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Regulating Estrangement: Human–Animal Chimeras in Postgenomic Biology

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Abstract

Why do laws and regulations marking boundaries between humans and other animals proliferate amid widespread proclamations of the waning of the species concept and the consensus that life is a continuum? Here I consider a recent spate of new guidelines and regulations in the United Kingdom and United States that work to estrange human bodies from other animals in biomedicine. Using the idea of a bioconstitutional moment to understand how state institutions deliberate over "human–animal chimeras," I address how nations differently establish separations between humans and other animals. New chimeric entities, containing human hereditary material, have consecrated regulatory ground and signify increased attention to fields of research that have long used interspecies mixing. Regulators and policy makers now find themselves in a curious position. On the one hand, they continue to regulate the estrangement between humans and other animals, but on the other, they support the creation of chimeric life—a form of life that draws into question the very basis of such separations.

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Introduction

What we have come to call the postgenomic era harbors fundamental transformations in the relations and differences between technology and biology, human and animal, and the body and environment. One place where these changes are evident is in the deliberations and governing practices that address the use of human biological material in other organisms. Tensions have materialized as the availability of human embryonic stem cells and induced pluripotent stem cells open the way for creating chimeric organisms, which involves the transplantation of human cells into animals that are in embryonic or early fetal stages of development. As a result, national advisory and regulatory bodies are confronting issues of responsibility and jurisdiction for boundary crossing entities that are not easily classifiable through traditional regulatory orders. How do regulators distinguish between species at the level of cells and tissues? How are divisions inserted into cellular worlds where species distinctions do not travel all the way down to the level of cells? Increasingly, such deliberations fall to regulatory authorities, advisory bodies, and government departments. Regulators and policy makers thus find themselves in the curious position of needing to sustain the legal estrangement between humans and other animals, while facilitating research on human disease that increasingly relies on the incorporation of human and animal material into new biological entities.

Here I present two case studies of the regulation of chimeric life forms from the United Kingdom and the United States. I develop these cases in the context of "bioconstitutionalism" as a framing device to provide a set of coordinates for comparing each state's responsibility for life as articulated in law and policy (Jasanoff 2011a). Bioconstitutionalism brings together an explicit focus on interconnections between the life sciences and legal practices, thus focusing on two powerful sources of authoritative knowledge making—biology and the law. Such an approach provides a vantage point from which to explore how understandings of life (bios) are tied to the categories that mark out the legal entitlements, rights, and protections provided for political subjects in contemporary societies. In both the United Kingdom and United States, legal practices and thought, particularly in the context of biomedicine, have focused primarily on the category of the individual human person.

Foregrounding this focus on the individual, in her recently edited collection, Jasanoff (2011b, 289) argues that "bioconstitutionalism directs us first and foremost to the position of the individual human within a constitutional order that recognizes liberties, grants rights and provides means of representation . . . ." Through a bioconstitutional approach, I explore both the biological and legal assumptions that underpin the politically salient concept of the individual human and how forms of chimeric life challenge these assumptions. In Europe and North America, the ethical regulation of biomedicine is largely premised on the idea of the individual human, with regulation being split into two categories: human and animal.[1] Such legal divisions have significant consequences for those beings protected under the rubric of human and those not. In the cross-national comparison detailed below, I argue that while each national culture is oriented toward maintaining regulatory estrangement between humans and other animals, how such estrangement is institutionally practiced and understood, as a matter of ethics and law, differs greatly. To do this, I draw on multisited fieldwork that I conducted with biomedical advisory groups and regulatory bodies as well as interviews with scientists, bioethicists, and policy makers in the United Kingdom and Unites States between 2011 and 2014. Such differences demonstrate an intriguing variability with respect to the supposedly settled notion of the individual human—so often assumed a foundational and unchanging figure of Euro-American political cultures.

While it is common to encounter sweeping claims about how new biomedical technologies change what it means to be human, such claims are rarely supported with fine-grained evidence about how scientists, policy makers, and institutions practically and technically approach the human across genetic, cellular, and organismal levels. Such definitional moments are illuminating for those interested in science and technology studies (STS), however, for two main reasons. First, STS has a deep analytical investment in what we can broadly call the nonhuman. However, in directing energies toward such domains, it is possible that changes in its assumed opposite referent (i.e., the human) are neglected and thus require some empirical reenchantment. Drawing on a bioconstitutional approach, I argue that we should not presume to know what materially constitutes the human and animal research subject in biomedicine. Second, while debates about human–animal chimeras may represent another permutation of regulatory hand-wringing, such deliberations, and their settlements, will have long-term consequences for the forms of life valued and recognized by our political communities.

Hereditary Materials in a Postgenomic Era

Human brain cells inside mice and monkeys, organs populated with human cells in pigs, and embryos that are 99.9 percent human—such entities have been anticipated as both vital and useful for bioscientific research (Ourednik et al. 2001; Han et al. 2013). While there is a long history of the use of animals for understanding human physiology and disease, advances in the power of techniques involved in these studies are producing an ever-widening range of mixtures. The creation of humanized animals as both research tools and therapeutic objects has been made easier by new gene-editing technologies like the CRISPR[2]/Cas system. For example, the *Guardian* newspaper (Davis and Rawlinson 2016) recently reported on US-based researchers who used the CRISPR gene-editing technique to knock out a section of a pig's DNA necessary for a pig embryo to develop a pancreas. Human induced pluripotent stem cells were then injected into the pig embryo, which matured for twenty-eight days, before development was terminated and the tissues analyzed. Such experiments are dedicated to cultivating human organs in pigs. This example shows how the ability to manipulate genetic sequences and advances in embryo and stem cell technologies make it increasingly possible to replace animal material with human tissues and cells. Often called human–animal chimeras, such entities are used both to support basic research into human biology, health, and disease and to develop and test drugs and other therapies.

The goal of humanizing other animals so that they literally embody human biological processes has reintroduced the question of what constitutes human biological material and at what threshold does the accumulation of this material in other biological entities result in what are considered human functions, capacities, and attributes. Davies (2012, 126) captures the intricacies, fragility, and potentials of these technologies when she poses the question "what is a humanized mouse?" She argues that chimeric mice move our attention toward the intimate geographies of corporeal equivalence between humans and animals and to the expansive geographies of translational research. The mouse is thus a site from which to view both the remaking of species boundaries and the politics and practices of biomedical research itself. Such shifts are also characterized by Friese and Clark (2012, 46) as "transpositions," where changing practices of modeling in the life sciences are part of larger social, material, discursive, and spatial reconfigurations of human and animal bodies.

Drawing on these characterizations of chimeric life, in this article, I approach chimeras as both the material manifestation of biological practice

and the very entities that cast doubt over the assumptions that guide that practice. Chimeras contain tissues or cells from genetically different organisms that coexist together, thus casting uncertainty over the natural basis of biological reproduction. This article focuses on contemporary entities, often created in a laboratory, whose existence is legitimized through the pursuit of human health. However, chimeras have a long history in botany, zoology, evolutionary theory, experimental embryology, and developmental genetics (see, e.g., McLaren 1976; Margulis, Asikainen, and Krumbein 2011; Friese 2013). Used as a research tool to investigate human disease and model human systems outside the body, chimeric organisms are part of long-standing histories of "culturing life" (Landecker 2006).

While chimeric entities have been fundamental to experimental research in biology since its inception, it is "human–animal chimeras" that have become a lightning rod of ethical, legal, and regulatory anxiety in many countries (see Danish Council of Ethics 2007; Deutsche Welle 2008; Taupitz and Weschka 2009; Academy of Medical Sciences 2011; Ho 2016). This has made them the histrionic entities of bioethical deliberation (Greely 2003; Baylis and Roberts 2007). However, the figure of the chimera has for a long time been a potent character in contemporary thought: "we are all chimeras, theorized and fabricated hybrids of machine and organism; in short, we are cyborgs" (Haraway 1991, 141).

In another chimera story, Margulis, Asikainen, and Krumbein (2011) explain that the earliest nucleated cell developed from a merger of a sulfide-gas-making archaebacterium and a eubacterium some 1,200 million years ago. This sulfate-metabolizing chimera is the ancestor of all nucleated life forms today (of which humans, other animals, and plants are made). Chimeras abound not just as engineered and precarious laboratory constructs but also in everyday life.[3] Those of us who have had a blood transfusion meet the definition of being an intraspecific chimera. That is, we carry a small number of foreign cells from another member of our species. For Margulis et al., "chimeras are real. Life is not shy" (2011, 4).

Chimeras thus provide a vantage point from which to consider how the tools, methods, and materials of biological practice have come under deliberation because of their potentiality for new forms of life and the possible suspension of species lines.

Waning Species and Regulating Estrangement

The chimeras of postgenomic biology present new forms of multispecies entanglements. Such entanglements challenge ethical and regulatory

systems premised on a stark division between the rights of constitutionally recognized human individuals and other beings who do not receive similar forms of legal protection. These divisions are brought into relief by groups like the *Nonhuman Rights Project*, whose members seek to change the legal status of nonhuman animals to "persons," as only persons can possess fundamental rights like bodily integrity and bodily liberty because, as they put it: "The only animal with legal rights is the human animal. No other animal has any rights at all."[4] These legally enshrined differences, however, cannot be so easily followed down to the level of cells and tissues where the postgenomic era has ushered in a consensus that life is a continuum.

Describing the technical practices underpinning this consensus, the chair of the recent UK Academy of Medical Sciences report, "Animals Containing Human Material" explained to me:

> The concept of significantly distinct species has waned as more organisms are genetically sequenced, more and more of these mixing experiments were done. We all got used to the idea that life is a continuum. You can take something from yeast and put it in a mouse and something else from a chimpanzee and put it in a cow and more or less you can map things onto each other and they sort of work. Obviously there are big and important differences but an awful lot of the basic machinery is fundamentally unchanged. (Animals Containing Human Material (ACHM) chair, interview with author, 2012)

The kind of continuum described here is analogous to other expressions of the species concept in postgenomic biology (e.g., Collins et al. 2003). Given these histories of mixing in biology and the waning of the species concept itself, why have "human–animal chimeras" become objects of regulatory anxiety and deliberation? Reflecting on this question of "why now?" the academy chair remarked: "It's all very well to say people have been doing this [mixing] for forty years and every scientist knows about it. But outside of the biologists doing this kind of work nobody knows about it. It's never spoken of" (ACHM chair, interview with author, 2012).

Not only is chimeric work rarely part of public discourse, the legal and ethical frames that govern this research are starkly divided between human and animal. To this end, the waning of the species concept in biology has not been met with a more elastic sensibility that recognizes our linked biology with other organisms. Rather, regulatory and ethical oversight in both the United Kingdom and United States has, at least so far, shored up these vast and abstract categories through processes of what I will call

regulatory estrangement. In both the United States and United Kingdom, biological entities, for the purposes of regulation, need to be either human or animal. They cannot be both at the same time. This is the principle of regulatory estrangement upon which bureaucratic and institutional authorities in the United States and United Kingdom both labor. The making of definitional boundaries between human and animal at the level of cells and tissues thus requires laborious forms of constant and ongoing disentanglement.[5]

However, in examining such "bioconstitutional moments" (Jasanoff 2011a) where disentangling occurs, it is also clear that who gets to draw boundaries, and with what resources, varies greatly between nations. This suggests that the ontological schemes under which scientists and lawmakers are assumed to labor in Western democracies are far from singular. Ontological schemes in Western science may not be so "settled" (Candea 2013; Franklin 2013a) as new forms of "ontological surgery" (Jasanoff 2011c, 61) are afoot in the spaces between law and biology.

For example, the legal and regulatory structure of biomedical research in the United Kingdom is highly targeted and specific. It focuses on the rights of living individual human beings and involves ethical commitments of informed consent and doing no harm to research participants (for a genealogy of this human subject, see Reubi 2012). Biological materials derived from the female human body, such as embryos, are also targets of explicit regulation. In accordance with the Human Fertilisation and Embryology Act 2008, the UK's Human Fertilisation and Embryology Authority (HFEA) governs any research or medical procedures that involve human embryos outside the body. Other kinds of detached human body parts are less clearly regulated and are variously subject to the UK's Human Tissue Act, principles for the use of genetically modified organisms, intellectual property (patent) law, and the Data Protection Act.

Conversely, the use of nonhuman animals in biomedical research is regulated by the Animals (Scientific Procedures) Act 1986 (ASPA). It is a division of the Home Office that is responsible for implementing this Act and operating the licensing and inspection system. The Home Office jurisdiction is particular here because regulating biomedical research is not a core objective of this government department, which is responsible for immigration, security, and law and order. All animals imported or bred and used for research in the United Kingdom must be approved through the inspection and licensing of facilities by the scientific procedures inspectorate of the Home Office.

The UK legislation that governs human bodies or their parts (such as embryos) does not attempt to define words such as human. However, the

Animals Act does define the animals that fall under its prerogative: "all living vertebrates, other than man, and any living cephalopod" (ASPA). Here the definition of animal rests on an assumed referent of "man" that does not exist in a legal or legislative sense. In this law, animals also include embryonic and fetal forms, particularly those living beyond the last third of their gestation or incubation period. Animal embryos fall under the purview of the Home Office, whereas human embryos are subject to a highly targeted and specific genealogy of protection and "special status" through the UK's HFEA (Warnock 1985; Jasanoff 2011c).

In the United States, the practical matters of separating humans from other animals in biomedical research follow a different ethical and legal topography. The most visible debates in the United States have been predominately focused on the status of human embryos, abortion, and stem cell research (Maienschein 2003; Bonnicksen 2009). Because of this, concerns about the impermissible mixing of human and animal have been less politically visible than in the United Kingdom where formalized public debate has occurred.[6] In the United States, there is no formal legal regulation of human–animal chimeras despite some failed legislative attempts. The United States does not have a body similar to that of the UK's HFEA. As a result, one of the ways in which controversial research becomes adjudicated is through funding moratoriums imposed by federal bodies.

For example, in late September 2015, the National Institutes of Health (NIH) declared a moratorium on funding a specific kind of chimeric research that involves the insertion of human stem cells into very early embryos from other animals. This kind of research seeks to develop human organs for transplantation in other animals as well as to humanize biological systems and parts of other animals to study disease. However, similar to other instances where federal research monies are removed from controversial research, as with human embryonic stem cell lines in the previous decade, such research can continue, but with private monies. The moratorium was met with some skepticism and criticism of researchers working in this domain who, in a letter to *Science*, argued that such a moratorium impeded the progress of regenerative medicine (Sharma et al. 2015). In 2016, the NIH announced that it would replace the moratorium with a new kind of review for specific types of chimera research.[7]

Roughly, the institutional governing structures in the United States look like this: institutional review boards (IRBs) deal with humans, institutional animal care and use committees (IACUCs) deal with animals, and embryonic stem cell research oversight (ESCRO) committees deal with human embryos or materials derived from embryos. The original mandate for these

oversight committees was set out in the 2005 National Academy of Science (NAS) guidelines, which operates as the de facto regulation for research involving human embryos and stem cells. These committees are tied to research institutions and are responsible for assessing the possible risk of human contributions to other animals in research.

While the legal and regulatory landscapes in the United States and United Kingdom differ, one common dimension is the recent and vigorous response from governing authorities to biological entities that do not easily fit into the established legal and political orders. In both countries, the practices of postgenomic biology, which feature unparalleled corporeal intimacies between humans and other animals, have been met with the need to determine how such entities belong to regulatory orders. There is a particular swiftness with which these countries have responded through, for example, the UK Academy of Medical Sciences report, "Animals Containing Human Material" (2011) and the recent moratorium in the United States on research that involves the introduction of human pluripotent cells into other animal embryos in the early stages of development. The effect of these combined responses has not been to eliminate the idea of the individual human research subject from ethical protection or to enter into some kind of posthuman regulatory era. Rather, as the species concept wanes, the new guidelines and regulations emerging to reorient divisions between human and other animal bodies are indicative of a bioconstitutional moment—a moment in which institutions and cultures struggle to make sense of biological materials and practices that de-stabilize the law's conceptual categories (Jasanoff 2011a, 3).

Regulating Estrangement I

In 2011, members of the HFEA, Home Office, Department of Health, and Academy of Medical Sciences met to discuss a regulatory predicament. This predicament was ushered in by the word "predominant" as part of the definition of a human admixed embryo in the recently revised HFEA Act. In the Act, a human admixed embryo refers to embryos that are either entirely or "predominately" human or "equally" human and animal. Here the legal categories of human and animal are brought into explicit recognition and dialogue. The "human admixed embryo" as a recent object of law has a long genealogy, stemming from a series of entities (some only proposed, some created) that were subject to public deliberation, parliamentary debate, and regulatory deliberation in the United Kingdom from 2006

to 2008, when the Act was revised (Brown 2009; Haddow et al. 2010; Parry 2010; Harvey and Salter 2012).

In a north London office building, with a ready supply of tea, coffee, and slightly warm sandwiches, these experts deliberated on chimeric organisms and other boundary crossing entities. In their discussions, they observed that while the definition of a human admixed embryo encompasses many different kinds of mixtures (such as hybrid embryos, transgenic embryos, and cytoplasmic hybrid embryos), the proposition of chimeric embryos was particularly unsettling. This is because the cellular makeup of an embryo that is manipulated to contain both human and nonhuman material may change over time. In such a case, the experts around the table all agreed, it would be extremely difficult to assess whether human or animal DNA is predominant. This would be particularly troubling because it would not be clear who had jurisdiction over such an entity—on one side of the table sat the HFEA, which has jurisdiction over only human embryos, and on the other side was the Home Office, which has jurisdiction over animal embryos. Those attending the committee meeting agreed that this posed a problem. Such a regulatory separation between animals and humans resulted in a cliff edge effect: any human embryo used for research cannot be kept beyond the fourteen-day stage, whereas an embryo judged to be animal (or predominantly animal) is unregulated until the midpoint of gestation and can in principle be kept indefinitely.

In looking to resolve this cliff edge problem, the group discussed a form of regulation where scientists would hold licenses from both the Home Office and the HFEA at the outset of the experiment in case embryos took a more human or animal direction. Yet this seemed cumbersome and incompatible with the current legal system in which entities are classified as either human or animal. For the purposes of regulation in the United Kingdom, entities need clear categorization as either human or animal. Such a designation is required to determine whether research is legal and on what basis.

However, as a result of the regulatory deliberations over the term "predominant," the HFEA and Home Office have begun to work together in a rather unprecedented partnership. Communicating across the abstracted categories of human and animal in order to provide guidance to UK researchers was unanticipated by both organizations. The former chief executive of the HFEA explains:

> The particular issue for us, which is very specific, is the diplomatic relations with the Home Office. We've got to work with them and we don't always

> have to work with another government department . . . their interest in animals is not where ours are. (Interview with author, 2012)

Whereas previously they could labor separately in their regulatory domains, the Home Office and HFEA are now sharing an interest in how to develop systems of metrics to ensure that no impermissible humanizing occurs in organisms used for research.[8] Both the Home Office and HFEA are working within a long history of regulatory estrangement between humans and other animals in the biosciences. And while members from institutional bodies across the United Kingdom recognize that it will likely be a rare case where jurisdiction and classification confusion might arise, clarity for future research is held paramount in UK national research culture.

For public bodies, such as the HFEA, the regulatory requirement of assigning biological entities to either the human or animal category is not just technical and legal but also symbolic. Living up to their mythical and monstrous associations, ''human–animal chimeras'' open up spaces of deliberation with strong affective ties to what is seen as natural and unnatural. In this way, the relationship between potentiality and humanization, and species closeness and separation, impinge upon how chimeric organisms are regulated. A leading UK geneticist at the University of Oxford explains how the push toward humanization and its increasing sophistication may be interpreted in terms of potential:

> I think there probably isn't a major issue with a pig or a cow or a mouse but there would be with a monkey because they're so very close. So their ability to become more humanized is a much more tenable concept. (Interview with author, 2012).

Within the United Kingdom, the mechanisms of law and regulation are being pushed in new directions, as humanization becomes a tenable concept and a material reality in biological practice.

The legal and regulatory meaning of ''predominant'' will likely be subject to further specification and change if it is challenged in law, thus forcing the definitional issue. Despite previous legal challenges in the United Kingdom to the HFEA Act (e.g., *Quintavalle v. HFEA* [2005] UKHL 28), the kinds of regulatory models developed in the United Kingdom hold great international appeal in other countries that are deliberating species separation in biomedical research, such as Singapore. Thus, as the former HFEA chief executive reflects:

> The kind of public body we are is a very British thing. You find that our members apply to be on it and they're selected not because they're very good at what they do (because most people who apply are very good at what they do). We end up with a group of people simply who are seen to be the kind of people that everybody else thinks should make these intractable decisions. (Interview with author, 2012).

Indeed, those around the meeting table deliberating over the question of how to know when a mixed embryo might take a more "human" or "animal" direction are acutely aware of the intractability of their own deliberations. But there is also recognition of the legal infrastructures that confine regulators to particular kinds of disentangling and species separation. Clarity, in regulation, is provided by carefully considered boundaries and robust regulation, aiming to remove elements of uncertainty.

In the case of the "predominant" predicament, there is a realigning of old separations based on previous settlements over embryo research, but there has also been the repositioning of new associations. Within the law, human embryos can have "animal DNA" in them and continue to be classified as legally human. While the figure of the animal has had a long-standing history in nation making as a mirror from which to view the development of the category human and its associated rights (e.g., Ohnuki-Tierney 1989; Carter and Charles 2011), here the animal is both mirror and material participant in refashioning regulatory formations. This adds fresh dynamics to the dusty reference to "man" in the ASPA. The act applies to any living vertebrate animal other than "man," but in legal terms, we can see that now "man" encompasses some new political subjects: "predominantly human" human–animal entities.

Regulating Estrangement II

Depending on techniques and procedures, in the United States, the creation of human–animal chimeras is regulated by a variety of federal and state statutes and court decisions. The most significant guidelines relating to the creation of chimeric entities are found in the 2005 US NAS guidelines, which have been revised numerous times and are currently undergoing another revision. The NAS is not a governmental agency nor does it have enforcement power, but the guidelines are viewed to be binding by governmental and institutional authorities. In 2005, these guidelines offered a common set of ethical standards for a field that, due to the absence of

comprehensive federal funding, was lacking national standards for research. The NAS guidance acts as the principal reference on the limits of permissible research for embryonic stem cell lines and sets out specific recommendations applicable to research using interspecies chimeras involving human embryonic stem cells and other stem cell types.

After former President Bush declared that only a few stem cell lines would receive research funding, the NAS appointed a committee to provide guidance about what researchers could do with the cell lines that matched the Bush criteria. The guidelines developed by these committees have become the community standard in the United States. A member of this committee explained to me that in developing the 2005 guidelines, "the big question was what would be considered acceptable and what would not" along with the issue of "how much you could humanize and in what ways you could humanize and what kinds of animals you could use" (former NAS committee member, interview with author, 2014).

Human Contributions

In the end, the NAS guidelines recommended that all research combining human embryonic stem cells with nonhuman embryos, fetuses, or adult vertebrate animals must be submitted to a local IACUC for review of animal welfare issues and to an ESCRO committee for consideration of the consequences of the "human contributions to any resulting chimeras" (NAS 2010, 32). ESCROs are both the result of and subject to the 2005 guidelines. Thus, in the United States, the regulation and proposed creation of "human–animal chimeras" has been delegated to the same extralegal bodies that consider the ethics of human embryo research: ESCRO committees. It is within these local-level committees (convened by research institutions) that deliberations over interspecies molecular mixtures occur. Unlike the HFEA, which is a national regulator, these committees operate at the level of the institution where the research is taking place.

Jasanoff (2011c, 73) provides an apt description of these committees, which, while not mandated by law, are steeped in particular forms of institutional and scientific authority: "a committee that operates outside the requirements of the law is a particularly interesting site for observing the influence of bioconstitutionalism: it is a private sphere, in that it is not governed by the state, and yet it is concerned with the legitimacy and enforceability of its decisions." These committees meet to discuss any experiment where a human contribution to an animal might be considered unethical. This includes, for example, the possibility that human cells could

contribute in a major organized way to the brain of a recipient animal (NAS 2010, 32-33). The guidelines also state that for experiments in which human embryonic stem cells, their derivatives, or other pluripotent cells are introduced into nonhuman fetuses and allowed to develop into adult chimeras, there needs to be careful consideration because "human contribution to the resulting animal may be higher" (NAS 2010).

Unlike IRBs, which are now registered at the federal level (e.g., you can request to know who was sitting on an IRB during a certain time), the ESCRO committee membership is not published. In this sense, ESCRO committees operate privately within their own institutions and there is no oversight at a national level in terms of compliance to policy and guidelines. But while deliberations and decisions are not available for public consumption,[9] the physical paper form that researchers must complete before ESCRO review usually is. These forms differ across research institutions. For example, Harvard University requests that researchers justify and specifically discuss "Research involving the introduction of hES cells into nonhuman animals at any stage of embryonic, fetal, or postnatal development. Particular attention should be given to the probable pattern and effects of differentiation and integration of the human cells into the nonhuman animal tissues."[10] In contrast, the University of Rochester requests that if HESC derivatives, HESC cells or other pluripotent cells are going to be introduced into nonhuman fetuses and are allowed to develop into "adult chimeras," that researchers "please explain the extent of human contribution to the resulting animal." The Rochester form also requests that researchers "please outline anticipated potential consequences of the human contributions to the resulting chimera" as well as any "anticipated effect of the human stem cells on the animal's anatomy, physiology and species-specific behavior."[11] This form draws more explicitly on the NAS guidelines phrasing of parsing out "human contributions" to other animals.

When I asked a former NAS committee member whether there was any specificity to what might constitute a human contribution to another animal, he replied: "No, it's totally intuitive. I mean, what's the metric?" (former NAS committee member, interview with author, 2014). He also addressed the issue of quantification of cell numbers (e.g., percentages of human vs. animal cells) and argued that this kind of rationalization did not make sense because "it's about what organs are being modified, it's not about the sheer numbers. And we are not in a position to know which modifications matter yet" (former NAS committee member, interview with author, 2014). Indeed, similar to those responsible for such deliberations in the United Kingdom, those tasked with untangling the categories of human and animal

in stem cell research are acutely aware of the intractability of their decisions, along with the many unknowns that characterize transposing stem cells across species at different levels of development. However, rather than being able to dwell on these unknowns and gray areas, decision makers are required to siphon new entities into existing regulatory orders. This means that ESCRO committee deliberations are oriented toward providing a space for research to happen, not about questioning the basis of legal and ethical categories. Reflecting on her involvement in the ESCRO committee at Berkley, Thompson (2013, 64) sums this up: "putting these regulations into action, then, is first and foremost about enabling research in an environment of ethical controversy, and not about ethical inquiry."

What is striking about the ESCRO committee form itself is the ontological paper trail that it creates: by asking for an account of human contributions to other animals, it brings into explicit discussion categories that have long been divided in law and policy. But unlike the United Kingdom where these categories have now been brought into much more intimate official legislative and public proximity, in the United States, the ESCRO committee structure keeps these deliberations largely private.

Conclusion: Realigning Separations

Deliberations over chimeric life point our attention to the instability of the legal category of the individual human relative to other ways of practicing and thinking biological relations, heighted by the waning of the species concept. To this end, regulatory estrangement is an expression of current trends in translational biomedicine where the potentials for life are changing (Svendsen 2011; Davies 2013; Rajan and Leonelli 2013). By casting national deliberations through the term estrangement, I have sought to point to the affective politics that are deeply embedded in how national bodies approach and deliberate entities that fall under the heading human–animal chimeras. Estrangement is characterized by being "alienated in feeling or affection" (Oxford English Dictionary). In focusing on moments of isolation, distance, and separation, we can see what becomes pushed aside, or repressed, in deliberations over human–animal chimeras, namely, that humans are animals. In order for a chimeric entity to be knowable (and hence be regulated or governed), the entity needs to be either human or animal. Entities that occupy a middle ground between human and animal cause significant consternation not only in the practical classificatory sense but also in the ethical and normative sense.

However, the forms of authority involved in efforts to address such changes differ, as do notions of what constitutes an adequate resolution. The United Kingdom has written into law a new kind of human entity that has legal status: the human admixed embryo. Such a legal entity does not yet exist in the United States. Also, despite criticism, the United Kingdom's HFEA is a widely respected public body, both nationally and internationally. Such an achievement, as Franklin (2013b, 312) argues, is a testament to how the HFEA has set a course to integrate the concerns of science, medicine, and society, making it "nothing short of a national treasure." Such sentiments about the ESCRO process, which is far newer and not mandated by law, are less strong: in a recent article, the bioethicist Hank Greely (2013, 44) asks "have ESCROs been worthwhile?" and his answer is "a strong, definite 'probably.'"

In sum, national advisory and regulatory bodies in the United Kingdom and United States are confronting issues of responsibility and jurisdiction for boundary crossing entities that cannot easily be siphoned into the traditional legal and regulatory orders of either human or animal. This article has explored how chimeric organisms trouble regulation and law that works to estrange human bodies and materials from other animals in biomedicine. With the advent of new and sophisticated forms of human and animal integration for the study of disease, keeping the human separate from the animal is becoming increasingly difficult. Novel forms of biological life are being created that confound long-standing divisions and have challenged the law's capacity to simply extend itself over new entities. As material entities, chimeric organisms embody new articulations about the plasticity of biology and the recognition that assumed species differences do not travel all the way down to the molecular level. Consequently, explicit deliberations for ethical approaches and governing procedures are also pushed and pulled in new directions. This remodeling of boundaries in biological practice and state governance has consequences for humans and animals alike.[12]

In describing how ethical and legal distances between humans and animals are being reworked in Western democracies, I have drawn on the theme of bioconstitutionalism to bring attention to the role of state institutions in shaping human–animal relations. The coordinates of bioconstitutionalism were used to situate the practical labors of regulators and lawmakers as they seek to place the entities that emerge between the gaps of cells, tissues, and bodies into regulatory orders. Moving between the meeting rooms and paper work of regulatory authorities, the article examined both the material and legal dimensions of the creation and use of chimeric entities. In doing so, I illustrated practical attempts to

disentangle human bodies and materials from those of other species within therapeutically oriented research in biomedicine. These instances of controversy over new entities also served to give tangible examples of the implicit conventions of biomedical regulations, which rely on the fraught, but often empirically underinvestigated, category of human in the life sciences.

Seen through the lens of regulation and law, institutional authorities must sustain the long-standing estrangement between humans and other animals in research. But in working within the frame of regulatory estrangement, there is not only the careful realigning of old separations but also the opportunity for repositioning associations. Animalizing humans, while associated with reductionism, is put into contrast with an ethics of humanization, which requires attention to the material practices of mixture and its unknown potential qualities. Chimeric organisms that contain bits of human and nonhuman thus perform a very similar function in law as they do in biology. In biology, chimeras and their complex constitutions both embody facts about natural reproduction and simultaneously render unstable ideas about the natural processes that underlie these facts. As living and changing entities, chimeric organisms make explicit the very terms of their constitution, both in law and biology.

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Notes

1. Humans are, of course, animals. While Western societies regard both humans and animals as living creatures, the legal rights, protections, and forms of recognition offered to each differ sharply. In biomedical research, animal experimentation most viscerally captures these divisions. Here my focus is on how these divisions are negotiated at the level of cells and tissues.
2. CRISPR stands for clustered regularly interspaced short palindromic repeats and is pronounced "crisper."
3. This article is focused on experimental chimeras; however, the study of what are called natural or "found" chimeras also shows how chimerism confounds ideas about what constitutes an individual person or organism. Martin's (2007) historical analysis of the discovery of "Mrs McK—the first human chimera" brilliantly captures such an episode in midtwentieth-century medicine.
4. See Nonhuman Rights Project: http://www.nonhumanrightsproject.org/.
5. I develop this focus on disentanglement through recent work that engages with multispecies ethnography in a variety of locations, such as Kelly and Lezaun's (2014) work on "The Pursuit of Interspecies Separation" in Dar es Salaam and Porter's (2013) work on "Strategies for Multispecies Coexistence" in Viêt Nam.
6. For example, the Human Fertilisation and Embryology Authority (HFEA) ran a public consultation from April to July 2007 to examine public opinion on the broad range of hybrid and chimera research.
7. This review will include experiments where human stem cells are mixed with nonhuman vertebrate embryos and for studies that introduce human cells into the brains mammals (except rodents, which will be exempt from extra review). These experiments will go to an internal National Institutes of Health steering committee of scientists, ethicists, and animal welfare experts that will consider factors such as the type of human cells, how they will populate in nonhuman organisms, and whether they may change an animal's behavior or appearance.
8. Official guidelines were published in February 2016 by the Home Office as a result of these deliberations, which involved collaboration with the Human Tissue Authority, the HFEA, and the Academy of Medical Sciences. See Home Office. "Guidance on the Use of Human Material in Animals," Advice Note 01/16. Accessed December 1, 2016. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/491496/Animals_Containing_Human_Material_Final_Guidance.pdf.
9. Few firsthand accounts of embryonic stem cell research oversight (ESCRO) committee deliberations exist in formal published research apart from Jasanoff (2011c) and Thompson (2013).

10. See the Office of the Vice Provost for Research Policy, ESCRO. Accessed November 1, 2015. http://escro.harvard.edu/icb/icb.do?keyword=k50382&tabgroupid=icb.tabgroup120259.
11. See University of Rochester Medical Center. Accessed November 1, 2015. https://www.urmc.rochester.edu/stem-cell/escro.cfm.
12. New research initiatives such as Laboratory Animals in the Social Sciences and Humanities signal important shifts toward interdisciplinary research on laboratory animal welfare that address these changing spaces and practices of biomedical research. See http://labanimalstudies.net/index.html and accompanying paper of Davies et al. (2016).

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