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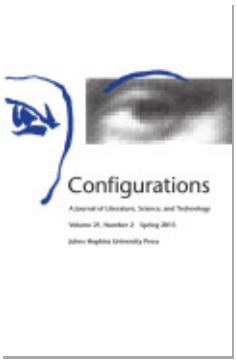
Configurations, Volume 21, Number 2, Spring 2013, pp. 183-200 (Article)



Published by The Johns Hopkins University Press
DOI: 10.1353/con.2013.0014

A Predicament: Animal Models and Human Tissue in Medical Research

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ABSTRACT: The use of the animal in medical research is deeply embedded within scientific culture, so much so that in spite of the European Union Directive (2010/63/EU) on the protection of animals, linked to the "3Rs" principle of replacement, reduction, and refinement, the recorded use of animals continues to increase. This essay explores the background to the utilization of the animal in experimentation. Using ethnographic data gathered in stem cell laboratories, the author explores attitudes toward the use of alternatives, specifically what is termed "waste" human tissue. A contrast is drawn between the refined framework surrounding the use of the "standardized" animal model and what appears to be the more ad hoc system for human tissue. At a time when the UK government is committed to reducing the use of animals in scientific procedures, it can be concluded that mundane practices, concepts, and values provoke resistance to the use of an alternative material.

Introduction

In medical research, the use of the animal is deeply embedded within the infrastructure of experimental science,[1] so much so that ethnographic material indicates attempts to use what is termed "waste"[2] human tissue in place of the animal model meets resistance

1. Robert A. J. Matthews, "Medical Progress Depends on Animal Models—Doesn't It?" *Journal of the Royal Society of Medicine* 101:2 (2008): 95–98.

2. The term "waste" is used prolifically within documentation referring to human tissue within healthcare. See http://www.who.int/water_sanitation_health/medicalwaste/002to019.pdf.

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in several ways. Considering that the translation of research from the animal model into the human is both complex and uncertain,[3] it would seem logical that, where appropriate, the use of human tissue be encouraged in place of a surrogate. However, ethnographic research carried out in stem cell laboratories between 2006 and 2010 points instead to frameworks of practice that hinder rather than enable both the collection and use of human tissue. This observation is important, not least because of European Union (EU) Directive (2010/63/EU) on the protection of animals that entered into force in November 2010 and that member states had to implement by November 2012. This directive is aimed at addressing the number of animals used in scientific procedures and, by implication, the ethical and moral arguments that underpin this attention to the release of animals, where considered possible, from scientific experimentation.[4]

The liberation of animals might not only arise from overt action at a macro-level, such as the EU Directive, but may also be prompted at the micro-level through the process of reviewing systems of mundane practice that employ animals. In the case of this essay, the review is of institutional practices employing animals in stem cell research. The scientists and technicians observed and interviewed in the research were noticeably sensitive to the value of animal life and the narratives of organizations like the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs), tasked by the UK government "to support the UK science base by driving and funding innovation and technological developments that replace or reduce the need for animals in research and testing, and lead to improvements in welfare where animals continue to be used." It was evident during ethnographic observation, however, that embedded practice and organizational structures produced day-to-day resistors to change, despite the positive and proactive action of research scientists.

In order to focus on, and discuss, the conditions and circumstances that limit the use of human tissue as an alternative to animals in laboratory experimentation, section 1 of this essay first contextualizes the rise of the animal as a central element of medical experimentation. By then describing the collection and use of human tissue in a stem cell laboratory in section 2, the predicament is

3. Christopher Anderegg, Kathy Archibald, Jarrod Bailey, Murry J. Cohen, Stephen R. Kaufman, and John J. Pippin, *A Critical Look at Animal Experimentation* (London: Medical Research Modernization Committee, 2006).

4. Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes (*Official Journal of the European Union*, L276/33).

drawn between the use of the animal and the use of the alternative. In so doing, several questions are raised concerning the place of human tissue in contemporary research. Importantly, this study points to several issues that impede the initiative to reduce animal usage in experimentation: the institutional resistance concerning the supply of, and access to, human tissue; the perception of human tissue as a nonstandardized material, in contrast to the concept of the standardized animal model; and the anxiety that experiments using human tissue produce fewer outputs.

Considering that EU policy aims to decrease the number of animals in scientific procedures, it would seem advantageous to reflect on the assumptions, concepts, values, and practices that constitute a way of viewing the supply and perception of human tissue in research laboratories. Such a deliberation has the potential to precipitate a positive change, mirroring the goals and aspirations of the increasing number of organizations dedicated to changing embedded practice, and, as the data contained in this essay indicate, on the part of those scientists interviewed, the desire to reduce animal usage in experimentation.

Methodology

Between 2006 and 2010, the author carried out qualitative research, both observation and interviews, at various sites across the UK involved in stem cell research, including university-based stem cell laboratories. Material from two specific laboratories is used in this essay to highlight the issues under consideration: one laboratory deals with the mechanisms that regulate adult stem cell maintenance and fate, and how this may be disturbed during aging or as part of disease processes; the other investigates the failing myocyte and the characterization of cardiomyocytes derived from embryonic stem cells, and their use in cardiac repair, tissue engineering, and drug discovery. In this context, the latter laboratory deals not only with animal models, but also with human tissue. By choosing to use an ethnographic approach aimed at understanding cultural phenomena, my intention was to elicit the way in which knowledge and systems of meaning guide scientific research in this area. My method involved observing the scientists and technicians at work during both experimentation on animal and human tissue and also while visiting associated animal houses. Lab 1 was primarily involved in animal experimentation, but serves as a model in its interface with members of the medical profession; lab 2 carried out comparative experimentation on animals, on a human stem cell line, and on human tissue. It is from these laboratories that the field

notes and quotes from practicing scientists and technicians used in this essay were gathered.

Section 1: The Animal Model in Medical Research

The use of the animal as a model for the human can be seen as far back as the third and fourth centuries BCE in the writings of Aristotle and Erasistratus, both of whom refer to experiments on living animals.[5] The rationale for this use of the animal is embedded in the principle of extrapolation—that by extending or projecting known information in the animal model, a successful translation into the human may follow. In the case of medicine, therefore, attention is focused on a biological justification of use; for example, the knowledge of mechanisms linking cause and effect, and the factors that interfere with those mechanisms.[6] This method of research is recorded as being the pathway to the successful adoption of the majority of novel medical applications, relying as it does upon the translation of scientific discovery from one animal model, or a collection of animal models, into the human. Hence the animal is said by scientists to "stand in" for the human, to "simplify" the process of knowledge attainment. Reasons for using the animal encompass the *ethical*—that it is not considered moral or just to experiment on humans—and *heterogeneity*, with every human body being different, nonstandardized in genetic and physiological detail. This is in contrast to the way in which the honed and standardized animal model is framed; in the case of the mouse, the model being described as "pure biological reagents."[7]

Standardization of the Animal Model

The setting of standards, particularly the requirement that organisms and procedures need to be regulated and controlled so that experiments can be repeated with the same, or very similar, outcomes, increased with experimental biology at the beginning of the

5. James G. Fox, Bennett J. Cohen, and Franklin M. Loew, eds., *Laboratory Animal Medicine* (San Diego, CA: Academic Press, 1984).

6. Daniel Steel, *Across the Boundaries: Extrapolation in Biology and Social Science* (Oxford: Oxford University Press, 2008).

7. The mouse became the standardized laboratory tool during the 1950s when Clarence Cook Little, the founder of the Jackson Laboratory in the U.S. state of Maine, used money from the Detroit car manufacturers to concentrate on breeding and distributing "the mouse model." Little circulated the mice as "pure biological reagents"—the JAX mice—said to be the gold standard of genetic purity in mouse models. See Karen Rader, *Making Mice: Standardizing Animals for American Biomedical Research, 1900–1955* (Princeton, NJ: Princeton University Press, 2004).

twentieth century. Reproducibility is seen as the cornerstone of experimentation, essential to the production of what are termed "entity signatures" (peculiar traces of biological identity), and to the arrangement, comparison, and analysis of inscriptions (the transformation of a material substance into diagrams or figures).[8] These inscriptions are not arbitrary, but are produced by replication in the laboratory according to a formalized protocol, and the fewer number of inconsistencies in the protocol the better the reproduction, hence the necessity to minimize all conceivable variables. Animal models are seen to resemble instruments, embodying layers of accumulated craft knowledge and skills and "tinkered" into new forms to serve the peculiar purposes of experimental life.[9] Tinkering in laboratories takes various forms, be it genetic manipulation or material intervention. Field notes from lab 1 reflect the researchers' speaking of "taking a licence to *make* a mouse."[10]

Historically, part of the process of standardization included bringing the rodent's breeding under control. As this latter management increased, diversity disappeared and individual variation was considered a nuisance, seen as "noise."[11] As Cheryl Logan argues,[12] in the late nineteenth century, laboratory researchers tended to use a wide range of organisms to study a particular problem, but as rats and mice became increasingly purpose-bred the diversity disappeared, so much so that the white rat became a carrier of *generality*—a model for generalized physiological processes.[13] Playing a part in this quest for standardization was the close connection between machines and the animal physiology they measured. This, along with control systems

8. Michel Callon, Pierre Lascoumes, and Yannick Barthe, *Acting in An Uncertain World: An Essay on Technical Democracy* (Cambridge, MA: MIT Press, 2009).

9. Robert E. Kohler, *Lords of the Fly:* Drosophila *Genetics and the Experimental Life* (Chicago: University of Chicago Press, 1994).

10. The use of animals in scientific procedures is regulated by the Animals Scientific Procedures Act (1986), which requires a three-level licensing system: personal license, project license, and certificate of designation (emphasis in original). http://www.homeoffice.gov.uk/science-research/animal-research/.

11. Lynda Birke, Arnold Arluke, and Mike Michael, *The Sacrifice: How Scientific Experiments Transform Animals and People* (West Lafayette, IN: Purdue University Press, 2007), p. 26.

12. Cheryl Logan, "Before There Were Standards: The Role of Test Animals in the Production of Empirical Generality in Physiology," *Journal of the History of Biology* 35 (2002): 329–363.

13. The white rat is an albino strain of the brown rat used extensively as a laboratory animal in biological experimentation. Merriam-Webster's Medical Dictionary, s.v. "white rat." http://www.merriam-webster.com/medical/white%20rat.

based on theories within the discipline of engineering, became the dominant theoretical framework in physiology by the mid-twentieth century, changing how living systems were perceived. Increasingly, standardized animals have been fitted to the production of standard machines and, with the emphasis moving away from diversity, the rodent has come to be perceived as a generic organism. As Joan Fujimura argues,[14] this has led to mouse breeding for genetic research being accompanied by the active elimination of diversity to create selectable traits for study: "In the avoidance of diversity and the search for generality 'the' laboratory rat and mouse were created. As a result they moved from being animals (as understood in the wider culture) and naturalistic objects of study, to being tools of the trade, part of the apparatus of science."[15]

The standardization of the animal model, therefore, relies not only upon animals being made into standard forms through breeding, but also upon additional, and hidden, activities that manage both variation and unpredictability. Today, from the moment of birth, or entry into the animal house via specific, designated mouse breeders, to its death, the animal is subjected to controlling and regulated practices. Seen as tools to be obtained from suppliers, mice are picked from catalogs extolling the virtues of particular species, specially bred for particular techniques—a commodity.[16] Housing, bedding, and feeding are standardized; lighting, temperature, airflow systems, and hygiene are monitored and contamination is kept to a minimum. Practices such as these are engaged in both to control the animal's environment in order to reduce experimental variability and to meet good practice and/or regulatory frameworks. The production and maintenance of animal models is a serious commercial concern, deeply woven into the fabric of medical research. Indeed, this leads one to ask whether the artifact—the animal model—has become such an integral part of experimentation that other materials, such as human tissue, are viewed as inappropriate within the scientific framework.

Yet, a challenge arises when attempts are made to translate findings from the animal into the human, for experience shows that causal relationships in biology typically depend on a *variety* of conditions that are subject to change, and it is rare that all such factors are known or can be measured. With organisms in flux, the variables

14. Joan H. Fujimura, *Crafting Science: A Sociohistory of the Quest for the Genetics of Cancer* (Cambridge, MA: Harvard University Press, 1996).

15. Joan Fujimura, qtd. in *The Sacrifice* (above, n. 11).

16. Birke, Arluke, and Michael, *The Sacrifice* (above, n. 11).

that affect translation can never be truly identified. So, for example, in stem cell research for diseases of the heart, there are variations between laboratory-induced infarcts in animals and naturally occurring injury in the patient suffering a heart attack, as multiple systemic injury and its complications change the milieu within the human body.[17] Size matters also, with a much smaller amount of muscle regeneration required to restore function in the mouse heart in comparison to a human heart. Yet, despite these and other differences, the mouse heart is warranted as a model system for the human heart. So when it comes to in vivo experimentation, justification for the use of the model organism is: 1) that it resembles the human heart, while 2) it engenders as little ethical debate as possible.[18] This perspective may be justifiable, but when considering in vitro experimentation the argument is different, and for the researcher there is a quandary: Might the use of human tissue be experimentally more appropriate than the use of animal tissue? This is not a simple question, for the answer does not pivot solely on a biological equation, but encompasses other factors. There may be a rationale for using human tissue to seek the repair of the human, but at the same time, it may not be considered conducive for researchers in the frame of their practice. Scientific research forming a structure that relies upon access to research material, minimum variables, replication

17. Kenneth R. Chien, "Stem Cells: Lost in Translation," *Nature* 428 (2004): 607–608.

18. In *Making Mice* (above, n. 7), Rader comments that historically "there was less scornful reproach, contempt, ignominy, shame or disgrace in their use, and it did not challenge cultural antipathy toward animal experimentation" (p. 29). It can be argued, therefore, that part of the reason for the use of rodents is the culturally indeterminate classification that rats and mice have. Historically identified as vermin, contaminators, and "polluters," rats and mice appear as loathed creatures of myth and storytelling. Regarded as transgressive animals, they provoke emotional reactions by intruding into human spaces and human concerns, producing a conflictive relationship where they can be regarded as destructive and/or polluting (see Birke, Arluke, and Michael, *The Sacrifice* [above n. 11]). In contrast, laboratory use turns rodents into the unsung heroes of medical progress (ibid.). The rat and mouse move from arenas that elicit vilification and horror to those that represent medical progress—aids in the struggle of biomedicine to conquer disease, and a validation of the practice of using animals for experimentation within secluded research. Not only are they transformed from wild, suspicious animals to relatively tame, docile inhabitants of laboratories (ibid.), they are also now contained within highly regulated spaces and practices. From behavior that elicited repulsion, the "unruly nocturnal animals have moved from the shadows into the spotlight—the primary inhabitants of this highly controlled, rule-bound, broad-daylight laboratory science." See Kenneth Shapiro, "A Rodent for Your Thoughts: The Social Construction of Animal Models," in *Animals in Human Histories: The Mirror of Nature and Culture*, ed. Mary Henninger-Voss (Rochester, NY: University of Rochester Press, 2003), pp. 439–469, quote on p. 441.

of experiment, the production of confirming inscription, the publishing of this data, and the subsequent funding and status that comes with a successful publication and citation record. My ethnographic research illustrates that the use of human tissue in certain circumstances challenges this framework.[19] Its supply is sporadic and the key concepts of control and purity—represented in the manufactured artifact of the manipulated, standardized animal model—are challenged because its heterogeneous nature threatens the replication of the experiments. Thus the use of human tissue places at risk the timely production of publications. These tensions produce an ethical and practical predicament: on one side of the argument, animal models are seen to be the best material to produce what is required—experimentation, results and output; and on the other is the logic of using human tissue to explore human disease. A consideration of this situation is important, especially at this time when the place of the animal model in scientific procedures is subject to an EU Directive.

The "3Rs" Principle of Replacement, Reduction, and Refinement

There is also an important policy framework for these issues. In November 2010, a new EU directive concerning the use of animals in research was published, and member states were required to incorporate it into national legislation by November 2012.[20] Centering on the ethical question of using animals in experimentation, the directive supports the EU's overall strategy on animal experimentation (including enhanced promotion of the development, validation, acceptance, and implementation of alternative methods) and provides a solid basis for a full implementation of the principle of the "3Rs": replacement, reduction, and refinement of animals in scientific procedures.

The 3Rs are a widely accepted ethical framework for conducting scientific experiments using animals humanely. The principle was first introduced in William Russell and Rex Burch's 1959 book *The Principles of Humane Experimental Technique*.[21] The National Centre

19. Jean Harrington, "Translational Space: An Ethnographic Study of Stem Cell Research" (Ph.D. diss., University of Exeter, 2011).

20. On September 22, 2010, the EU adopted Directive 2010/63/EU, which updates and replaces the 1986 Directive (86/609/EEC) on the protection of animals used for scientific purposes. The aim of the new directive is to strengthen legislation and improve the welfare of those animals still needed to be used, as well as to firmly anchor the principle of the 3Rs in EU legislation. The directive went into effect on January 1, 2013. See http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=Oj:L2010:276:0033:0079:EN:PDF.

21. William M. S. Russell and Rex L. Burch, *The Principles of Humane Experimental Technique* (London: Methuen, 1959).

for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs), launched in September 2004, was intended as a current focus for this movement in the UK. Bringing together diverse stakeholders, it facilitates the exchange of information and ideas and the translation of research findings into practices that are regarded as beneficial to both animals and science. The NC3Rs funds research, organizes workshops, and develops 3Rs information resources. It is an independent organization funded by, amongst others, the Home Office, the Medical Research Council, the Biotechnology and Biological Sciences Research Council, the Association of the British Pharmaceutical Industry, and the Wellcome Trust. This financial investment reflects the status given to the 3Rs among the UK biomedical establishment. However, in spite of this move, in the UK, the number of animals used in scientific procedures has been rising,[22] indicating that this initiative does not directly address underlying practices that render nonanimal models an unattractive choice.[23] The NC3Rs is not the only organization promoting the humane use of animals in scientific procedures and human tissue as a biotechnology that liberates animals. Others include the Fund for the Replacement of Animals in Medical Experiments (FRAME) and the Campaign for Safer Medicines. The Hadwen Trust campaigns for just one of the 3Rs—replacement—as do several other international centers and university departments dedicated to nonanimal alternatives.[24]

There are technical and social science questions about how both animal and other models, including human tissue, are regarded in contemporary bioscience regulation. Elsewhere, a coauthor and I describe the 3Rs agenda as a "socio-technical accomplishment" in order to stress the relatedness of the technical (understanding cell culture, programming computer simulation, and so on) and the social (network formation, systems of prestige, and funding) aspects that constrain and facilitate development in this area.[25] The two do not develop separately: the social always informs the technical, and the

22. Excluding the breeding of GM (genetically modified) animals and HM (harmful mutants), the total number of procedures increased in 2011 (an increase of 71,300 [or +3 percent], from 2.10 to 2.18 million). Statistics at Home Office, *Statistics of Scientific Procedures on Living Animals: Great Britain, 2011*, July 10, 2012. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/115853/spanimals11.pdf.

23. Ibid.

24. Marcel Leist, Thomas Hartung, and Pierluigi Nicotera, "The Dawning of a New Age of Toxicology," *ALTEX* 25:2 (2008): 103–114.

25. Jean Harrington and Neil Stephens, "A Social Science View on the FRAME Symposium: Identities and Networks," *ATLA: Alternatives to Laboratory Animals* 38 (Supplement 1) (2010): 101–104.

technical always informs the social. The 3Rs and the other movements identified above are examples of how the mobile intersection of regulation, technologies, infrastructure, and shaping values molds scientific development. At a 2009 symposium organized by FRAME, the clear message stressed that successful moves toward the increased use of human tissue required increased access to reliable tissue supplies. Yet, direct observation in stem cell laboratories from 2009 provides an insight into how existing frameworks of practice are severely challenged by the use of human tissue. How practical and routinized resistances within the practice of scientific research challenge the accomplishment of 3Rs strategies.

Section 2: The Human Tissue Laboratory

What follows is a report on my ethnographic data collected in a laboratory that invested in the use of both animal models and human tissue. The reflection and discussion demonstrate the challenges faced by those trying to instantiate the practices advocated by 3Rs groups in regard to human tissue. It makes explicit the role for, and limitations of, this animal-liberatory narrative as applied in a real-world context.

The setup of lab 2 that works with human tissue is similar to that of lab 1, which works only with the animal. It has its separate "wet" and "dry" areas. In the wet area are the devices for heating, cooling, spinning, and keeping cells free from contamination: the sprays, the gloves, the sterile hoods. The work surfaces also have their neat collections of pipettes, and underneath, in cupboards, are stacked boxes of Petri dishes with different surface materials, plus flasks and phials of different shapes and sizes. Field notes record that the human tissue element in lab 2 becomes apparent with the technician heating water butts ready for a specific experiment. A sample of tissue from a baby's heart, probably obtained from an operation to repair a hole there, is expected to arrive later that day; the ensuing experiments will take precedence over any other work that has been scheduled. This practice of prioritizing the arrival into the laboratory of human tissue underscores the value the researchers place on this hard-to-obtain material.

The head of lab 2 is particularly focused on the movement of research into the clinic, and the team strives to make its research as appropriate to the human as possible, as the team leader states in an interview:

> I have to say, I have always been most pro translational research, much more than my colleagues. I started because I was always writing these paragraphs in the beginning of proposals—you know, "These things are very important in

> the failing human heart and now I am going to do this bio-chemistry," and I'm thinking, "Well why don't I just go and work on the failing human heart then, it's there, it's over there!"

The human tissue comes to lab 2 via a small-scale collaboration with a local hospital. This is what could be described as a small-scale network, in comparison to the larger, commercially based networks.[26] The relationship has been established for many years, yet there still appear to be fundamental problems with, as the researchers describe it, "getting the tissue." The scientists' understanding is that the medical profession does not fully comprehend the specifics of the scientific concept of tissue for experimentation; they regard the surgeon or clinician as viewing the tissue as "waste" material and, thus being no longer viable in a living organism, the act of sending it to scientists is considered a kind of unnecessary labor-intensive disposal. The value the researchers place on the tissue is not, according to them, reciprocated by the medical profession. To underscore this perspective, the following description from an interview with a postdoctoral researcher refers to the handling (on more than one occasion I am told) of a defective human heart after it has been removed from a patient in the context of heart-transplantation surgery:

> We've had occasions, after the heart is taken out, when it's been left on the side on a tray. The incoming heart, the donor heart, comes in a big box of ice and this cardio solution I think, and for our purposes if they just—once the donor heart is out—if they just put the failing heart in that bucket of solution of buffer, that would preserve it so much better for us, even if they did nothing else—rather than leave it on the side.

This lack of attention to the tissue leads researchers to question the medical teams' sympathy with the needs of labs. There have been instances of tissue arriving at labs immersed in water or formaldehyde solution, which render the human tissue useless for research purposes. It is apparent that these acts of "negligence" frustrate the scientists; however, they discuss the situation pragmatically, revealing an understanding that the medical teams are focused on the patient and not the waste tissue.

These examples point to an inherent tension between *medicine* and the *science of medicine*. Medicine is focused on the healing of the patient, and, in general medical terms, human tissue that does not function is viewed as waste or debris. It only loses that status and acquires value when it is seen through the prism of human tissue

26. For example, commercial companies like Asterand plc; see http://www.asterand.com/Asterand/.

research. The boundary across which the tissue has to go in order to be used in research captures this tension, requiring the medic to visualize the tissue's value through the eyes of the researcher. In the high-pressure and rule-bound environment of the hospital this can be challenging, requiring, on the part of the medical team, added procedures that may not seem worthwhile within the context of its primary duty.[27] Scientific researchers appreciate that making tissue available for purposes of experimentation requires extra paperwork in order for the material to be accounted for and tracked. These factors consequently need to be considered within an environment constrained by space, time, and funding. Surgeons and pathologists, who handle and classify tissue samples, as well as providing the clinical data that accompanies specimens in order to maximize their use, work under time constraints, in addition to the fact that many pathology departments suffer from a lack of funding.[28] Recognition of their role in moving tissue from clinic to laboratory is scarce, besides being minimally resourced or compensated. In a situation where the patient is the priority, access to human tissue therefore requires the cooperation of the medical team as "gatekeepers." When seen through the prism of research, however, it may be said to be perceived as the hierarchy of the clinical in a translational environment.[29] This imbalance of power is further complicated by the fact that human tissue, accompanied as it has to be with the consent of the donor, can also be said to be a "gift."[30] This raises an interesting concept of exchange disequilibrium between scientist and clinician. Marcel Mauss argues that gifts create relations of indebtedness and

27. I have deliberately refrained from discussing human tissue that has a direct monetary worth here—for example, umbilical cords that have cash value—because financial recompense adds a dimension that brings into question the ownership of tissue in a different manner. A discussion of this kind should include a composite interrogation of commercial companies that specialize in tissue collection and distribution, such as Asterand plc (see ibid.), and is beyond the scope of this essay.

28. The Royal College of Pathologists, Pathology: The Science Behind the Cure, "Review of the UK Health Research Funding—The Cooksey Review: Comments from the Royal College of Pathologists," July 20, 2006. http://www.rcpath.org/resources/pdf/CookseyReview-CollegeResponse-July06.pdf.

29. Joan H. Fujimura, "Crafting Science: Standardized Packages, Boundary Objects, and 'Translation,'" in *Science as Practice and Culture*, ed. Andrew Pickering (Chicago: University of Chicago Press, 1992), pp. 168–211.

30. Catherine Waldby and Robert Mitchell, *Tissue Economies: Blood, Organs, and Cell Lines in Late Capitalism* (Durham, NC: Duke University Press, 2006). A contemporary issue also related to the concept of gift is the broader debate on the "opt-in/opt-out" question of organ donation. http://www.uktransplant.org.uk/ukt/newsroom/statements_and_stances/statements/opt_in_or_out.jsp.

obligation between parties, whereby the recipient is bound to the giver by obligation to reciprocate.[31] In the case of the scientists, the act of reciprocation can be said to be manifest in the experimental findings that can ultimately be applied in the clinic. There is, however, a particularly tenuous quality to this relationship of indebtedness and obligation, and medical staff members, described as having a "cavalier" attitude toward human tissue, from the researchers' perspective are seen "not to understand the urgency from our point of view" (according to the postdoc).

The "Laboratory Phone"

The researchers' behavior in the receiving and utilizing of human tissue is quite different, as the following scenario demonstrates (as related in the interview with the postdoc):

> So, we've got a rota. We've got one phone. Whoever's got the phone gets the phone call from the hospital and needs to contact the others [in the lab]. Because you've got the phone, technically, you're supposed to be the first one coming into the lab to start setting up. So, say we've got a chunk of heart, which is a bit sad to say but . . . when the cells are very good we try to make the most of it, so sometimes we stay here all night, until the next morning [*laughs*], and if the cells are not that good—if they are arrhythmic, then it takes less time because if the cells are not stable you don't really rely on what you are going to measure.

Given the importance of the human tissue for the laboratory team, when the material is on its way to the laboratory, then the schedule for the day is altered. The effort made to receive the tissue does not rest there; because human tissue can become available at any time of the day or night, there is a dedicated telephone that members of the lab take turns in having custody of. This "laboratory phone" is a medium that signifies the value of the human tissue and the tensions surrounding the handling of it by the researchers. The staff member with custody of the telephone has to be ready to prepare the tissue for use.

Having custody of the telephone is considered a great responsibility. Researchers describe the onus to prepare the tissue in a manner that will provide maximum usage. This is not only so that members of their research community may benefit from it, but also because there is an access value to the material and as such produces a paradox. On the one hand, the researchers perceive that, in contrast to

31. Marcel Mauss, *The Gift: Forms and Functions of Exchange in Archaic Societies* (London: Routledge, 1922).

working with animal material or human stem cell lines, experimenting with human tissue is fraught with problems. Not only is the tissue implicitly a gift, but also its availability and quality is in the hands of gatekeepers whose performance is determined by other priorities and individual attitudes. Collectively, this gives human tissue a very different status than the animal model. On the other hand, working with human tissue provides an opportunity to undertake medical research for the human—on human tissue, not on a model of human tissue. This tension highlights the interesting human/animal problematic that is played out within scientific laboratories. The use of animal models in itself acknowledges the porosity of species boundaries; in fact, it is this very porosity that is central to the animal's use as a stand-in for the human. Importantly, it also highlights species hierarchies.

Outputs and the Draw of the Publication

Concerns over the access to, and supply of, human tissue are not the only reasons given for why working with an animal model is regarded as being more productive. In the academic world of science, where the mantra is "publish or perish," the animal has become a readily available model enabling experimental results and academic papers to be achieved in the minimal time necessary. Working with human tissue is considered to be poor in the production and quantity of outputs. As the head of the lab explains, because of the vagaries surrounding human tissue, many colleagues prefer not to collaborate with the group on these studies. For example, on offering human cells to one colleague (a physiologist), the response was "No, it's uncontrolled. It's going to be in the middle of the night and you'd never get enough to write a paper." The term "uncontrolled" not only refers to access and supply, but also to the unknown variables because of the nonstandard nature of this material. Many researchers do not regard human tissue as sufficiently *pure*. Their opinion is that it brings with it too many unknowns, hence it is considered to be too uncertain and a risky material to work with. As another colleague of the head of the laboratory has reportedly said, "This messing about with human tissue is just a pointless waste of time because you will never get anything, you know, definite from it."

This sense of control over the experimental material is to some extent illusory, for despite the regulating and standardizing practices put into place, the local animal house and laboratory settings themselves produce variables that may have a system-wide impact on the animal model and resulting tissue.[32] Researchers' careers are,

32. Anderegg et al., *A Critical Look at Animal Experimentation* (above, n. 3), p. 21.

however, inextricably connected to funding, and funding is related to high-impact publications that are seen as providing proof of expertise. Experiments using animal material are seductive and, as such, perpetuated by practice. A scientist trained in animal experimentation techniques may be reluctant to change to working with human tissue for several reasons: not only would she not maximize her tacit knowledge and skill, but she would also be faced with the challenges outlined above.

Therefore, the dilemma between the use of the animal model and human tissue in translational research is of significance. In a research paradigm that relies upon extrapolation, it is significant that the use of human material is seen as challenging and unproductive. As the head of the laboratory observed suggests, it would seem logical to use human tissue for research into human disease, yet cultural frameworks surrounding the use of human tissue would appear to impede both its collection and use. What is of further significance is the impact that wider social structures have on the field of medical research.

Impact of the Human Tissue Act

Existing regulations and laws also support staying within the established routines. A recent inquiry into the circumstances leading to the removal, retention, and disposal of human tissue, including children's organs, at the Royal Liverpool Children's NHS Trust (commonly called the "Alder Hey Scandal") stimulated a growing focus on research governance—the regulation of research on human subjects, including their tissue and data. In 1999, it emerged that Professor van Velzen, head of the Foetal and Infant Pathology Unit at the University of Liverpool and Honorary Paediatric Pathologist at Alder Hey, and his associates had been retaining organs and tissue for research purposes. These had been taken from around 850 postmortems without the knowledge of the hospital, its doctors, or the parents of the children.[33] These events and other similar discoveries, such as the retention of babies' hearts at Bristol Royal Infirmary in 1999, led to changes in the law concerning the retention and use of human tissue. Now, all human tissue used in research is tracked, and the Human Tissue Act of 2004 regulates all research involving the use and storage of human tissue for research purposes. For a research lab, this means recording every item of human tissue that comes into the lab and subsequently what happens to it. Although

33. Rob Innes, "The Alder Hey Case: The Institution," in *Rebuilding Trust in Healthcare*, ed. Jamie Harrison, Rob Innes, and Tim van Zwanenberg (Oxford: Radcliffe Publishing, 2003), pp. 47–57.

this is not seen as an insurmountable problem and the ethical reasoning behind it is accepted, scientists have pointed out its potentially stifling effects on research. The Human Tissue Authority (HTA) commissioned research to test the veracity of this notion, and the published results show divided opinions among the respondents.[34] Those appointed as designated individuals pursuant to the Human Tissue Act licensing regime were less likely to be negative about the impact of the legislation than were pathologists and those working in the National Health Service (NHS). Indeed, the majority of those questioned (59 percent) believed that the human tissue legislation and subsequent regulation by the HTA had a negative impact on research, with 68 percent of respondents believing that the legislation made it more difficult to obtain human tissue samples, and 61 percent believing that potentially valuable samples were being disposed of without any consideration of their scientific utility. This opinion is reinforced by the 2009 National Cancer Research Institute report[35] on fostering the involvement of pathologists in research, and the accompanying survey conducted by onCore UK in its advisory capacity to the Pathology Society.[36] The latter report addresses the need for the NHS to provide incentives for pathologists to engage both as researchers and tissue suppliers through capacity-building exercises. This includes a particular focus on streamlining the regulatory processes relating to access to tissue in diagnostic archives. The onCore UK survey demonstrated widespread confusion among pathologists concerning the relevant regulatory framework in place.

As described above, network formation is an essential part of scientific knowledge–making and success; networks have to achieve recognition and acceptance in order to be successful.[37] In order for the 3Rs imperative to be considered part of scientific mainstream practice, supply chains of human tissue have to be institutionalized,

34. Human Tissue Authority, "The Impact of Legislation and Human Tissue Authority Regulation on Research," September 2009. http://www.hta.gov.uk/_db/_documents/Impact_of_legislation_and_Human_Tissue_Authority_regulation_on_research,_September_2009.pdf.

35. National Cancer Research Institute, "Fostering the Role of Pathology in Research" (2009). http://www.ncri.org.uk/includes/publications/reports/NCRI_PathologyReport_electronic2.pdf.

36. onCore UK, "The Effect of Regulation and Governance on Research Led by Pathologists or Involving Pathology in the UK: A Report of the Survey Conducted by onCore UK . . .," July 2009. http://www.pathsoc.org/files/news/EffectofRegulationandGovernanceSurveyReport-onCoreUK2009-09-07o.pdf.

37. Harrington and Stephens, "A Social Science View on the FRAME Symposium" (above, n. 25).

and work with human tissue would need more support within the mainstay of contemporary biomedicine—namely, in peer-reviewed research, by universities and commercial structures, and by government funding. Challenges to the 3Rs agenda will come from the entrenched invested interests of animal-procurement industries, and hence, by necessity, the replacement, reduction, and refinement of animals in scientific procedures will need both top-down and bottom-up support, including systems that make the use of nonanimal models conducive in day-to-day practice. The quote below by the head of the lab captures the manner in which a moral and pragmatic analysis of the replacing of animal models is framed against the achievement of funding. It highlights the negotiation of aims that takes place in the context of justifying the move away from animal models:

> I have the techniques that we use to analyze adult cardiomyocytes to try to adapt them to look at the stem cells that have their own particular sort of features, I won't say problems, but features. . . . So this is why I have sought funding from the NC3R's, for example. I can see that there is a very clear possibility of replacing some of the [animal] models we use. . . . We don't really have a very good [stem] cell line for cardiac and we have to use neonatal cardiomyocytes, which means you have to kill litters of rat pups and so that's a big use of animals. Not a very nice use of animals, obviously something they want to get rid of. . . . So, in terms of funding, I am looking not only for what we can do, but what we can do that other people can't do—that is what you are looking for when you write a grant.

Conclusion

The ethnographic study I carried out in stem cell laboratories indicates that the laboratory space is composed of various collectives that are dependent on a niche environment. Researchers build up a platform for their core area of expertise with resources such as the skills of long-term personnel, preferred animal models, specific technologies, and relationships with certain stakeholders, including, in some cases, collaborations with hospitals in order to receive human tissue. These are complex constellations. The main focus of each laboratory is on experimentation, analysis, and the writing of articles for peer-reviewed publication. This practice legitimizes and reaffirms the constellation of the groups, both human and nonhuman, providing the resources in order that the laboratory may continue its work. It is the location where models, be they animal, human, or otherwise, are worked on in order to procure and transfer knowledge. The successful extrapolation of this knowledge has

then to be interwoven into the translational program—the laborious transformation of knowledge through successful clinical trials and out into the wider population. In such a tenuous environment, it would seem logical that all conceivable routes to effective medical breakthroughs should be optimized. However, in spite of the acknowledged complexity of translational research and the changing attitudes in European society toward animal research, as indicated by the recent EU directive, my findings show that there are distinctive obstacles and resistors to a change in practice. Specifically, there is a dependency on medical teams to cooperate in the supply of human tissue to research facilities, which is set against the backdrop of an economically challenged NHS—resulting in variable institutional support for this activity—and the complexity of the Human Tissue Act that regulates the collection and use of waste human tissue. As a result, research labs, working in collaboration with hospitals in order to access human tissue, are faced with ad hoc systems of procurement; supply often occurs outside of what are considered to be normal working hours, thus making the model of human tissue seem exceptional in comparison to the mundane animal model that is so well-established within the infrastructure of the experimental lab. The performance captured in the ethnographic detail in this essay captures the practice of science in its daily minutia and embedded habits. EU directives and mission statements from the NC3Rs and other likeminded organizations can elucidate the contemporary narratives that present human tissue as a biotechnology that liberates animals. However, it is only when consideration is given to how this can be filtered into established daily scientific practice, with its embedded experimental systems, structures, technologies, regulations, and so forth, that the desired replacement of animal models with human tissue may occur.

Acknowledgments

This work was funded by the Economic and Social Research Council (ESRC) as part of the project "Stem Cell Research in Context" (Project no. RES-349-25-0002, April 1, 2006 to March 30, 2009), which was part of the Research Programme of the ESRC Genomics Network at Egenis (ESRC Centre for Genomics in Society). The support of Dr. Christine Hauskeller and colleagues at Egenis, and the ESRC is gratefully acknowledged.