might have been expected, finding application in cultures well outside the liberal heartland of Western Europe and North America, adopting a principle such as human dignity that is the formal international foundation of *universal* human rights puts bioethics on a much firmer footing in its attempts to become a truly transcultural authority.

Bioethical power and the co-production of 'good science'

If this analysis of the power and ambition of bioethics is correct, we would expect to find its components manifest in the methods and ideas used by bioethics to deal with the potential governance issues raised by the creation of human/animal chimeras. To what extent is bioethics helping to define the governance agenda in this new territory in ways favourable

to science and what is the contribution of the principle of human dignity to the making of governance decisions?

Defining the governance agenda

In their study of the stem cell discourse in the United States, Wolpe and McGee note that in public policy debates 'the first battle is often a struggle about definitions, and the winning side is usually the one most able to capture rhetorical primacy by having its definitions of the situation accepted as the taken-for-granted landscape on which the rest of the game must be staged' (Wolpe & McGee, 2001: 185). In relation to hESC science, bioethics established its authority by defining a limited set of components – embryo source, embryo age, embryo creation date, and so on – as the matters that were relevant for the debate and hence appropriate for the policy agenda. These components, 'simultaneously scientific and ethical objects' (Salter & Salter, 2007: 568), became the counters that were valid for use in the ethical trading game of governance formation.

> Similarly, in the field of the production of animals containing human biological material, the first definitional task for bioethics is to work out how to draw the line between ethically unproblematic and newly ethically contentious science. In their *Ethical standards for human-to-animal chimera experiments in stem cell research* the International Society for Stem Cell Research (ISSCR) achieves this division by the simple expedient of stating:

One common type of human-to-animal chimera study is the use of human embryonic stem cells (hES cells) to form teratomas in immunodeficient mice to assess stem cell quality and developmental potential. While this routine practice raises no ethical difficulties, other forms of chimera research may—such as preimplantation studies resulting in high but transient levels of human-to-animal chimerism in vitro, and the transfer of differentiated human stem cells into the central nervous systems of higher-order animals (Hyun *et al.*, 2007: 159). The dividing line thus becomes a temporal one: those chimeras currently produced as 'routine practice' in bioscientific research are 'ethically unproblematic' while those that are novel are 'potentially ethically challenging'.

The ISSCR then goes on to consider the specific issues raised by chimeras produced using hESCs. It argues 'that fears are directly related to the degree of deterministic biological agency that is attributed to the ''fundamental units'' that get mixed' (Hyun *et al.*, 2007: 159). Genes and stem cells, it suggests, are considered (by the public who potentially have

ethical concerns) to contain the essence of the organism, such that putting a human gene or stem cell into another animal confers a fundamental 'humanness' on that animal (such 'humanisation' of the animal being constructed as problematic in ways that we discuss in the next section).[5] One key element then is the type of human biological material that is transferred to the non-human. Elsewhere, the other criteria that come into play once the material has been defined as a 'fundamental unit' have been considered. Focusing on human/non-human neural grafting, particularly grafting of human stem cells into non-human primates, Greene *et al.* propose six elements that should comprise the starting framework: (i) proportion of engrafted human cells, (ii) neural development of the animal recipient (neonatal vs postnatal), (iii) NHP species, (iv) NHP brain size, (v) site of integration of donor material within the recipient brain (e.g. whether introduced into the cerebellum, which is the site of higher brain functions, or elsewhere), and (vi) brain pathology (whether the recipient is an NHP model of human neurodegenerative disease and thus has a different level of cognition from a 'normal' member of the species prior to introduction of human neural material) (Greene et al., 2005: 386).

Many of these 'criteria for concern' are also ones identified by Henry Greely in his comprehensive discussion of human/animal mixing (Greely, 2003). Starting with a broad definition of 'chimera' as 'a single biological entity that is composed of a mixing of materials from two or more different organisms' (2003: 17), Greely produces a detailed exposition of the issues, summarising the concerns over human-to-animal transfer thus:

> Creating a mouse with a brain made from human neurons, as proposed by at least one researcher, has attracted some press attention and does raise some concern. Putting human brain tissue into nonhuman primates can be even more problematic. ... Chimeras made by moving human parts into nonhuman beings would raise concerns when they are significant enough to raise the question of the possible humanity of the recipient. In both cases the "importance" of the parts—brains and gametes are more important than heart valves or skin—and the number of parts moved—transplanting five visceral organs would be more troubling than transplanting one—seem significant. So do the uses of such part-human, part-nonhuman chimeras. Making a chimera of a human and a nonhuman is much less controversial when done for medical purposes than if such a creature were made for entertainment or "art." (2003: 19)

[5] Stem cells *per se* are not an issue (Karpowicz, Cohen, & Van der Kooy, 2005); human blood and skin stem cells, for example, have been introduced into animals with little concern 'perhaps because they are not identified with what is essential to being human' (2005: 108). Rather, the problem comes with pluripotent stem cells – stem cells capable of regenerating into many different tissue types.

Alongside the nature of the donor (human) material (whether it contains a fundamental essence of humanness), the recipient species is a criterion for concern. Transfer into a species such as a non-human primate, which is already more like a human than, say, a mouse, is regarded as problematic because there is less leeway for adding human material before the creature becomes too human for (human's) comfort. Relatedly, the greater the amount of human material introduced into the animal, the greater the potential for problems. The stage of development of the recipient species is a further criterion for concern because introduction early in development (into the fetus rather than an adult animal) gives greater opportunity for the animal material to integrate and proliferate.

In all cases, the definition of the criteria for concern is derived from the principle that it is culturally inappropriate to create an animal that is 'too human'. As Greely puts it in the quotation above 'chimeras made by moving human parts into nonhuman beings would raise concerns when they are significant enough to raise the question of the possible humanity of the recipient' (2003: 19). In this, there is political utility in keeping the terms loosely defined – not explicating definitively what counts as 'too human' – at this early stage, so allowing for the negotiations that are necessary for the governance function to occur. In parallel to its definition of the governance agenda through its identification of the criteria for concern, bioethics is therefore also working to define and develop the principle that can be used to adjudicate on the implementation of this agenda . We now turn to examine how bioethics is working to make 'humanness', articulated in terms of 'human dignity', the principle to be used.

Defining the operating principle of governance: exclusion

Having established the parameters of the governance problem, bioethics then moves to define the principle that should guide the operation of the governance mechanism through a process of adjudication. In so doing, and as is customary, bioethics is itself guided by its own internal operating principle of 'utility to science'. A number of possible candidates for principles that can be used to adjudicate on the permissibility of human/animal mixing have been put forward for discussion within the bioethics community. '(Un)naturalness' has been considered, but firmly discarded; it is described as the argument most often considered and also most often rejected (Streiffer, 2009). The concern that scientists are tampering with nature in ways that are impermissible has been put forward as central to public disquiet over biological mixing in agricultural biotechnology (NCoB, 1999: 7; Shaw, 2002; Macnaghten, 2004). However, most scientists and philosophers find themselves unable to make sense of this distinction between 'natural' = good and 'unnatural' = bad.

From their perspective, humankind has been acting on nature for millennia, making it hard to distinguish between 'natural' and 'unnatural'. Further, many such interventions have met with approbation. As Greene *et al.* forthrightly state:

> Stipulating that research is "unnatural" says nothing about its ethics. Much of modern medical practice involves tools, materials, and behaviors that cannot be found in nature but are not unethical as a consequence. (Greene et al., 2005: 385; see also Karpowicz et al., 2005: 113-115)

As such, for bioethics (un)naturalness cannot be supported as a principle for deciding what mixing between species should be allowed because there is no firm link between the naturalness of an action and its ethical acceptability.

Related to (un)naturalness, the specific unnaturalness of crossing species boundaries has also been discussed as a potential evaluative principle (Robert & Baylis, 2003 and responses; Karpowicz et al., 2005: 115-118). Again, for scientists and philosophers of biology the concept of 'species boundary' is problematic:

> Biologists are unsure about the extent and even the definition of "natural species boundaries". Indeed the meaning of the term "species" is itself far from clearcut, depending very much on the context in which it occurs. (BBSRC, 2000: 14)

For scientists, species are not fixed entities with immutable boundaries; for example, they change over time with evolution (Boyd Group, 1999: §2). Further, biological science is increasingly recognising that any boundary between species is fluid; for example, gene transfer occurs between species (APC, 2001: 18). Against this, some bioethicists acknowledge that despite scientific and philosophical doubts as to the validity of species boundaries,

> fixed species exist independently as moral constructs. That is, notwithstanding the claim that biologically species are fluid, people believe that species identities and boundaries are indeed fixed and in fact make everyday moral decision on the basis of this belief. (Robert & Baylis, 2003: 6)

The transgression of culturally prescribed boundaries involved in interspecies mixing, Robert and Baylis argue, would cause a 'moral confusion' about how the resulting part-human entities should be treated, and as such the argument against boundary crossing deserves at the least consideration.

However, such an emphasis on the importance of the social construction of species definition is a minority and isolated strand in the debate. The general consensus within the bioethics community is that the culturally perceived inviolability of species boundaries cannot form the bases for moral judgment on production of chimeras because it lacks both scientific and ethical foundation. One ethicist has claimed that while species typologies might be 'useful for responding to animals with stripes and big teeth when strolling in the Bengali forest', when it comes to making moral judgements 'arguments using typological thinking [...] are so weak they can be toppled with pea shooters' (Castle, 2003: 29). Specifically:

> the species integrity argument provides no reliable criteria for assessing when the lines between species have been crossed, and, were it to do so, no clear argument about when and why crossing them would be ethically unacceptable. If offers no reasons why society should not accommodate new ways of classifying living organisms. [...] That one is used to thinking about things a certain way is not a strong reason to argue against the development of new ways of thinking. (Karpowicz et al., 2005: 118)

So, it is argued, while the species concept might provide a useful way of ordering and making sense of the world, the fluidity of the concept means that it is impossible to use it to determine which crossings are legitimate and which illegitimate. Further, for bioethics, just because we do use the species concept to make moral sense of the world, it cannot be used to argue that this is the way we *should* think about the world.[6]

A third candidate for an ethical principle to be used in judging arguments about chimera production is that of 'moral status' (Greene et al., 2005; Munzer, 2008; Fiester & Düwell, 2009). This principle is premised on an understanding that a distinction can be made

[6] Indeed the scientific concept of 'species' is only one way of classifying the natural world (Dupré, 2002). The classificatory systems employed by different cultures may have implications for the public acceptability of different biological mixings carried out by science (Roberts et al., 2004).

between humans and other animals. In contemporary understandings, people are considered to have equivalent moral status by virtue of being human, such that we have a moral obligation to treat other human beings as the same kind of being as ourselves. Animals are considered to be 'not persons' in this sense although the argument as to whether non-human primates, in particular Great Apes, do have moral status is prominent in discussion over the use of such animals in research. Here there is considerable debate as to 'whether they have properties or characteristics which make them sufficiently similar, in morally relevant ways, to humans' that their use as means to human ends should becomes untenable (Boyd Group, 2002: 33) (For discussion see reports on the use of NHPs in research (Boyd Group, 2002; Wetherall, 2006)).

The issue with chimera research is whether introduction of human biological material into non-humans would alter the recipient animal's morally relevant capacities in such a way as to confer on them the moral status of persons.[7] Again, bioethics advances both scientific (practical) and philosophical objections to the principle of moral status. For science, there is difficulty in coming to agreement on what constitute morally relevant capacities (Savulescu, 2003; Fiester & Düwell, 2009), and how to determine experimentally if they have been enhanced (Greene *et al.*, 2005). For philosophy, a drive to maintain the distinction between humans and other animals on the basis that the former have moral status while the latter do not is problematic when assessed on a social cost-benefits basis:

> We might be confused about the status of such interspecies beings, and this might create social disorder. [However] many people are confused about many things [children produced by surrogacy, clones, hESC and 'racists were confused about the moral status of race']. We should not base social policy and law on such confusions. [...] The social costs of acceding to irrational confusion are, at least historically, much greater than the costs of clearing it up and reforming society.' (Savulescu, 2003: 25)

That is, historically those entities classified as having moral status has been open to change. In the past, various categories of human (women, slaves, those of other race) have been adjudged of lesser moral status and hence not entitled to full rights of personhood. Today, the personhood of, for example, the fetus or the embryos, or those in a persistent vegetative state, or (as previously noted) Great Apes, has been opened to philosophical questioning. In debates within the epistemic community of bioethics, the very fluidity of the

[7] Or, in a refinement of this argument, that if such manipulation did confer full moral status on the animal, it would not be possible to afford the creature the respect due from the 'moral obligations entailed by that status' (Streiffer, 2009; see also Streiffer, 2005).

boundaries drawn using the concept of 'moral status' is used as argument against its utility as a principle to adjudicate on disputes over the permissibility of creating human/animal chimeras.

Defining the operating principle of governance: inclusion and implementation

Unsurprisingly, given its growing prominence in bioethics generally, the emerging front runner for a principle to be used in adjudicating on ethical issues in human-to-animal chimera production is that of 'human dignity' (Johnston & Eliot, 2003; National Research Council, 2005; Karpowicz, Cohen, & van der Kooy, 2004; Karpowicz et al., 2005; Baylis & Fenton, 2007; deGrazia, 2007; Hyun et al., 2007; Melo-Martin, 2008). 'Human dignity' is related to 'moral status'. Both concentrate on the human-like capacities that might be developed in chimeric entities, but the human dignity principle focuses attention on how this mixing creates problems for humans:

> By giving nonhumans some of the physical components necessary for development of the capacities associate with human dignity, and encasing these components in a nonhuman body where they would either not be able to function at all or function only to a highly diminished degree, those who would create human-nonhuman chimeras would denigrate human dignity. (Karpowicz et al., 2005: 121)

This is the spectre of a human being trapped inside the body of a mouse (Ahuja, 2006). Unable to realise the full potential of its dignity-associated capacities, the argument goes, in this creature the principle of 'human dignity' is violated – either in the sense of offending against the dignity of the creature, as a human individual, or in the sense of diminishing the dignity of humanity as a species (Johnston & Eliot, 2003). The emerging dominance of the principle of human dignity in the area of human-to-animal mixing is attested to by the way that discussion has developed in the bioethics literature on the subject. In early papers where human dignity is considered it is put forward as one possible principle for evaluation (e.g. Karpowicz et al., 2005). Latterly, it is the principle itself that has become the topic for debate (Hyun *et al.*, 2007; Melo-Martin, 2008). Bioethics is no longer debating *whether* human dignity is a suitable principle; it is arguing about *how* that principle can be applied to evaluate the permissibility of chimera production. In governance terms, the bioethical discussion has moved from whether the principle should form part of the governance agenda (it should) to how best can it be operationally implemented. Here, as noted earlier, the ambiguity of the concept of 'human dignity' has political utility, making space for the relative stabilisation of its meaning as a product of power relations in the policy making process.

We have shown how bioethics is establishing the elements that are allowed entry for consideration in the debate over the permissibility of creating human/animal chimeras (the type and amount of human material used, the recipient species and its stage of gestation) and the principle to be used in adjudication (by reference to whether the proposed chimera infringes human dignity). We should be clear here that the principle for adjudication and the elements allowed into the debate are being co-established. Notably, the elements that are considered valid are those that relate to the issue of introducing a problematic degree of humanness into the non-human animal, and in synergy with this the principle for adjudication that is being settled on is that of 'human dignity'.

In this debate within bioethics, the animal perspective is excluded from both the governance agenda and its operational implementation. No attention is paid to any problems for the animal that is modified to be more like a human. The focus is entirely on the problems for humans of creating human-like animals. Commenting on the 2005 US National Academy of Sciences *Guidelines for Human Embryonic Stem Cell Research* recommendation that experiments introducing hESC into an NHP blastocyst should not be permitted, Alta Charo, one of the report's authors, commented that such research 'might humanize animals in ways that are unnerving' (quoted in Scott, 2006: 490). In this vein, the question of recipient species is allowed into discussion on the basis that if the animal is closely related to humans, there is less leeway for adding human material before it becomes 'too human' for our comfort. An alternative argument could be made, but is not, that a closely related species is more likely to suffer like us from this experimentation.

The exclusive agenda setting power of the emphasis in the bioethical governance discourse solely on problems that accrue for humans is revealed through its sharp contrast with much of previous debate on the ethics of this kind of research. For example, in debates over the genetic modification of animals, the problem of the possible negative impact on the animal's wellbeing from the gene introduced has been a significant part of the debate (ECVAM, 1998; Boyd Group, 1999: 4.2.1; APC, 2001: 24). The 'Beltsville Pig', genetically engineered with genes to increase growth rate, suffered a range of disorders including painful bone and joint problems and diminished vision, and was frequently cited as an example of the negative impact on the animal of transgenic technology. The focus on the human also runs counter to existing regulatory frameworks for the use of animals in scientific research. In the majority of countries, these are based on well-established ethical frameworks for animal welfare, with the principle of the '3Rs' (of *Replacement* of animals where possible, *Refinement* to scientific procedures and husbandry in order to minimise actual or potential adverse impact on the animal, and *Reduction* in the number of animals

used through, for example, improved experimental design or use of new imaging techniques), first outlined by Russell and Burch (1958), have attained the near hegemonic status in relation to use of animals in bioscience that the principle of autonomy has attained in biomedical ethics.

Conclusions

The anticipatory co-establishment of the principles and operational rules of governance at this early stage in the development of the human-to-animal research field is likely to result in a framework for bioethical decision making that is in support of science. Through a combination of scientific/technical and philosophical arguments, the candidate principles of (un)naturalness, species boundaries, and moral status have been rejected. Technically, bioethics argues that it is impossible to determine what is 'natural', where species boundaries lie, or what qualities are relevant for conferring 'moral status'. In other words, these categories are social constructs with no firm foundation in biology and therefore should be discarded. Philosophically, bioethics rejects the elision of 'is' and 'ought' by which the existence of such systems of classification in the present is used to justify their continued utility in the future. Because such categories are used to make moral sense of the world, the philosophers charge, is no reason that we should rely on them in perpetuity. The social constructs that elicit unease at the thought of mixing between human and animal can (biologically) and perhaps should (ethically) be deconstructed.

In the epistemic community of bioethics, then, the co-production of new governance knowledge is characterised by the entwining of the scientific and the philosophical so that judgements against science are also found to be philosophically unfounded, and conversely, those activities that are permissible are deemed so on both scientific and ethical grounds. Through what is presented as an organic process of co-production, the emerging bioethical framework for human-to-animal chimera research becomes a legitimating framework within which 'good' science can safely progress. Science gives bioethics access to new governance territory, bioethics give science access to political acceptability.

This is not to say that bioethics is working to eliminate boundaries between the human and other animals: rather, it is working to manage these boundaries. At the heart of the scientific use of animals is a paradox. The idea that there is a boundary between humans and other animals is necessary to allow the latter to be used in ways that it would be ethically unacceptable to use humans in the research lab. However, this distinction between human and other animal exists in tension with the Darwinian concept, foundational to modern biology, that humans are 'other animals', part of a continuum of

biological existence, and it is because of this continuity that other animals can act as substitute for the human in scientific experiments Animals are sufficiently similar to humans for data from experiments on them to be useful in understanding human biology, human disease, and potential ways of treating human diseases. Bioethical input into the debate over human/animal chimeras is working in synergy with science to establish a boundary (about which animals can be used, and in what way) that allows the scientific work to create and use such animals to proceed. For ethicists, the 'yuk factor' (the instinctive response elicited to proposed science) is not good grounds for stopping that science, and as such alternative understandings of the boundary between human and other animals rooted in different (non-scientific) cultural values may have to change.

Our analysis of this 'upstream' phase of the co-production of scientific and governance knowledge is necessarily confined to the bioethical framework that is emerging from discussions in journals and reports. As the co-production process moves closer to the policy domain so the exclusive grip of bioethics may be challenged but it is difficult to see how its control of the governance agenda can be overturned in the absence of an alternative source of viable governance knowledge. National bioethics committees with an input to policy making will add new voices to the discussion but these participants are more likely to be concerned with the details of implementation rather than with challenging the governing principles themselves. Policy makers in their turn will want to be reassured that the bioethical consensus on human dignity can be translated into broad support from public opinion and so may choose to broaden the constituencies consulted. In addition, the degree to which the early stage, anticipatory work of bioethics can be readily accommodated by a particular country will depend on the synergy between this work and the host nation's regulatory culture. For example, it has been suggested that 'the concept of dignity does not explicitly play much of a role in the UK debate or regulation' (Beyleveld, Finnegan, & Pattinson, 2009: 663) and so the use of human dignity as an adjudicating principle may be less readily accepted in the UK than elsewhere.

Nonetheless, for bioethics the case of human/animal chimeras demonstrates its capacity as a rapidly maturing epistemic community to engage in proactive governance knowledge production at the edge of what is scientifically possible. No longer simply the functionary summoned to respond to difficult socio-cultural issues generated by a novel science that has gone too far too fast, bioethics is now self-confident enough to begin to anticipate and define the governance agenda as scientists reflect on what is possible. As a necessary partner in co-production, the journey bioethics embarks on will always be one initiated by science, but the enhanced capacity of bioethics for early intervention may mean that it can determine the itinerary followed.

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