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Creating problems: bioethical expertise and the governance of human/animal chimeras

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Introduction

The UK Academy of Medical Sciences (AMS) will shortly produce its report on 'the scientific, social, ethical, safety and regulatory aspects of research involving non-human embryos and animals containing human material' (AMS, 2009a: 1). As the Academy's press release makes clear, the ambition is that:

> [The report] will stand as comprehensive text on a burgeoning area of research and will reinforce the UK's lead in developing policy and legislation in challenging areas of medical science that is recognised world-wide. (AMS, 2009b)

Self-confident in tone, the statement enunciates the belief that the Academy's work can and will stand as the authoritative voice on what science should and should not be done in this area. If this belief has political substance, it may reflect the maturation of bioethics as an epistemic community and a consequent re-orientation of the relations between science, state and bioethics in the governance of science.

In exploring this possibility, this paper employs the debates over the production of human/animal chimeras in biomedical research as the vehicle for analysing the evolving role of bioethical expertise in the governance of science. It is now reasonably clear that bioethical expertise has become a resource that states employ to legitimise policy making on contentious issues in bioscience, as 'a device for bridging potentially troublesome divides: among disciplines, professions, and institutions; and increasingly also among science, state and society' (Jasanoff, 2005: 188). What is perhaps less clear is how this political contribution may be changing as the epistemic community of public bioethics moves from a predominantly *responsive* mode, providing input where it is asked to do so in cases where the science is already contentious, to a *proactive* mode, seeking out emerging science that it can problematise as 'bioethical' and to which it can then provide 'bioethical' solutions.

If this is the case, and if the proactive engagement with science is successful, it would mean that the status of bioethics as an epistemic community is enhanced. More generally, it would suggest the evolution of the role of bioethics in policy debates beyond that of a facilitating resource for the negotiation of the competing demands from science, state and society and into an independent power player with its own agenda . This then leaves the residual question of whether the ascent of bioethics has had the effect of marginalising the contribution of 'society' to the production of science governance through the promotion of an exclusive engagement between the expert communities of science, state and bioethics.

This paper proceeds to address these questions by analysing the engagement of bioethics with the matter of human/animal mixing in bioscience. First, we describe our conceptual approach to the role of bioethics as an epistemic community in the governance of science, drawing on the work of Bauman (1987) and Osborne (2004) on the nature of contemporary intellectual expertise. We then present our case study of the way that bioethics has constructed the matter of human/animal chimera production as a bioethical do-able problem by first identifying the science as a potential governance problem, then configuring the problem as a *bioethical* problem, and finally producing a solution to that problem that is to the advantage

of both science and governance. We conclude by discussing the enhanced role for bioethics in science governance that our analysis suggests.

Bioethics and the governance of science: epistemic communities and epistemic forms

The emergence of bioethics as a significant contributor to the governance of science forms part of the political response to the inadequacies of the technocratic mode of science policy formation. Operating 'behind closed doors' with very little public scrutiny (Irwin & Michael, 2003: 44), this traditional mode operated as a form of 'club government' (Weale, 2002) with policy makers making decisions informed by the input of expert scientific advisory committees, [Figure 1]. In the UK, this close relationship was destabilised in the 1980s and 1990s by a series of very public controversies over science – such as the public questioning of scientific knowledge claims (for example, the likelihood of transmission of bovine spongiform encephalopathy (BSE) to humans) and public opposition to proposed scientific developments (for example, the introduction of genetically modified (GM) crops) (Frewer & Salter, 2002). It became apparent that 'Society' could no longer be held at arm's length, that scientific expertise no longer carried sufficient weight to legitimise its own governance and that a fresh model of science policy making was required that explicitly incorporated the 'the social' aspects of science [Figure 2] (Irwin & Michael, 2003: 47-55; Irwin, 2006; examples of policy documents in which this shift is illustrated are the Cabinet Office and Office of Science and Technology *The Advisory and Regulatory Framework for Biotechnology: Report from the Government's Review*, 1999; the House of Lords Select Committee on Science and Technology *Third Report: Science and Society*, 2000; and the Office of Science and Technology *Guidelinse 2000: Scientific advice and policy making*, 2000). This shift can be understood as a decline in the influence of the epistemic communities of science where 'epistemic community' is conceived as a network of professionals with recognised expertise and competence in a particular domain, and an authoritative claim to policy relevant knowledge within that domain, which acts to provide policy makers with the ideas, tools and legitimacy relevant to particular governance problems (Haas, 1992, 2001, 2004; Adler & Haas, 1992; Adler, 1992).

However, merely because the authority of science had declined did not mean that an alternative epistemic agent would be able to exploit this political opportunity. Indeed, much of the initial debate over how best to resolve the tensions between science, the state and society understood these tensions as matters of disputed facts, requiring either education of a (deficient) public to equip them with the correct, scientific, understanding of the issues, or engagement of an (expert) public to achieve consensus through dialogue, in the form of initiatives such as consensus conferences, citizens' juries, and public debates such as the *GM Nation?* debate (Irwin & Wynne, 1996; Rowe & Frewer,. 2000, 2005, Irwin & Michael, 2003). It was only when the governance issue began to be framed as a conflict of *values* between science and 'the public' that the opportunity for an epistemic community specialising in the negotiation of values *per se* became manifest.

To what extent can bioethics be regarded an epistemic community capable of responding to this opportunity? Bioethics emerged as a term with social currency in the early 1970s when academics from, predominantly, medical ethics, philosophy and law became engaged in the study of what a standard text on the field describes as 'the moral dimensions – including moral vision, decisions, conduct and policies – of the life sciences and health care, employing a variety of ethical methodologies in an interdisciplinary setting' (Reich, 1995; see also

Martensen, 2001). Interpretations of the development of the new field of bioethics differ markedly in terms of such basic questions as what it is and where it is going (see e.g.Carson & Burns, 1997; Elliot, 1996). Pellegrino posits an orderly process of evolution through three phases of 'proto-bioethics' (the articulation of human values), the enunciation of philosophically defined principles to guide bioethical debate and, finally, 'global bioethics' where the perspectives of social science, the humanities, and medical ethics are combined to produce a more flexible understanding of issues (Pellegrino, 1999). Others perceive disorder. Internally there has been energetic debate over the need for bioethics, on the one hand, to adopt coherent principles and rules and, on the other, to incorporate an appropriate recognition of cultural diversity (Callahan, 1999). Meanwhile, some external critiques have viewed its origins as more political than ethical, driven by the utilitarian service of interests rather than the search for truth (Maclean, 1993; Rothman, 1991): to that extent bioethics may be portrayed as performing the classic function of an ideology as much as that of a moral philosophy (Nelson, 2000: 15).

As Haimes notes in her review of the social research into bioethics, part of the difficulty of gauging the precise nature of its identity (or identities) is the absence of empirical work on its institutions, ideologies, knowledges and notions of 'ethical expertise' (Haimes, 2002: 110). The evidence suggests, therefore, that as an epistemic community bioethics may be emergent but it is certainly not yet fully formed (see e.g. Kapstein, 1992). Rather, what we have is a hybrid community drawn from a variety of disciplinary backgrounds with a common occupational interest in the definition, organization and application of ethical arguments regarding new health technologies (De Vries *et al.*, 2009). Some parts of that community are more able, interested and willing to engage with the policy process than are others.

It is this latter field of bioethics, commonly referred to as 'public bioethics', that has responded to the governance opportunities offered by the decline in the epistemic authority of science by providing a new form of expertise, bioethical expertise that can deliver 'a formalized procedure to define public values for policy purposes' (Tallacchini, 2009: 283). Unlike academic ethics, public bioethics does not see to achieve through academic argument a position of substantive moral agreement as to what should be done. Rather it sees its role as facilitating an articulation between the competing demands of science, state and society that leads to 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), thus allowing both science and policy making to proceed [Figure 3].

In part the legitimacy of this bioethical contribution is derived from the claim of bioethics that it is acting as a proxy for 'the public' in policy debates (Kelly, 2003). From this perspective, bioethics operates to purify the ethical discourses circulating in society, reframing them in 'proper' language and addressing them using 'proper' techniques of evaluation (Moore, 2010). In so doing, it can be characterised as an 'interpretive' form of expertise through its ability to act as a vehicle for 'translating statements, made within one communally based tradition, so that they can be understood within the system of knowledge based on another tradition' (Bauman, 1987: 5). This form is in contract to that of the expert as legislator, whose role is to make 'authoritative statements which arbitrate in controversies of opinions' (Bauman, 1987: 4), suggesting that the 'modern' model of the intellectual as legislator has been displaced, and a 'post-modern' model of the intellectual as interpreter has come to prominence. This not to claim an epochal shift, the disappearance of legislative expertise, nor is it to propose a sharp dichotomy between interpretive and legislative expertise. Rather, legislation and interpretation are different but complementary epistemic

forms, equally available to those involved in the construction of governance (Osborne, 2004: 437). In the governance of science, the legislative epistemic form typified by the reliance on advisory committees has experienced a decline in its authority. At the same time, the interpretive form as manifest through public engagement and public bioethics has gained political ground as it has become *de rigueur* to incorporate attendance to the perspectives of the public in order to achieve policy legitimation. For the most part the interpretive exercise in unidirectional, turning the value statements of wider society into a form that can be understood and evaluated by science policy makers.

It is perhaps unsurprising that the interpretative epistemic form has acquired favour in policy making circles where it helps but does not hinder, challenge or rebuff. As one member of the epistemic community of public bioethics based at the Centre for Practical Bioethics in Missouri observed with regard to the intense value conflicts surrounding the human embryo debate,

> The Center's role in these "cultural wars" is not to advocate for a particular position but to provide well researched and objective information, perspective, and advocacy for the ethical justification of policy positions; and to serve as a neutral convener and provider of a public forum for discussion. (Christopher, 2007: 28)

Such modest political aspirations portray bioethics as a handmaiden to policy makers, feeding bioethical analyses into policy debates but not actively involved in shaping agendas or determining outcomes. It is a view that contrasts sharply with the unambiguous aim of the AMS for its project on human/animal chimeras to produce a 'comprehensive text' that will 'reinforce the UK's lead in developing policy and legislation' (AMS, 2009b). Where does the balance lie? The following analysis examines the extent to which the epistemic community of public bioethics may be adding to, and perhaps moving beyond, the employment of interpretation as an epistemic form. Does it still configure itself solely as the ostensibly neutral conduit through which ethical discourses are channelled into the policy process or does it also actively work to create ethical problems to which it can provide ethical solutions that satisfy science and the state? If so, is the typology proposed by Osborne now applicable where, through its problem creation/solution activities, public bioethics is increasingly drawing on the epistemic form of mediation, the mediator being the 'enabler, fixer, catalyst and broker of ideas, ... the one who *gets things moving*' (Osborne, 2004: 440)?

The argument is developed through a case study of debates over the production of animals containing human biological material in bioscience research and in particular recent debates over the introduction of human stem cell material into non-human animals. We draw primarily on documentary material, supplemented by semi-structured interviews with key players in the UK human/animal chimera debate. Interviewees were identified through their membership of working groups engaged in policy-relevant ethical debates that have produced or are producing reports on human/animal chimeras designed to feed into policy making. In that respect they are public bioethicists drawn from a range of disciplines and backgrounds including academic ethicists, scientists, lawyers, and members of animal welfare groups. Those interviewed were: one philosopher/bioethicst, one lawyer/bioethicist, one animal scientist/bioethicist and three neuroscienticst/bioethicists. The interviewees were asked to reflect on our analysis of documentary material, and as such the interviews were designed to allow refinement of our findings from the main phase of documentary data analysis.

Constructing bioethical do-able problems: a case study of human/animal chimeras

In the case of human/animal chimeras, the construction of scientific problems susceptible to bioethical treatment in ways that will resonate positively with the needs of policy makers can be explored in terms of three phases of bioethical endeavour. Firstly, a particular area of science has to be defined as a governance problem requiring a bioethical response through the appropriate ordering of the scientific context. Secondly, the problem has to be constructed in such a way that it can interact usefully with the tools of public bioethics. Finally, in order to be implemented, the bioethical solution has to be politically acceptable both to science and to state policy makers.

Ordering the context: problematising human/animal chimeras as a 'bioethical issue'

Two different histories of human/animal chimeras can be written. In one, they are the latest in a long line of chimeric entities produced in the bioscience laboratory. As described by one scientist, there is a 'long heritage of human animal chimera research that has provided important insights into human physiology, disease, and drug discovery' (Behringer, 2007: 262). Cytoplasmic hybrids fusing human and non-human (mouse or hamster) cells were developed in the 1960s and were used in early studies mapping the human genome. Chimeric animals produced from xenografting of human tissue are used in a variety of research contexts, for example mice containing human tumours are used in cancer research both to develop new understandings of disease processes and as tools to screen new therapies. Human stem cells are routinely introduced into laboratory animals (usually the mouse) as a test of their pluripotency (Lensch *et al.*, 2007). There is also a significant history of mixing neural matter, including neural stem cells, between human and non-human animals. The first report of work transplanting human fetal neural tissue into the brains of monkeys is Redmond (1988). Research involving human stem cells dates from the late 1990s, with experiments introducing fetal neural stem cells into mice first reported in 1998 (Flax *et al.*, 1998). In the last decade, work using human stem cells has expanded to include human *embryonic* stem cells (Zhang *et al.*, 2001; Muotri *et al.*, 2005) and the use of neural stem cells in non-human primates , including those with features of human neurodegenerative disease (Parkinson's Disease, PD) (Ourednik *et al.*, 2001; Bjugstad *et al.*, 2005; Redmond *et al.*, 2007; Bjugstad *et al.*, 2008).

In this history, contemporary scientific work that involves the introduction of human pluripotent stem cells into non-human animal brains is the obvious next step in neuroscience research, a necessary requirement if science is to understand and find therapies for neurodegenerative disease. It is also part of an ongoing line of enquiry, an incremental step in human/animal mixing that does not raise novel ethical issues. As one UK scientist/ethicist interviewee put it, 'my feeling is that this is a non issue, this is really no issue, you know, no ethical issues of any substance associated with that', while a US lawyer/ethicist observed 'I view this as an interesting sideline, I don't think the chimera issues are likely to be a big deal'. In this history, technologies where human biological material is introduced into a non-human animal host have become an accepted, and for scientists essential, part of scientific practice with very little in the way of open controversy or ethical debate, and in this context there is no reason to consider further work in the same vein as potentially problematic.

While individual members of the public bioethics community might consider the matter of human/animal mixing a 'non issue' or an 'interesting sideline', in its engagement with the policy process the community as an epistemic actor has produced an alternative history where the scientific production of human/animal chimeras is configured as an ethically problematic activity that it is positioned to address. As noted earlier, the AMS has recently completed a

project on *Animals containing human material*, on the basis that 'Consideration of this rapidly advancing area of science is needed to ensure that research into our understanding of diseases and their treatment can take place in the UK within a robust ethical and regulatory framework' (AMS, 2009b). Other public bioethical bodies are similarly engaged with the issue. 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 select 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/). In the wider bioethics community, the ethical issues raised by human-to-animal chimeras has received considerable attention in articles and debates in bioethics journals (e.g. the target articles 'Crossing species boundaries' by Robert and Baylis (2003) and by Greely and colleagues (2007) 'Thinking about the human neuron mouse' in the *American Journal of Bioethics* and their associated responses), articles on ethical issues in scientific journals (e.g. Greene *et al*, 2005; Karpowicz *et al.*, 2004; Robert, 2006), 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).

This second history of the human stem cell/non-human animal chimera situates the creation of animals with part-human brains made from human pluripotent stem cells in the context of recent contentious issues in science rather than in the context of existing scientific custom and practice. In particular, it positions itself at the intersection of two areas of bioscience that have provoked societal concern: genetically modified (GM) crops and human embryonic stem cell (hESC) science. While GM crops had a relatively unproblematic introduction in North America, in Europe there was fierce opposition to their development. This opposition has been multifaceted, ranging from concern over the risks they pose to human health to antagonism towards the growing power of the multinational companies developing and marketing GM products. It included opposition to the idea of genetically modified organisms on the grounds that they are 'unnatural' and research shows that 'those who disapprove of their development and use for this reason are among the strongest critics of GM crops' (NCoB, 1999: 7). In this respect the biological mixing involved in production of GM crops conflicts with cultural values that hold 'nature' in high esteem. The impact of the negative public reception of GM crops on policy, particularly strong in Europe, illustrates how swiftly and effectively the scientific enterprise can be derailed if public opinion is against it. For those involved in the governance of science it generated an increased awareness of the need for strategies that anticipate and avert potential opposition to new developments in science. Such strategies include 'public education' (improving the scientific literacy of those deemed deficient in understanding), the more recent approach of 'public engagement' (engaging in dialogue with a public understood as having their own 'lay expertise' to bring to the discussion), and the use of bioethical expertise.

In the second history of chimeras, the context of governance sensitivity over 'unnatural' biological mixing generated by the GM crops issue is complemented by the high profile

debate on human embryonic stem cell science. Here the use of human embryos to generate stem cell material, in the process destroying the embryo, has clashed with values that accord a high moral status to the embryo, notably those of Catholicism. In this respect, hESC science forms part of the wider and continuing debate over biomedical technologies that act on the embryo, such as assisted reproductive technologies (ART), preimplantation genetic diagnosis (PGD), and abortion with its focus on the later stage of development of the fetus (Salter, 2007; Salter & Salter, 2007). Despite the arrival of the 'cellular alchemy' of induced pluripotent stem cells (iPS cells) from adult stem cells that avoid the human embryo problem (Vogel, 2008: 1766; see also Yu *et al.*, 2007), hESCs are likely to remain a prominent component of stem cell science and therefore a continuing source of governance concern. (It is as yet unclear whether iPCs have all the features that scientists find desirable in hESCs, or whether the method of their production (involving re-programming cells using oncogenes, genes that cause cancer) will limit their clinical utility (Gottweis & Minger, 2008), such that the scientific and clinical demand for embryo-derived stem cells is unaffected).

The ordering of this history by the Academy of Medical Sciences and the direct descent of its work on animals containing human material from its work on hESC science is clearly and deliberately apparent. In 2007 the Academy published a report on *Interspecies Embryos* which examined the ethical and scientific issues associated with the use of admixed embryos, comprised of an animal oocyte in which the nuclear material (DNA) has been removed and replaced with the nucleus from a human cell, as a source of material for generation of pluripotent stem cells. While this Report focused on the use of human embryos incorporating animal material, it noted that the converse situation has thus far had little attention, providing it with the opportunity to remedy that deficiency:

> The creation and use of *non-human* animals and embryos incorporating human material (transgenic or chimeric animals/embryos) already has a long and successful research history. However, the transfer of human ES cells, or increasing amounts of human genetic material, into non-human animals and embryos is likely to present increasing regulatory and ethical challenges in the future. The current review of legislation around human embryos represents one facet of the developing framework, but further consideration should be given to the interfaces between the regulation of animal research, human embryo research and human ES cell lines. The Academy of Medical Sciences will be undertaking further work on this issue (AMS, 2007: 4)

Public bioethicists interviewed in both the UK and USA also expressed the view that it was the prior existence of hESC science as an ethically and politically troublesome issue that allowed for the formulation of 'animals containing human material' as a potential ethical and governance problem:

> it's grown out of the debate around the stem cells. The whole human/animal chimera issues, you know, putting human genomes into animal oocytes was the fundamental technology. And I think it's emerged at about the same time that people realised that they were talking about situations where the entire genome would be human, or it was sort of 50/50 chimeric split. But I think it occurred to people during the course of that debate that the more modest combinations whereby, you know, the smaller numbers of human cells or human genes were put in to animals was an area that simply wasn't covered. So suddenly it came to the fore as something that was kind of non-regulated and not really addressed issue (UK scientist/ethicist).

> I think that's what has, that gives a political power that led to these issues being considered at the level they were considered. If this had happened 15 years earlier, before embryonic stem cells, I think there would have been some discussion and concern, but it was the fact that it happened at about the same time as the broad discussion and very heated discussion about the propriety of embryonic stem cell research that led it to being discussed. I think that provided the political fuel that maybe took this from what would have been a fairly minor issue to what was a medium sized issue (US lawyer/ethicist).

It is the prior existence of a scientifically contentious issue to which a new area of science can be linked that provides public bioethics with the opportunity to constitute this new area of science as a 'problem' – that is, an activity with the potential to arouse societal disquiet and *ipse facto* a need for a governance response.

Importantly, establishing a lineage between the human embryonic stem cell debate and human/animal chimeras also serves to facilitate the configuration of the problem as an *ethical* one. The debate over hESC science itself joined a continuing philosophical stream of discussion over the point at which human life begins and the permissibility of technological interventions at the pre-natal stage. Long prior to the 'ethical turn' in science governance, the development of new ways in which biomedical technologies *could* intervene in early human life went hand-in-hand with philosophical debate about whether such technological interventions *should* be employed. Building on that tradition, the hESC debate itself was centrally about the moral rights and wrongs of the science with other concerns such as safety coming into play in only a minor way. As a result, in presenting the issue of human/animal chimeras as emergent from the ethical debate about hESC science, the epistemic community of public bioethics ensures that it has relatively little work to do to configure human/animal chimera production as an 'ethical problem'. This does not deny that there are other potential ways of problematising human/animal chimeras. For example, there are safety issues with mixing biological material between species with the potential to generate novel, more virulent, pathogens that could pose a risk to human health. Indeed, the health risks associated with use of animal material in humans has featured prominently in the discussion of xenotransplantation (NCoB, 1996). However, characterising the problem of human/animal chimeras as an ethical one ensures that the epistemic skills of public bioethics are a necessary component in the in the formation of the overall governance response.

Constructing a problem that is do-able by public bioethics

The epistemic community of public bioethics has worked to configure the creation of novel human/animal chimeras as the site for a potential clash of cultural values between science and the wider society, situating it as part of the continuing controversy over hESC science. Given its assumed potential to be contentious, the production of human/animal chimeras is therefore a concern for policy makers keen to pre-empt public disquiet. For the maturing community of public bioethics, this creates an opportunity to contribute to the governance of science by providing a solution to the nascent issue it has created. This assumes that the bioethical problematisation of human/animal mixing has been constructed in such a way that the problem is amenable to resolution by bioethics: the potential solution has shaped the problem to render it solvable by that solution (Koch & Svendsen, 2005), and that specific shape renders it amenable to action in certain ways, by certain actors (Osborne, 1997: 174; see also Callon, 1986).

It is important to note that the solution is defined by the epistemic community of public bioethics rather than that of philosophical bioethics and that public bioethics configures the problem of human/animal chimeras as one fit for its attentions. Public bioethics thus has the task of formulating the problem in such a way that the solution to that problem meets the dual criteria of academic philosophy and science governance: it demonstrates both intellectual integrity and policy utility. In this respect the approach of public bioethics to problem solution is akin to the Fujimura's understanding of the creation of 'do-able' problems in science and technology (Fujimura, 1987). In Fujimura's analysis, a problem is made 'do-able' through the work that goes on to align the different levels of activity that are required to bring about its solution. For example, in the world of molecular biology, the three levels of experiment, laboratory and social world must be brought into alignment. The experimental work might involve the researcher ensuring that a piece of equipment is available for her to use at the necessary time, at the level of the laboratory the work might be providing enough equipment for all researchers to do their work, and at the level of the social world the matter is one of securing funding to purchase equipment. It is only when activities at all three levels are aligned that a solution to the problem is possible. For public bioethics, the creation of do-able problems involves not so much the articulation between different *levels* of activity, but articulation between different spheres of knowledge. It must align the demands of the epistemic communities of science, governance and philosophical ethics to make a problem that is do-able, and seen by other communities as do-able, by public bioethics.

A solution acceptable to science and policy makers

To make the problem of human/animal chimeras a doable public bioethical problem, public bioethics configures it in narrow terms. Much of the discourse of public bioethics on the topic consists of delineating those aspects of the science that do not warrant attention. The clearest example of such definitional work comes from the International Society for Stem Cell Research (ISSCR) in their publication *Ethical standards for human-to-animal chimera experiments in stem cell research.*

> 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).

Here, the ISSCR is at pains to distinguish between human/animal mixing that has been going on for some time in science and that has not previously been considered ethically problematic, and possible new ventures in this area that it can label as 'ethical issues'. It signals its commitment to leaving continuing scientific work producing chimeras, which has become established by familiarisation as acceptable, untouched by its investigations. At the same time, it identifies a potential ethical issue in the new direction that this science is taking, an issue requiring the attention of bioethics to allow the proper formation of policy to govern its activity.

Public bioethics is confining its attention on the question of animals containing human material to animals containing *human pluripotent stem cells*. This is clearly articulated in the Stanford Encyclopaedia of Philosophy entry on 'human/non-human chimeras' which commences by stating that it is restricting itself to 'chimeras formed by the introduction of

human pluripotent stem cells (hPSCs) or their more specialized derivatives into non-human animals' (Streiffer, 2009). Such a narrow focus might seem a missed opportunity to examine a broad range of scientific work given that, as noted by one of the interviewees above,

> it occurred to people that the more modest combinations whereby, you know the smaller numbers of human cells or human genes were put in to animals, was an area that simply wasn't covered' (UK scientist/ethicist).

However, as this same scientist/ethicist observed:

> people have been putting, for example, haematopoetic stem cells, human blood stem cells in mice for donkeys' years, and nobody gives a damn. But if you're using much more potent pluripotential cells, then issues start to raise up now about what they might incorporate into. Could they incorporate, for example, into the germ cells, could you end up with a mouse producing sperm or something. That's the kind of slightly scary Frankenstein type scenario.

Opening up for investigation the various forms of human/animal mixing that are established in science as 'routine work', whether this is the use of human stem cells other than pluripotent cells (stem cells that have already moved into a pathway towards regeneration into a specific tissue type, such as blood, neural or skin stem cells), or the widespread production of animals containing human tumours or tumour genes, or the creation of cytoplasmic hybrids, would risk disrupting an established, and for science essential, area of activity. By confining itself to the use of human pluripotent stem cells in animals, public bioethics makes a problem that it can solve to the satisfaction of science. Established avenues of scientific work are unchallenged by ethics. However, the epistemic community of science is given the opportunity to acknowledge that its activities do carry moral import, and to open itself to ethical scrutiny, while being sure that that scrutiny will be limited to a small part of its activities and so will not challenge its fundamental epistemic foundations.

In providing itself with a narrow remit focused on the use of human pluripotent stem cells in animals, public bioethics also ensures that it is creating a problem that it can address to the satisfaction of the policy-making community. The creation of human/animal chimeras sits at the intersection of two extant forms of science governance: the regulation of use of human material and the regulation of use of animals. Bioethical investigation of ethical issues raised by the science is configured by the epistemic community of public bioethics in such a way that that investigation does not threaten to challenge either of these pre-existing governance structures, while at the same time contributing to both the governance of science and expansion of the role of public bioethics in that governance.

In the main, the regulation of the use of human material is guided by the principle of autonomy: a central component of the 'principlism' which both dominated the emergence of bioethics in the US from the 1970s onwards and subsequently influenced the development of bioethics worldwide (Beauchamp & Childress, 2008 [1977]; see also Lopez, 2004 and Salter & Salter 2007). Indeed, autonomy 'has emerged as the most powerful principle in American bioethics, … and has become the "default" principle of applied principlism, the principle to be appealed to when principles conflict' (Wolpe, 1998: 43). The vehicle for ensuring autonomy is realised in practice is 'informed consent'. The autonomy of the patient in biomedicine or the participant in biomedical research is upheld, and demonstrated to be upheld, by following procedures to obtain their informed consent to undergoing treatment or

participating in research. The use of human tissue for research is similarly covered by procedures to ensure that consent is obtained from the tissue donor, and in debates over the use of human tissue in animals the existing procedures are considered perfectly adequate. For example, in their report on a proposed piece of research designed to replace the brain of a mouse with human neurons, Henry Greely and colleagues note the need to consider 'whether the tissues are used with free consent of the proper person'. In this case, where the tissue would be neural material from aborted fetuses, the 'proper person' is the woman who carried the fetus, and Greely's team conclude that existing (US federal) legislation 'contains provisions to help ensure that the consent is freely given and that no one was coerced into or even influenced toward getting an abortion to acquire fetal tissue' (Greely *et al.*, 2007: 34).

Given the perceived adequacy of the current procedures, in much of the debate on human/animal chimeras, and in our interviews with public bioethicists involved, discussion of the ethics and policy implications of use of human material is limited. However, the topic does provide a bridge for the community of public bioethics to expand into a new (for it) area, that of animal research. As an ambitious epistemic community, bioethics has a natural interest in expanding its remit into new territories. While it initially devoted its attention to issues in bio*medicine*, it now considers it has the authority to pronounce on wider aspects of bio*science*. For example, 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). Similarly, in its discussion of human/animal chimeras, public bioethics is stretching itself into issues of animal ethics and use of animals in research, where the established bioethical principles of autonomy and practices of informed consent do not apply.

Animal research has its own trajectory of governance. Ethical debate has been important in establishing the policies and procedures governing animal experimentation and, as with biomedicine, the debate has centred on identifying the principles that apply in this domain. The guiding principle established in the UK, the USA, and elsewhere, for governance of animal experimentation is that of animal welfare. In practical terms, the optimisation of animal welfare is realised through adherence to the '3Rs' of *replacement* of animals where possible, *refinement* to scientific procedures and husbandry in order to 'minimise actual or potential pain, suffering, distress or lasting harm and/or improve animal welfare in situations where the use of animals is unavoidable', and *reduction* in the number of animals used through, for example, improved experimental design or use of new imaging techniques (NC3Rs, undated). The 3Rs, first laid out by Russell & Burch in their 1958 book *The Principles of Humane Experimental Technique* (Russell & Burch, 1958) have attained a parallel status in the regulation of animal experimentation to that accorded to the idea of informed consent in the regulation of the enrolment of human participants in research.

Polices governing animal research have then coalesced around the principle of animal welfare realised in practice through regulations to ensure adherence to the 3Rs. At the same time, other value positions such as the anti-vivisection view have been excluded from the regulatory policy discourse. Such views do, nonetheless, continue to circulate in public discourse. Public bioethicists in the UK are aware of these sensitivities and dangers of opening up this line of investigation:

> this knocking genes out willy nilly created these pretty serious phenotypes in some cases. And the animal rights people haven't really latched on to that, and you don't, you know, want to excite animal rights people, and divert them into what we already do (scientist/ethicist 2)

However, public bioethicists are clear that the scientific work they are considering, limited to the introduction of pluriopotent hESC into animals, will produce no greater animal suffering than that already inflicted on animals in the name of science and permitted under current regulations:

> from an animal welfare point of view, almost all the things that are being considered are very, very mild. So, you know, you only have to think of some of the things we currently do to mice, modelling human disease for example, you know, if we're modelling, for example, motor neuron disease in mice, motor neuron disease is a horrible condition that kills the mice in fairly awful circumstances, as of course it does humans, in a fairly short but the same time, somewhat prolonged and chronic way. That's horrible for the mice. Nothing anybody can consider ,or at least any of us have heard of in humanising a mouse [with stem cells], comes close to mimicking that degree of pain and discomfort (scientist/ethicist 1).

> we already do as much bad things as you can do to animals already, and it's mainly through knock-out technology, transgenic mice. I mean, you know, we're knocking out every gene, one by one. We probably have three, four, five thousand mice with a particular gene knocked out, and some of these are pretty horrific phenotypes, because you can't predict. You wouldn't do it if you could predict. [...] So the question is, is there something you can do in this way of humanising the mouse brain by putting in human cells to create suffering that's worse than giving a mouse Huntington's Disease or Alzheimer's Disease or Motor Neuron Disease. You know, it's just, I can't imagine, what could it be? (scientist/ethicist 2)

Public bioethics is not, then, proposing to open up either the field of human/animal mixing or the fundamental question of animal experimentation to its enquiries but aims to limit its focus to the specific area of the use of human pluripotent stem cells in animals. As the public bioethics community is at pains to stress, this area does not raise ethical issues that threaten to disrupt the existing policies and procedures governing the science of human/animal mixing, either those pertaining to use of animals or those related to use of human material.

A solution that advances bioethics

The problematisation by public bioethics of human/animal chimeras created using human pluripotent stem cells raises ethical issues that may require additional regulation but it is regulation that can be integrated into the existing systems of governance of this field and does require the challenging, redrawing or replacing of such systems. The fear that public bioethics identifies is that pluripotent cells with their the potential to proliferate into different cell types may confer an uncomfortable degree of 'humanness' on the recipient animal: in particular if they 'humanise' the brain, gametes or physical features, and/or if they are introduced into animals that are already human-like such as other primates. As one lawyer/ethicist has commented: 'transplant a human kidney into a pig and it will remain a kidney; transplant human embryonic stem cells into a pig and they might take the form of any kind of cell–muscle, brain, skin, egg, or sperm' (Greely, 2011). The potential social disquiet

that bioethics anticipates is driven by the spectre of a human being trapped inside the body of a mouse (Ahuja, 2006).

As with use of human tissue and use of animals in science, the approach of the bioethics community is to establish the principle to be used to adjudicate on the ethical permissibility of creating animals containing human pluripotent stem cells. The principle that is emerging from the debate within the bioethics community to guide the governance of this area of potentially ethically troublesome science is that of human dignity (Harvey & Salter, 2010). Creation of a creature that is 'too human' for comfort would infringe the principle of human dignity because while too human for comfort it remains not fully human and therefore unable to realise the full potential of its dignity-associated capacities – 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 (see for example Johnston & Eliot, 2003; Karpowicz *et al.*, 2005; Cohen, 2007).

In proposing 'human dignity' as the principle to be used for guiding decisions on the permissibility of creating human/animal chimeras, the bioethicists working on this topic are reflecting and reinforcing a trend within the wider public bioethics community. Human dignity is coming to have increasing prevalence in bioethical discussions and, associated as it is with discourse on human rights, it has considerable rhetorical power (Andorno, 2009; Jordan, 2010). However, human dignity has by no means displaced autonomy as a guiding principle and its utility is not undisputed particularly among academic ethicists. It has been described as a 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). Nonetheless, 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). As a result, it 'has emerged as a key point of reference for the regulation of modern science and technology' (Caulfield & Brownsword, 2006:72), albeit one that has not as yet formed a clear linkage with an ethical tool for its practical application, as in the case of the autonomy/informed consent or animal welfare/3Rs pairings.

Taking 'human dignity' as a core principle allows the ambitious community of public bioethics to extend 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. Many of the ethically contentious issues in bioscience cannot be reduced to the level of their impact on an individual and cannot be evaluated using an approach based on the protection of individual rights. Invoking 'human dignity' is a way of articulating a disquiet about scientific developments that may impact on humanity as a whole. Thus, the United Nations Declaration on Human Cloning calls on members to 'prohibit all forms of human cloning inasmuch as they are incompatible with human dignity' (United Nations General Assembly, 2005). Second, the principle of human dignity allows bioethics to cross cultural boundaries more easily. While 'autonomy' as a principle has proved reasonably mobile and has found application in cultures well outside the liberal heartland of Western Europe and North America, the potential for human dignity to

act as a vehicle for the transcultural authority of bioethics is greater because it builds on the formal international foundation of universal human rights.

From interpretation to mediation: the enhanced role of bioethics in science governance

The engagement of public bioethics with the issue of human/animal chimeras illustrates how as an epistemic community it is beginning to take the initiative in enhancing its role in the governance of science. To date, much of bioethics' expansion as an epistemic community has been responsive. It has shown itself willing and able to adapt to take on new issues in new areas but it has largely addressed topics identified through public controversy, media unease, or political concern. In other words, much of the work of defining an issue as 'ethical' and problematic has been carried out by communities other than the epistemic community of bioethics.

The case of human/animal chimeras marks something of a shift in the relationship between bioethics, science and state. The 'problem' of human-to-animal chimeras did not exist in science or in the public domain as a matter about which there was public disquiet to which bioethics was then asked to give a response. Rather, public bioethics itself took the initial question and worked to turn it into a problem. It acted to 'ethicize' a previously uncontested terrain and, by so doing, produced a new area of potential governance over which it could exert its authority. Such an approach to the acquisition of power has strong echoes in the policy analysis field where it is recognised that solutions tend to look for problems to which they can become attached (Kingdon, 2003:172). Here, the solution – bioethics – is doing something more. It is actively working to create a problem to which it can apply itself. Furthermore, the way that bioethics problematises the issue of human/animal mixing ensures that the problem is characterised in such a way that bioethics is perceived by policy makers, scientists, and academic ethicists as the only appropriate legitimate authority qualified to address it.

This analysis suggests a different role for public bioethics from that of proxy for the public, identifying moral discourses in circulation and re-articulating them in a language that the scientific and policy communities can deal with. In the case of human/animal chimeras, its role is to articulate between the demands, concerns and interests of the epistemic communities of science, governance and bioethics itself. Here, the work that public bioethics is carrying out is not articulation in the sense of enunciation but articulation as alignment, bringing things together in a way that ensures they fit and function together. In this articulation work, public bioethics cannot be said to be acting straightforwardly as an interpreter of different cultural positions although interpretation may be a part of the work it does. Neither is it performing as a legislator, making authoritative statements. Instead, its mode of action conforms very much to that of a third type of expert activity elucidated by Osborne as a complement to Bauman's typology, that of the mediator who acts as the 'fixer',

> a motivator of syntheses that 'work', and have purchase, rather than ideals that dimly reverberate; an expert as much in the contexts and fields in which ideas operate as in the intellectual content of ideas themselves. (Osborne, 2004: 435)

This 'fixing' activity ensures that things are got moving and the momentum then maintained. In articulating between the epistemic communities of science, state and bioethics, public bioethics ensures that any stalemate that might arise due to tensions between the approaches, aspirations or worldviews of the different parties is avoided. Through its mediating activities, policy making is legitimated, science receives authorisation for its activities and societal

conflict is neutralised. Science and policy making are provided with the security of knowing they can proceed according to the tenets of the status quo without risking the challenge to their epistemic authority that may arise when a scientific development becomes a matter of open public debate.

By assuring the continuing mobility of scientific progress and its associated policymaking, public bioethics enhances its own status as an epistemic community as it proves its worth in the anticipatory governance of science. As interpreter, public bioethics sat astride the different communities of science, state and society [Figure 3] but its role was as the ostensibly neutral conduit through which ethical discourses are passed into the policy process. In this model, bioethics acts as the facilitator of the agenda of others and does not itself have a direct input into policy decisions. As mediator, bioethics is working alongside the epistemic communities of science and governance and 'society' has been displaced. This not to say that social concerns are excluded from consideration. The work of public bioethics, in the form of projects and reports by various commissions and committees, commonly incorporates a 'public engagement' exercise. A public dialogue was, for example, a prominent feature of the AMS project on animals containing human material, 'ensuring this work is informed by public opinion' (http://www.acmedsci.ac.uk/p209.html). However, in this context society becomes a minor player subject to the agenda promulgated by public bioethics. Its subordinate position reflects the reorientation of science governance in the field of human/animal chimeras where policy is increasingly shaped by the expert communities of science, state and public bioethics (Figure 4).

Conclusions

The science of human-to-animal mixing may be emergent but it is emerging along an established and thus far unproblematic, though not unchallenged, trajectory regarding the use of animals in research. The analysis presented in this paper suggests that public bioethics has problematised the activity of chimera production to configure it as a problem that bioethics can solve and which bioethics has the legitimacy to address. This problem creation/problem solution has benefits for all parties. In the wake of the public controversies over science during the last few decades, states are increasingly nervous about the potential for opposition to science to explode unexpectedly, leaving governments flat-footed and derailing scientific, and associated commercial development. There is thus a government interest in anticipating and pre-empting 'issues' as has been evidenced in the case of technologies such as nanotechnology (Anderson, 2007; Barben *et al.*, 2008) and animal biotechnology where the UK Agriculture and Environment Biotechnology Commission (AEBC) noted: 'as we have seen from the controversies surrounding GM crops, the challenges for society and in particular for Government can be acute - hence the urgent need to consider the issues in advance in this new domain' (AEBC, 2002: 28).

For the state, the change in posture of public bioethics from responsive to active supports such anticipatory governance through the identification and containment of issues at the potential stage, before they erupt into full blown social controversies. Similarly, science is interested in doing science, so the pre-emption of issues allows it to focus on with its core activity. Science may recognise that engaging the public is a necessary activity if opposition is to be defused or deflected but if public bioethics can carry out this task on its behalf then the political efficiency of the scientific enterprise is duly enhanced. Although this requires public bioethics to act in the service of science, the evidence from other scientific fields

where bioethical expertise has been employed suggests that it is likely to do so, not least because scientists tend to dominate the composition of bioethics commissions (Salter & Jones, 2005; Salter & Salter, 2007).

The problem creation/problem solution activity is also to the advantage of the public bioethics community that undertakes it. By making the problem, the epistemic community can ensure that the problem is constructed in a way that it itself can solve, allowing it to take control of the terrain. By so doing, public bioethics advances its own position from a facilitator of science governance to an active participant providing solutions as part of the policy making process. It has been judicious in selecting a topic for problematisation. The question of human/animal chimeras emerged from the debate over human embryonic stem cells and was pre-figured as an 'ethical issue' ripe for the attentions of bioethics. Furthermore, the way in which the UK debate over hESCs and the proposed use of interspecies embryos as a source material evolved was encouraging for a fledgling epistemic community seeking an area where it could test its mettle. Following the organised advocacy of hESC science by the scientific community (Watts, 2009), the favourable reporting of the issue by the media (Williams *et al.*, 2009) and a general acceptance by the public of the technology (HFEA, 2007), the UK government passed legislation permitting the creation of interspecies embryos in the 2008 Human Fertilisation and Embryology Act. The interspecies embryo issue illustrated the 'doability' of such problems to the bioethics community and others. A potentially contentious issue was resolved to the satisfaction of science and governance, while averting public controversy.

There will always be the criticism that the attempt to identify emergent issues in order to pre-empt them focuses attention on matters that otherwise would never have developed beyond the proto-problem phase. Clearly public bioethics has to be sensitive to this criticism. Given the analysis advanced here, its response is likely to be that it only generates bioethical problems that it knows it can solve. From the perspective of the state and science, the origins of the problem are less important than that it has been solved and science policy duly made. Whilst it is successful in problematising and then providing the ethical principles for the governance of human-to-animal chimeras, public bioethics is likely to increase its prestige as an epistemic community that can legitimate policy in the anticipatory governance of science.

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Figures:

Figure 1:

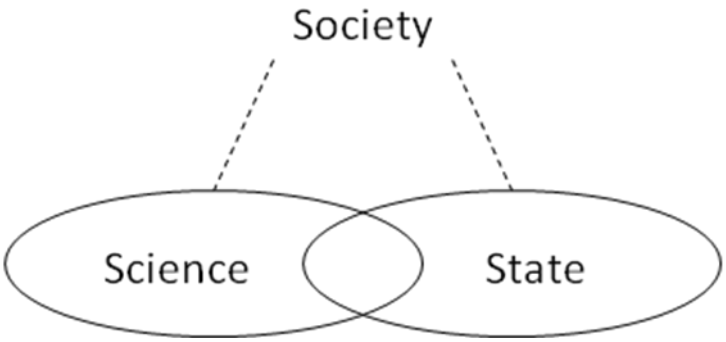
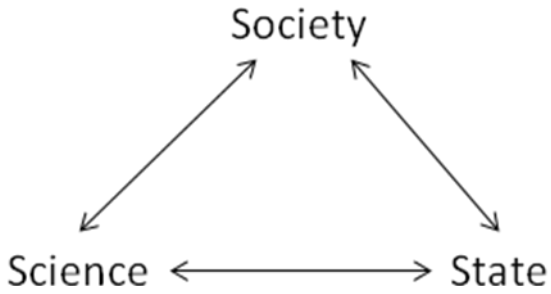


Figure 2:



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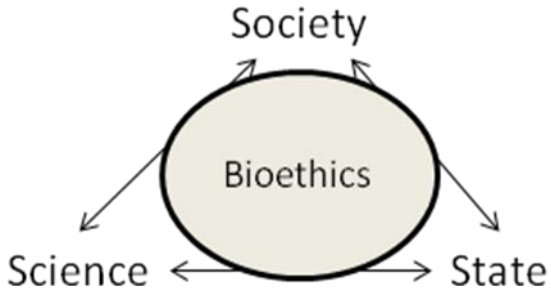

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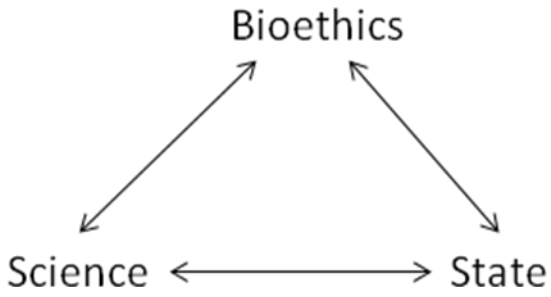
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