Between the Species

Animals-as-Patients: Improving the Practice of Animal Experimentation

ABSTRACT

In this paper we propose a new way of conceptualizing animals in experimentation: the animal-as-patient. Construing and treating animals as patients offers a way of successfully addressing some of the entrenched epistemological and ethical problems within a practice of animal experimentation directed to human clinical benefit. This approach is grounded in an epistemological insight and builds on work with so-called "pet models". It relies upon the occurrence and characterization of analogous human and nonhuman animal diseases, where, if certain criteria of homology and mechanism are met, the animal simultaneously becomes a patient and a spontaneous model of the human disease.

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1. Introduction

Experimentation on nonhuman animals for human clinical benefit is a highly contentious practice. In this paper we outline a new way of approaching animal experimentation through construing animals as patients. We argue that this approach can address some otherwise seemingly intractable epistemological and ethical concerns raised by research with animals. The paper will begin by setting out what the animal-as-patient involves, before showing how this new model can meet some of the epistemological and ethical challenges arising from animal experimentation practices. Finally, we will turn to consider some of the limitations of re-conceptualizing animals in experimentation on the patient model.

2. Who are animal patients?

As the name suggests, treating animals-as-patients involves regarding nonhuman animals in experimentation as akin to individual patients rather than mass-produced and expendable instruments or tools. Practically, it means enrolling animals into a clinical trial in a way analogous to that in which human patients are enrolled into multi-centre clinical trials (i.e., trials run simultaneously at a number of locations). When animal patients present to a veterinarian and are diagnosed with a condition or disease of interest for which experimental subjects are being sought, the owner of the animal is offered to allow or disallow the animal participation in the research. If an owner consents to their animal becoming a research participant, then they can remain in the owner's care, and, depending on the nature of the experiment, they may continue to reside in their own home environment while participating in the research.

On our definition, animal patients share a number of key features. Such patients should be what scientists call "natural" or

"spontaneous" models i.e., animals which, without deliberate human intervention, develop a condition or disease analogous to that found in humans. This distinguishes natural models from induced or transgenic ones where the disease or condition to be studied is brought about artificially in the experimental animal. In the case of induced models, otherwise healthy animals are subjected to an intervention that produces a specific disease or physiological condition, while transgenic disease models are genetically modified to create a disease or condition of interest. For the purposes of this paper we are not concerned with defining what constitutes an analogous condition or disease and instead accept that researchers deploy this model category and have well-formulated criteria on which they do so. Finally, rather than being bred solely for the purpose of experimentation and housed in laboratory conditions, animal patients have some other form of value or use for their owners, e.g., they are assistance or companion animals, creatures used in agriculture, zoo animals etc.

Animal patients therefore lie between two existing model types used by scientists: natural models and pet models. As explained above, patient models are effectively a subset of natural models. While so-called "pet models" (companion animals recruited into research with pre-existing diseases or conditions) are a subset of the larger cohort of potential animal patients, since pets only represent one source for animal patients. Clinical trials that employ the pet model are typically run from veterinary specialist centers and teaching hospitals. These otherwise owned and cared for experimental "patients" can be found in many domains of therapeutic research. For example veterinarians and biomedical researchers are currently working in partnership to develop techniques that use autologous adult stem cells to treat osteoarthritis in dogs (Black et al. 2008).

Therefore, although the animal-as-patient represents an innovative conceptual framework, it is worth noting that its relationship to existing scientific models demonstrates that it is not a fanciful or implausible category.

Before moving on to consider the advantages of construing animals as patients, we want to acknowledge an intellectual debt. The term "animal-as-patient" is our own, but has its genesis in the work of both Stephen Pemberton (Pemberton 2004) and Donna Haraway (Haraway 2008). Pemberton (a medical historian) has outlined what might be regarded as the paradigmatic case of a natural or spontaneous model—the development of the canine model of hemophilia A. He describes how a particular litter of Irish Setters with a blood clotting disorder came to the attention of medical researchers in the 1940s. Key to this discovery were veterinarians at Cornell University who identified the resemblance between this canine pathology and a kind of hemophilia found in humans. Once alerted to the unique characteristics of these animals, medical researchers acquired the remainder of the litter and began a program of experimentation to further examine these similarities.

At first glance it might seem that these hemophilic dogs became little more than a fruitful heuristic for investigations into human disease. However it is possible to argue that there is more going on here. In her 2008 book *When Species Meet*, Haraway suggests that the manner in which experimentation was undertaken on these creatures and the intensive efforts required to simply keep them alive illustrates how the diseased animals became in some sense patients, rather than merely experimental tools. "The puppies had to become patients if they were to become technologies and models... Lab staff could not function as researchers if they did not function as caregivers. Dogs could

not work as models if they did not work as patients" (Haraway 2008, 59).

3. Meeting the epistemological and ethical challenges of animal experimentation

The epistemological problem

The central epistemological problem for animal experimentation directed to human clinical benefit revolves around assessing the validity of extrapolation. This is the crucial step in translation when knowledge of the response of the animal model to an intervention is employed in an attempt to predict the likely effect of the intervention upon the human target. What has become increasingly apparent is that there is frequently a poor translation; that the desired correlation between the results obtained in the laboratory with nonhuman animals and the outcomes for human patients is lacking. One of the implications of such a poor correlation is that the results obtained with animals may be worse than futile for humans, they may actually be harmful since they furnish misplaced confidence about the safety and effectiveness of drugs, procedures etc. Instances where testing in animal models failed to predict disastrous reactions in humans include the widely referred to cases of thalidomide and diethylstilbestrol, and more recently the trial of TGN1412.

We suggest that three main reasons explain the poor translation between animal experiments and their application to human patients. First, and perhaps most obviously, the basic heterogeneity of living organisms means that differences in physiology, metabolism etc., contribute to different outcomes across species (LaFollette and Shanks 1996). Second, it has recently become apparent that animal experimentation is often poorly conducted and inappropriately evaluated (Pound et. al. 2004),

again limiting the possible contribution information derived from this practice can make to human health and wellbeing. Third, new research has shown that environmental factors can skew scientific results. For instance small cage size, lack of environmental stimulation, high levels of noise etc. contribute to animal stress which in turn has a demonstrated impact on physiology and the reliability of scientific data obtained from animals (Baldwin et al. 2006; Burwell and Baldwin 2006).

A number of strategies have been deployed by researchers to address these epistemological shortcomings. We will briefly outline these strategies before showing how animal patients can address such shortcomings in a more comprehensive manner. We will later expand on the additional ethical advantage of our approach.

Some researchers have sought to address the inadequate experimental design common to animal-based medical research and toxicity testing. Closer scrutiny of these practices has revealed that animal-based trials are rarely randomized (a process intended to avoid bias in selection of individuals to receive a drug or treatment being investigated that might skew trial results) or blinded during allocation and outcome assessment (blinding is a means of addressing bias in how outcomes are measured). These critics and would-be reformers argue that given this inherent bias it is unsurprising that the majority of "positive" animal trials are rarely reproduced during subsequent human testing (Hackam 2007). On this view, improved experimental methods would likely result in better translation from animal studies to human clinical benefit, though it is difficult to see how such an approach would meet concerns regarding fundamental biological differences between humans and experimental animals.

Other biomedical practitioners take a different approach. Self-identified "translational researchers" promulgate an alternative "discovery-based" investigative strategy that is directed by clinical and epidemiological observations of human diseases, rather than the bottom-up bench-to-bedside hypothesis-testing practice that characterized much of the animal-based research in late-twentieth century biomedicine (Marincola 2007). They argue that this comparative and clinically-focused research strategy (which attends to naturally occurring human and nonhuman animal diseases) has the potential to solve many of the present epistemological quandaries. However the advantages of such an approach remain speculative and as yet unproven. Beyond the different philosophical justifications given for the utility and fallibility of extrapolation, there is a paucity of empirical work on the relative contribution of different types of scientific research to medical advances. The merits to scientific progress of basic, observational, clinical, animal model based, epidemiological and in vitro studies etc. remains largely unknown. Commenting over twenty-years ago on a poorly undertaken attempt to make such an assessment, Richard Smith stated: "we need to research research so that we can allot funds in a more intelligent and less empirical and… anecdotal way" (Smith 1987, 1406). Unfortunately this deficit is yet to be rectified.

As will be explained below, the animal-as-patient offers a way of overcoming each of the translational shortcomings identified above, and in so doing enhances the quality of data captured in animal experiments, making such data more directly applicable to human patients.

The heterogeneity challenge is addressed because, as will be recalled from our definition of animal patients, these creatures

must be natural or spontaneous models of disease. Though systematic research on this question is yet to be undertaken, our provisional hypothesis is that such spontaneous models are epistemologically superior to other model types and they hold this promise for at least two reasons. In the first instance it would seem that treatments tested on natural animal models are more likely to function in a way analogous to how they will perform in humans because, just like humans suffering from a particular disease, naturally occurring models have not had a disease or condition artificially imposed on them. Theoretically at least, imposing a disease on an animal to which that animal is not naturally predisposed, and then using the resulting creature as a research subject, appears problematic in a way that undertaking research on a spontaneous model does not. Second, there are empirical cases that support this hypothesis. For instance, the hemophilia in dogs noted above and widely reported as an exemplar of predictive animal models in the pro-testing literature, is an example of the successful deployment of a number of different spontaneous models to characterize the variety of patho-physiological mechanisms that cause hemophilias in humans. In this case, geneticists, veterinarians, biomedical researchers and hematologists worked together to identify, characterize, and verify these breed-specific canine diatheses with a view to developing knowledge that benefited the health and well-being of individual humans. Rather than spend time and resources attempting to produce an artificial simulacrum of a human pathology, research was directed towards understanding the etiology and patho-physiology of an analogous canine disease. These creatures could then function as a source of biomaterials, as well as predictive models of human disease.

The key to the success of this type of animal-centered clinical research has been a reinvestment in the science of comparative

pathology, rather than any attempt to build a diseased animal on the bench-top. The potential of pet models to generate biomedical knowledge has been further enhanced by the extension of increasingly elaborate forms of medical care to companion animals. For example the utility of modern genomic medicine rests on an assumption that an individual's pathology should be understood and hence characterized as a manifestation of the interaction between the organism and its environment. The recently completed description of the canine genome has provided a facility to include the comparative investigation of gene/environment interactions in the etiology and treatment of many of the diseases we share with our animal companions (Ostrander 2000). On this basis there are a number of pilot studies and clinical trials being undertaken treating pet canines using drugs that have the potential to benefit human patients with similar types of cancer and malignancies (London et al. 2009; Vail et al. 2009).

Treating animals as patients rather than disposable resources or tools will also support higher standards of care in animal experimentation and reduce the kind of methodological shortcomings that have plagued the practice. Arguably researchers accountable to animal owners may perceive animals in experimentation as less expendable and more valuable than creatures purchased or bred for experimental purposes. Such an attitude may ensure data is collected in such a way that protocols and entire experiments are not needlessly repeated. Tracking and longer-term follow up of animals would also be enabled by the enrollment of animal patients through veterinary clinics.

Finally, the use of animal patients can address the problem of environmental stressors which distort the outcomes of laboratory experimentation. Animal patients will deliver better

quality data because, where possible, they are taken away from the traumatic laboratory environment, removing the possibility that trial results are skewed by adverse or abnormal laboratory conditions. This will also more closely mirror the experience of human patients, since animal patients are functioning in their everyday context, like similarly afflicted humans.

The ethical problem

The ethical issues that arise with animal experimentation are perhaps more widely appreciated than the epistemological ones. In short, and without entering into the contested territory of different theoretical approaches to animal ethics (rights based, utilitarian etc.), a concern about the ethics of animal experimentation arises because it is a practice which both causes harm to those animals involved (either directly as part of the experiment or as a result of the conditions in which they are kept), and generally furnishes no compensating benefit to individual experimental animals or their species of a kind which might be considered to ameliorate such harms. It should be noted that although on first blush it might seem that appeal to the language of costs and compensating benefits to describe the ethical problem is to beg the question in favor of a utilitarian/consequentialist approach; this is not the case. Distributive justice frameworks can also appeal to a fair allocation of burdens and benefits in a way that is entirely consistent with a non-consequentialist ethics.

The current strategy adopted to address these ethical issues, and one widely favored amongst scientists and animal research ethics committees, is to suggest that a kind of truce or agreeable middle ground is possible if Russell and Burch's 3Rs are followed i.e. to Replace, Reduce and Refine the use of animals in experimentation (Smith 2001). The impetus provided by the

3Rs is for researchers to use alternative "non-sentient" models when they are available (Replace); to use as few animals as possible to generate the predictive data (Reduce); and to develop and deploy techniques to minimize animal pain and suffering (Refine). The 3Rs' focus is explicitly on welfare, on improving the conditions borne by the nonhuman animal subjected to the experiment and so begins from the premise that provided attempts are made to fulfill the 3Rs, then the practice of animal experimentation is itself morally permissible. According to the 3Rs, animals who qualify as experimental subjects (i.e., those who are not excluded by virtue of the Replacement and Reduction strategies) are still treated as expendable tools and are generally killed at the experiment's completion or after participating in a series of experiments. The 3Rs also do not attempt to address the deeper epistemological issues implicated in experimentation, rather they are predicated on the fact that experimentation is scientifically sound. So although the 3Rs can meet some of the ethical concerns with experimentation, they do little to satisfy those who doubt the epistemological validity of these animal-modeling practices. Implementation of the 3Rs may however unintentionally deliver epistemological benefits. For instance, the pursuit of replacement strategies might result in the collection of higher quality data.

As noted above, treating animals as patients provides a means of dealing with these epistemological issues, while simultaneously addressing substantive ethical questions. Regarding animals as patients leads to a significant shift in the balance of harms to benefits for animals involved in research. Unlike conventional experimentation on nonhuman animals, if an individual animal is suffering from a particular disease or condition and is treated as a patient, then they may receive any benefits that flow from the experimental drug or treatment they receive,

just as human participants may in Phase II and III clinical trials (Phase II trials test for safety and efficacy and involve a small group of participants suffering from a particular disease or condition that a drug or intervention seeks to treat, while Phase III trials enroll an expanded patient cohort). This is not to deny that animal patients may be harmed (just as human participants in clinical trials may), but simply to affirm that harm is not an inevitable outcome of patient based experimental practice. In addition to individual animals potentially benefiting through receiving an effective treatment, animals involved in research are not routinely killed, nor are otherwise healthy animals exposed to alien diseases. Beyond any individual benefit, the data collected as part of the comparative research strategy can also feed into veterinary medicine in terms of both baseline biological knowledge about a particular natural disease or condition, as well as mechanisms to treat such diseases and conditions. This is in stark contrast to animal experimentation as currently practiced which (unless specifically oriented to veterinary questions) is solely concerned with deriving benefits and knowledge for human clinical medicine.

As discussed above, on a patient based approach it is possible to conceive of moving much experimentation out of the laboratory, a source of both ethical and epistemological concern. The frequently sterile conditions in which experimental animals are kept with the lack of nurturing, an absence of access to their fellow animals and species normal activities etc., present major ethical hurdles which presumably do not exist if patients are living in their usual 'home' environment, being cared for by their owners.

4. The limitations of animal patients

Though we argue that animal patients demonstrate both epistemological and ethical promise, the limitations inherent in such an approach need to be acknowledged.

There will not be spontaneous models available for all the diseases suffered by humans. This seems to be clearly the case where diseases and pathologies are the result of the particular range of options and choices available to humans which are not readily available to other creatures - for instance humans can smoke, consume recreational drugs, eat large quantities of fast food etc. and all these behaviors result in well recognized adverse health outcomes, conditions and diseases. The relationships we now develop with our companion animals, however, mean they may increasingly experience similar diseases to us. For instance the recent rise in lifestyle diabetes among cats appears to furnish a spontaneous model for human lifestyle induced diabetes. A further limitation of this approach is that the use of animals in testing for disease only represents one way in which animals are used in research. Nonhuman animals are also used in toxicology testing, vaccine development, for education and research training etc. Where the purpose of the experiment does not relate to examining diseases or conditions, animal patients are not immediately applicable.

5. Conclusion

Adopting a patient based approach to experimentation on nonhuman animals would represent a significant departure from the status quo. It would result in a much more limited and modest experimentation, as fewer animals (both in raw numbers and in terms of animal species) would qualify as patient models compared to those currently deployed, and the range of diseases and conditions investigated would be curtailed.

However, given the epistemological and ethical problems that continue to plague the practice of animal experimentation, it is a strategy that is surely worth evaluation. We maintain that construing animals as patients rather than disposable tools or materials can facilitate a shift in how they are both regarded and in turn treated in experimentation. Such a re-conceptualizing move can highlight similarities in experimentation as practiced on human and nonhuman animals that might otherwise be passed over, and can therefore enable lessons learned from experiences with the former to be extended to the latter. The patient based approach is also attractive because it represents a type of compromise, conceding something to the two opposed sides of the debate over animal testing, while failing to assent to either extreme. The patient model effectively represents a denial both that all experimentation undertaken is essential to safe and theoretically well-grounded medicine, or that all experimentation is futile and should be abolished. It should also be clear that this proposal does not represent idle philosophical speculation entirely untethered to reality; experience with pet models shows the empirical plausibility of animal patients when considered in terms of data obtained and the willingness of owners to participate in such research. Even if the patient model in its strictly articulated form proves too radical to be widely adopted, it offers a new position in an old debate and a way of re-conceptualizing the territory that has the potential to move forward reform of animal experimentation.

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