

BETWEEN THE SPECIES

Animal Models for Human Disease: Reflections from an Animal Researcher's Perspective

ABSTRACT

Neuronal ceroid lipofuscinoses (NCL) are a group of lethal inherited neurodegenerative disorders in humans and many animal species. My research on sheep and cattle with NCL raises critical questions on a range of ethical issues, specifically the claim that sheep and cattle are useful models for the disease in humans and other related moral problems. My reflections on moral status of animals and validity of animal models are outlined in this paper.

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1. Introduction

As a veterinarian and animal geneticist, my key research interest has been the development of diagnostic tests for inherited disorders in livestock. More recently, I developed an interest in bioethics as my research on sheep and cattle with the lethal inherited neurodegenerative disorder neuronal ceroid lipofuscinosis (NCL), and the claim that these animals are useful models for NCL in humans, created a need to reflect on the validity of these animals as models for human disease. Furthermore, meeting children suffering from NCL and their families and attending NCL conferences created awareness of many other ethical dilemmas in relation to rare inherited disorders, genetic testing and the difficult task to find a cure.

This paper, which focuses on the use of animals as models for human disease, introduces NCL as a rich case study for bioethical considerations relevant to the use of animals as models for human disease. I argue that the utilitarian approach that underpins legislation relating to animal research is not resolving scientists' need to assess if their work is permissible. I also suggest that a principlist approach might be more useful for dealing with the complexities of specific medical research questions, the moral status of animals and the validity of animal models, as this approach allows various stakeholders to engage in discussion and in decision-making processes.

2. Neuronal Ceroid Lipofuscinoses

Neuronal ceroid lipofuscinoses (NCL) are a group of recessively inherited neurodegenerative disorders in humans and animals. NCL have been described as the most common inherited neurodegenerative disease in childhood, affecting an estimated 1 in 12,500 children worldwide (Rider and Rider 1999). These disorders are characterised by common clinical

signs and pathology, such as progressive visual impairment leading to blindness, progressive mental and motor deterioration, seizures, brain and retinal atrophy and accumulation of fluorescent storage material in lysosome-derived organelles. NCL result in premature death as there is currently no cure for any form of the disease. Different variants of the disease have been described—initially, based on differences in age of onset of disease, rate of progression and type and structure of storage material—and more recently based on the more than 10 genes identified as having disease-causing mutations (Mole 2011a). The identification of disease-causing genes has improved diagnostic approaches (Kousi et al. 2012) but the identification of these genes has not yet provided a breakthrough in the understanding of the disease mechanisms. Various experimental therapies (e.g., gene therapy, stem cell therapy and various pharmacological therapeutic approaches) are being evaluated in clinical trials on children affected with some variants of NCL (BDSRA 2011, Mole 2011b).

Numerous ethical issues can be identified in relation to this group of diseases (e.g., dilemmas relating to research and clinical trials involving vulnerable participants; use of new biotechnologies such as DNA testing, gene therapy, stem cell therapy and enzyme replacement therapy; and public health issues relating to rare diseases such as delayed diagnosis and limited funding for care of affected children, support for families and research)—which will not be discussed in this paper.

The disease has also been identified in many animal species including dogs, sheep, cattle, ferrets, cats, horses, goats and pigs (Palmer et al. 2011) and mice (Cooper et al. 2011). The forms of NCL found in domesticated production and companion animals and some mice are caused by naturally occurring

mutations. In all these cases, diagnosis and research into NCL in animals is of veterinary interest in its own right. The use of these animals as models for human disease has been claimed by many researchers to be crucial in the investigation of this group of diseases and has been proposed to be central for the development of a better understanding of the disease mechanisms and the development and evaluation of possible therapeutic approaches. Some of these large animals have therefore been bred and used successfully as models for the human diseases (Palmer et al. 2011). In addition, genetically modified mice as well as yeast, nematode worms, fruit flies and zebrafish have been generated to create models for the many variants of NCL.

My own research focuses on sheep and cattle that are affected with NCL (Houweling et al.2006; Tammen et al. 2006;Frugier et al. 2008). Initially the research concentrated on the identification of disease-causing mutations in these animals for diagnostic purposes in livestock industries. Meeting human patients and their families at conferences, and exposure to funding opportunities from human medical research grants, created an interest in maintaining and using sheep as models for the corresponding human disease. As I am directly involved in this research, and thus biased, I will not aim to defend specific aspects of the NCL research in this paper. Instead, I will reflect on more general issues relating to the use of animals as models for human disease.

3. Personal reflections on moral status of animals and validity of animal models

As a veterinarian and animal geneticist I have a strong interest in conducting ethical and scientifically valid research. The shift from conducting research on animals for the benefit of animals to conducting research on animals as models for human

disease instigated reflections on the moral status of animals and the validity of animal models. The use of animals as models for human physiology and pathology has a long and at times controversial history (e.g., Guerrini 1989; Paixão and Schramm 1999; Baumans 2004) and is debated widely from divergent and constantly evolving standpoints. Key issues in this debate are disagreements among philosophers relating to the moral status of animals, as well as disagreement among philosophers and scientist in relation to the validity of animal models.

4. Moral status of animals

There are three major positions in relation to the debate on the moral status of animals (Sandøe et al. 2008). There are the two extreme positions: animals either don't have a moral status at all (and thus can be used for any research), or they are considered to have a moral status equivalent to the moral status of humans (and thus cannot be used as a mere "means to an end"). In between these extreme positions is a third position that comprises a continuum of viewpoints held by representatives of various philosophical frameworks (and apparently the majority of the population): that animals have some moral status although of a lesser degree than the moral status of humans—which allows the use of animals with varying levels of limitations. This continuum of viewpoints reflects differences in philosophical standpoints, as well as differences in cultural, socio-economic and religious backgrounds (Legood 2000; Gilbert et al. 2005). Even within a philosophical framework, views on the moral status of animals are often debated. Another important issue is that the perceived moral status of animals often depends on the species concerned. This perception can be based on scientific (e.g., phylogenetic relationship to humans, complexity of nervous system or level of sentience) or emotional considerations, which are often associated with the role

that different animals are perceived to have in our society (e.g., companion animals versus livestock versus rodents).

A moderate utilitarian viewpoint has been adopted to underpin animal welfare legislation and regulation in many countries. Moderate utilitarianism considers that animals have some moral status and accepts a balancing of the costs to one moral agent versus benefits to another moral agent. This should create some certainty for scientists on how to assess if their research is permissible—at least on legal grounds. It provides a basis for comparing the implicit need to minimise suffering in animals and to prove adequate benefits of research, these being key criteria that allow for the development of workable compromises in animal research (Ryder 2006; Sandøe et al. 2008). Unfortunately, what sounds like a simple requirement is in reality a difficult task, specifically as there remains uncertainty on how to accurately define and measure the suffering of animals, how to exactly weigh suffering between moral agents of different species (including humans), as well as how to assess how moral agents benefit from research conducted in other moral agents (of the same or different species). It thus remains often difficult (for animal researchers and animal ethics committees) to decide where to draw the line between what is ethically acceptable and what is not. Even if the difficulties of the utilitarian calculus could be overcome, animal researchers are still faced with the need to defend their research against those disagreeing with the moderate utilitarian approach.

A principalist approach (Beauchamp and Childress 2001) might be more useful to guide moral action in relation to the assessment of dilemmas concerning animals. Due to the failure of most normative approaches in biomedical context, Beauchamp and Childress (2001) suggested that a process of “shared

moral reflection”, with the aim of balancing the four principles of respect for autonomy, non-maleficence, beneficence and justice, can guide moral action in situations of difficult-to-resolve ethical dilemmas. In contrast to utilitarianism, some norms cannot be balanced, and disagreement is a tolerable component of this approach due to the acceptance of validity of pluralistic views. Disagreement about the moral status of animals and lack of exact measures for suffering of animals and benefits of research are thus not limitations for this method. Mepham (1996) has applied principlism in an animal context by developing the “Ethical Matrix”, which allows for the additional complexity when agents beyond just the single class of humans need to be considered. This ethical matrix has been considered by others as a useful decision-making tool in relation to issues concerning animals and humans, as it provides structure in participatory interdisciplinary approaches without pre-empting content or evaluation or ignoring pluralism (e.g., Kaiser and Fosberg 2001).

5. Validity of animals as models for human disease

In the discussion about validity of animal models in biomedical research it is important to first consider how models are used in scientific research and to consider any differences in how models might be used in different disciplines. Scientific research identifies “gaps” in current knowledge and aims to fill these gaps with generalisable knowledge using appropriate methods.

The notions of truth and knowledge in science are contested, especially in relation to medical science. Traditionally, scientific validity was associated with the concept of research being “rational”, “objective” and “morally neutral”. More recently there

has been a shift (e.g., Fleck, Kuhn, Foucault and feminist philosophers such as Lloyd, Wylie and Potter) towards acknowledgement that research is “contextual” and “value-influenced” with an increasing awareness that ultimate truth does not exist in science. Orthodox medicine has defined itself and differentiated itself from non-orthodox medicines with the claim that it is based on unbiased scientific method (Sullivan 1993). It has to be noted that medicine is different from many other scientific disciplines (such as mathematics or physics), largely due to the complexity of biological systems. Knowledge in medicine is unlikely to be absolute but in most instances probabilistic; bio-medical theories often lack generalizations of broad scope and have been described as “structures of overlapping interlevel temporal models” (Schaffner 1986).

Models are generally accepted as valuable tools in scientific experimentation and a large number of model-types have been defined and discussed in the scientific and philosophical literature. From a philosophical position, discussions about models explore questions relating to the representational function they perform (semantics), to what they are (ontology), and to how they assist in learning/knowledge-generation (epistemology), to how they relate to theory and to how their use sits in the contexts of debates over what science is (Frigg and Hartmann 2008).

In semantics, models can be understood as representations of a selected part of the world which are used to picture phenomena or data, or they can represent a theory and are used to test these theories (Frigg and Hartmann 2008). Animal models can be understood as representational models of phenomena and are largely understood as analogical models (i.e., animals have certain relevant similarities to humans) but can also have

some aspects of idealized models (e.g., simplification of genetic variation and environmental factors using inbred mice lines under laboratory conditions). However, in regards to analogical models there is debate as to what level of similarity is needed or which similarities are relevant. Interestingly, Mary Hesse distinguishes between positive, negative and neutral analogies (positive analogies are those features which are shared by both systems, negative analogies are those features which are present in one system but absent in the other, and neutral analogies are those features whose status as positive or negative analogies is uncertain at present) (Frigg and Hartmann 2008). This is of interest in the context of animal models for human disease as the neutral analogies (i.e., those properties of animals for which it is not known yet whether they are similar to humans or not), which are often used to criticise the validity of animal models, are considered by some researchers to be of great importance, as they are useful for the development of questions and hypotheses (Frigg and Hartmann 2008).

The epistemologic discussion of how we generate knowledge using models is of great importance. Hughes (1997) suggests that learning with models happens in three stages—denotation, demonstration and interpretation. We learn in the process of choosing the “best” model as we explore differences in “representation relation” or analogy between different species/breeds/age groups and humans (denotation). We then conduct experiments with the animal model and learn about the model (demonstration). Finally, we draw conclusions from the research in relation to human disease (interpretation). In relation to the discussion of validity of animal models for human disease, concerns are related to all three steps.

IMKE TAMMEN

Firstly, it is not always clear which species is the best model for a specific biomedical question—and the most similar species is not always the most practical model. Furthermore, the increase of similarity/analogy between different animal species and humans is for many associated with an increase in moral status of animal species (e.g., Nordgren 2002; Wolfensohn and Lloyd 1995) and thus the most similar/best model might be least defensible on ethical grounds. It can be argued that the use of multiple species as models for different aspects can increase validity of animal models for human disease, e.g., genetically modified knock-out mice might be useful to generate some knowledge about which genes cause which inherited diseases but large animal models are increasingly considered to be more useful in the context of evaluation of therapeutic approaches for inherited diseases (Ellinwood and Clay 2009).

Secondly, concerns have been raised with the quality of the research conducted on animal models, suggesting that research design and methodology in this research field are often flawed (Pound et al. 2004; Perel et al. 2006). However, many other studies defend the validity and relevance and thus implicitly the quality of research on animal models (e.g., Botting and Morrison 1997; Morrison 2002). This debate is useful, as it is likely to improve the quality of research related to animal models and provides some arguments that a strong focus on reduction in animal numbers needs to be carefully balanced with considerations for appropriate research design.

Thirdly, research on animal models has been critiqued because knowledge gained from animal models does not reliably translate to the human context. Awareness that an interpretation stage is an essential part in the process of learning from models clearly identifies that any assumption that knowledge from ani-

mal models can always be directly applied to the human context is unrealistic. This interpretation needs to consider that animal models are representations of and not identical to humans and there needs to be awareness that negative and neutral analogies exist between animal models and humans and that many animal models are simplifications or idealizations of disease in humans (e.g., the above-mentioned inbred mouse lines, which lack genetic variation and the use of experimental designs to minimise environmental variation). Furthermore, it needs to be remembered that disease in humans is often complex and probabilistic in relation to its causes. As a consequence, converting knowledge about the animal model into knowledge about human disease should always occur with considerable caution. Not all animal models provide results that are directly and reliably transferable to the human context and thus research on animal models alone is not sufficient proof to confirm research hypotheses relating to human disease. However, I argue that this is not expected if one understands semantics and epistemology of models and although the knowledge might not be directly transferable, knowledge is generated and new hypotheses can be developed that will ultimately assist in the development of better understanding of disease. Consequently the model still has validity from an epistemological view.

Validation of animal research in the human context is necessary and, consequently, carefully supervised clinical trials in humans must follow the results of research on animal models. From my position, research using animal models can be valid as long as the representational function of the model is clearly understood and care is taken when knowledge is translated to the human context.

6. Conclusions

It has been observed that “...*moral reality is less tidy and more complex than many theories portray*” (Li 2002, 589).

In relation to ethical questions, the co-existence of well-informed divergent views, which are based on different philosophical, cultural, social and/or religious frameworks, is the norm. It is only respectful, considerate and open-minded discussion of these divergent views that enables society to develop approaches to deal with the underlying ethical dilemmas. The continuum of views in relation to the moral status of animals is the main reason for an ongoing and intensive debate. Inherent in the “middle way” view of the moral status of animals is the acceptance that in some situations animal use in research can be morally justified, e.g., if alternative approaches of equal effectiveness are unavailable, if humankind benefits from the research and if every attempt is made to reduce the suffering of animals. Much healthy debate is related to defining how much suffering is acceptable for what benefits, and these discussions have resulted in many improvements to regulation, legislation and transparency of animal use and consequently improved animal welfare.

As our understanding of animals’ capabilities and limitations improves over time, it is important to recognize that what is considered as permissible today might not be permissible in the future. This requires researchers to continuously reflect on their practice.

As a scientist who is involved in research on an animal model for human disease, I acknowledge that I am biased when defending the validity of animal models to generate knowledge that is useful in the context of human disease. It needs to be

stressed that not all animal experimentation is acceptable and not all of animal-model research is valid, that animal models are only one of many routes to gain knowledge in the medical context, and that there are matters of degree in validity, partially relating to the species used, the medical question investigated and/or the type of knowledge that is claimed to be gained (e.g., explanatory or predictive information). Furthermore, research relating to animal models needs to be conducted to high professional standards: it needs to fulfill ethical, legal and professional requirements. Also, care needs to be taken in what conclusions for human disease can be drawn from the results of animal experimentation. It needs to be clear that a model is a model and thus a simplification and/or analogue of the target of interest and that the target of interest—disease in humans—is often complex and probabilistic in relation to its causes. It is therefore the researcher's responsibility to clearly outline the advantages and constraints of using animal models, and not to over-generalise or overstate the results obtained from such research—especially in communications with non-scientists.

Considering that animals can be understood as vulnerable research participants with difficult-to-define moral status, and that the moral benefits of research are also difficult to define, it follows that the calculus of the moderate utilitarian approach to the use of animals in research (the approach that underpins current animal research regulation), appears unattractive. Principlism presents itself as an interesting alternative. It is widely accepted as a practical approach for ethical decision-making in the medical context and is increasingly used in animal contexts using Ben Mepham's "Ethical Matrix". A key strength from my point of view is the acknowledgment of existing uncertainties, recognition of the need to interpret ethical principles in case-specific context, acceptance of validity of pluralistic

views and the emphasis on identification of ethical dilemmas for various stakeholders in the system. This encourages interdisciplinary participation (e.g., animal ethics committee members would not be restricted to the utilitarian framework and more researchers as well as humans benefiting from animal research might feel encouraged to actively engage in ethical debate and decision-making processes). It appears crucial to educate researchers involved in animal experimentation in regards of bioethics so that they can effectively participate in such “shared moral reflection”.

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IMKE TAMMEN

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IMKE TAMMEN

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IMKE TAMMEN

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