

# The Animal as Sentient Being

Some Implications for Guidelines, Regulations, and the Wider World of Biomedical Research

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*The Science can Change the Policy, and the Policy will Change the Science*

-- Sebastien Farnaud

On December 1, 2009 European Union member states ratified the Treaty of Lisbon, which grants legal status to animals by virtue of sentience. This was a defining moment in the age-old debate about whether animals feel pain and if so, whether they know it and suffer. It was also the culmination of decades during which animal welfare had risen in political importance.

Conferring sentience signalled the coming of comprehensive guidelines and tighter regulations regarding treatment of live animals used for experimental and other scientific purpose. Henceforth, investigators will not only show cause for a design using animals; the design would incorporate best practice in animal well-being. Among other things, that means delimiting suffering at every stage, from transportation through experimental procedures and levels of pain, and where applicable, to end of life. It means showing due diligence in providing an environment within which each animal may express species specific behaviour and consistently monitoring for stress. And, it will mean transparency.





This last, the demand for transparency, goes beyond the legislator's office and the lab. Biomedical research is under the microscope in many European as well as North American countries where members of the general public hold very strong views about animal welfare and animal rights. In the United States, there are 117 animal welfare courses taught at law schools and undergraduate universities. In Switzerland, there are animal advocate lawyers in many cantons and in Zurich, one who is a public prosecutor. This is not surprising considering that in 1992 the Dignity of Creatures was embedded as a principle of the Swiss constitution, and in 2008 the Dignity of Animals was the pivotal proviso for the country's first Animal Welfare Law. In the Netherlands' 2006 election, a new political party, Party for the Animals, won two of the 150 seats in the Dutch House of Representatives, and in the 2007 Provincial States elections, Party for the Animals won nine seats in eight provinces and one of the seventy-five seats in the Dutch Senate. Finland has established a National Ethics Committee which aims to harmonise practices that reduce the number of animals and both reduce and streamline procedures. In the UK, the high ground on animal welfare, once sparsely populated by passionate humanitarians and also by some outlaws, is a busy place now and the call of many voices is a familiar chorus: we will move ahead proactively on the 3R's. The UK already has some of the EU's strictest licensing regulation.

## THE YIN AND YANG OF BIOMEDICAL RESEARCH

Unifying the interested parties is a rising tide of conviction that the animal as sentient, dignified being stands right alongside the need to treat and cure serious disease. Reflection on this duality, for many the yin and yang of biomedical research, has raised compelling ethical, scientific, and philosophical dilemmas for many biomedical professionals.

To begin with, there are distinct and different conceptions of sentience, and there is a continuum of beliefs about whether sentience confers rights. There is much rhetoric on whether all living creatures, rather than only those with vertebrae, are sentient and whether early-stage embryos are protected. There are deliberations about whether an animal's phylogenetic status can justify or disqualify an animal as ethically and morally allowable for use in research.

Other, practical questions arise. Party for the Animals writes that our ecosystem is largely an arrangement whereby nearly all animals kill other animals in the natural course of survival, but we may not

take that fact per se as license to kill for other reasons. Yet, an EU staff member reminds, thanks to expertise in biomedical research, the EU has developed, and now produces, over 80% of the world's vaccines. Where is the compromise? Another practical matter: the animal as sentient, dignified being is entitled to express species specific behaviour; where is the balance to be struck between replicating natural environments and what's possible in a vivarium—and could any of that that be regulated?

And, there are some contentious, some would say indelicate, questions. Do animal studies earn their keep in treatments that succeed at clinical trial? Will stringent regulation send investigators to places where animal welfare is much less well regulated? Should investigators themselves, instead of technicians, kill their animals in order to confront the complexity first-hand? And for some there are poignant questions such as: once you agree that an animal is sentient and also that you will use the animal for experimentation, are you judging that all lives are not created equal?

"There are always the two forces", says Susana Chuva de Sousa Lopes, Head of the Mammalian Germ Cell and Stem Cell Biology Group at Leiden University Medical Centre, a teaching and treatment research institution specialising in complex medical issues. "I have feeling for each animal, no matter how many I work with. And I feel always that I want to do the research—that I must do it. So the most responsible thing I can do is to make sure that every project using animals is essential and is the most efficient design; and of course I am always looking for ways to reduce the number of animals I use—and to be sure my work is meaningful".

## INTERNATIONAL LAW

Beyond the internal conversations and debates, there are questions of international law.

"This is a very sophisticated matter," notes Andrea Gavinelli, Head of Animal Welfare for the European Commission Health and Consumers DG. "The stature of the animal as sentient being is established. Research managers across Europe must implement higher standards uniformly and also as quickly as is reasonable. I believe this will not be a problem, since on their own initiative, individual investigators all over the world work enthusiastically to refine and reduce. But few states have legislative frameworks as in the EU. Yet, we must keep competitive outside Europe. Since we don't have possibility of extraterritorial animal protection rules, this is fast becoming a matter of negotiation and influence".



Dr Mark Matfield, Director, the European Biomedical Research Foundation and a steady voice of lab animal research professionals for many years, agrees. "The very first legislation was in the Cruelty to Animals Act of 1876, and since then the drive for excellence and careful documentation has evolved to a very high standard of good practice. But there's a big gap, and actually animal protection is not common around the world. In many places there are non-specific high level statements, and in too many places animal welfare doesn't get a mention".

### CHANGING SOPS

Despite the dilemmas and challenges, biomedical professionals across Europe continue to raise the bar on standard operation procedures.

"Animals are increasingly treated with dignity", Susana Chuva de Sousa Lopes says. "Electronic databases assign each animal a number. That facilitates monitoring and ensures that each animal is used only for an ethically approved project. In the area of husbandry, there is a gradual change to more sophisticated SPF (specified pathogen free) conditions".

The minimum size of the cages has increased, and inside the cage you are more likely to see shredded paper or paper tissues, fatty seeds, and hollow tubes that the animal may use to retreat from light and for nesting. "The tubes are made of red plastic that the mice experience as black so we can see them inside but they experience darkness there", Dr Chuva de Sousa Lopes continues. "The tubes have a couple of holes that the animals can use as different entrances. When these tubes are available, the animals usually sleep and raise their nests inside those devices.

"Anaesthesia devices and equipment used for recovery from surgery are more sophisticated. Everyone is more aware of the 3R's; when requesting permission to use experimental animals you need to justify explicitly what will be the social and medical benefits and well as what type of alternatives are available to the use of animals to solve your specific scientific question.

"In developmental biology research, embryonic stem cells allow investigators to use fewer animals, as the use of these cell lines allow researchers to study developmental mechanisms in a more homogeneous and controlled environment, in particular if we want to understand how specific organs are formed and can be repaired. Even though to generate bona fide embryonic stem cells we use a very early embryo of about 100 cells (three days after fertilisation in the

mouse), the application of such a cell line worldwide by different labs to answer many scientific questions helps greatly to reduce and (partly) replace the need to use experimental animals".

### AUTOMATIC ALERTS

At the Netherlands Cancer Institute, an electronic system alerts technicians and investigators when an animal starts to develop an anomaly or show signs of illness. Marco Breuer, Head of the Lab Animal Facilities of the Netherlands Cancer Institute, explained how it works.

"We have 25,000 mice residing here on any day. Sometimes tumour development or other clinical signs causing distress is an anticipated result of an experiment or the animal has become ill in other ways. In any case we wanted to improve the time between an animal showing these signs and the investigator attending to it.

"That would mean reducing to absolute minimum an animal's discomfort or suffering, and improving the speed with which the investigator could collect data. Toward that end, we developed an automated email system. If an animal shows signs of distress or anomalies, the animal caretaker scans the animal ID and a welfare code corresponding to the observed clinical signs. The system then automatically sends an email with all the information to the investigator. At the moment we are planning to supplement this with text messaging alerts during weekends. Using this system we are confident that the investigators are informed about the health status of their animals and thereby reducing the animal's discomfort and loss of data".

### IMPROVING METHODS

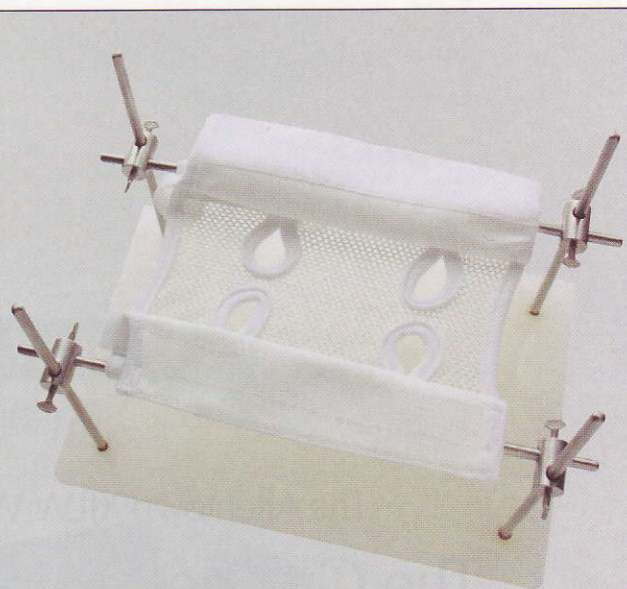
At the University of Oulu in Finland, Veterinarian and Director of the Laboratory Animal Centre Hanna-Marja Voipio says she is exacting when it comes to reduction and refinement. "To me it is important to follow regulations and recommendations strictly and help researchers to prepare experimental protocols considering all possible refinement. This means taking the time to pay close attention to small details in daily work. Our animals have a lot of space, nesting boxes, and other types of enrichment. Rabbits run in pens every day which clearly makes them happier and the chance for good results is improved. We take every chance to refine procedures; for example, we take all the DNA samples when making the identification by ear notches. This means only one procedure instead of two and we very rarely need to cut the tail tip.



"We are especially careful to use the number of injections and eliminate pain. For example, after abdominal surgery, pain killers are used for three days or even longer when necessary. During the three years of its action, our new National Ethics Committee has harmonised many such practices. It has been many years since we disallowed orbital puncture with any animal that would awaken from the anaesthesia. Since orbital puncture is not allowed in chronic experiments, the blood samples are taken from the tail vein or hind leg vein. And for analgesia after different types of surgical procedures, we have discreet recommendations, prepared by the Finnish laboratory animal veterinarian association. Furthermore, inhalation anaesthesia is used much more than earlier and the use of imaging methods are increasing in every institute as a way of refinement."

"Along with many colleagues here and in other countries", Dr Marie-Claude Georges Courbot, Head of the Diagnosis Unit at specialist Laboratoire P4 Jean Mérieux, INSERM noted, "we are creating limits for experiments in which the animal will endure pain and suffering. Beyond that, we are developing guidelines for observing animals so we can see early indicators of illness. For example, we see if the fur is not beautiful or if the animal is not enjoying food in the usual way". To provide another dimension, Dr Georges-Courbot said, she and her colleagues consult often with their ethics committee, which notably includes, among others, an historian. And to ensure a community-wide understanding, PhD students are reminded throughout training how important an animal's life is. "Otherwise", Dr Georges-Courbot explained, "enthusiastic students may forget to ask the first question: has this already been done".

As many scientists are, Glaxo Smith Kline research teams are investing in all of three R's, including adding in new technologies wherever possible. "In the past, when we were testing an antiviral compound, we'd give mice a viral infection. The animal would become ill and death would be the endpoint. Today within twelve hours we can measure the amount of virus in an animal's lungs and the animal doesn't need to become increasingly ill," Gill Fleetwood, a scientist from GSK said. Dr Fleetwood offered another example. "Previously, when we were looking at animal models of arthritis we would allow a gradual swelling of joints. As the disease progressed, at each stage we would kill a number of the study animals so we could examine the tissue under a microscope. As the study progressed, you would need



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## feature | Animal as Sentient

a sample number of animals at each study point. Today we can use modern imaging techniques to see changes in the joint and monitor candidate compounds impact or uptake over time. This means that we can look for those changes in the same animal over time. The result is far fewer animals over time and much better science, as the control is the animal itself at different time points”.

### MANAGEMENT AND CONTROL

Not surprisingly, the granting of sentience in law has raised some issues of management and control.

With status of the animal in research a matter of public policy, inevitably there are lengthy, discreet evidentiary schemes that some investigators say are counterproductive overregulation. Dr Chuva de Sousa Lopes describes one such frustration. “We obtain permission per project, rather than per procedure. So for example, in the UK we ask for permission to use a number of mice for five years for specific scientific procedures. Here I must specify the project—for example to take stem cells from a strain of mouse we breed. But unless I specify a heart project in my proposal, I cannot share a dead animal’s heart with a colleague, even when we are using the same strain of mice and my colleague will use a different dead animal’s heart. Also, we keep the animals breeding even if there are no immediate uses for, or we are not yet permitted to use, those animals. And even when we dispose of animals, we cannot use their organs for experiments unless we have a new project approved. I will tell you, it causes pain in my heart”.

Another concern is that private sector pharmaceutical companies may do business outside the EU, thereby avoiding the EU rules. “Only about five percent of our research involves the use of animals”, GSK’s Gill Fleetwood explains, “yet we hear a lot of concern about private sector pharmaceuticals conducting research where animal welfare legislation isn’t a consideration. In fact, our core principles at GSK dictate guidelines and requirements wherever in the world we are working.

“To document our 3R’s work, a Champion of the 3R’s visits our units and locations worldwide to document initiatives and progress. Then we share global best practice with investigators, veterinarians, and animal technicians around the world. This helps broadcast news about our efforts to protect the animals, prevent harm, and move toward non-animal models to the wider GSK community. We want people who aren’t involved in animal studies to know

that we are acting on our commitment to the 3R’s. So concern that we will abuse our status as a private sector company to avoid rules is entirely misplaced, and we look to share our knowledge and advances”.

“With the new treaty on the European Union”, notes Andrea Gavinelli, “the stature of the animal as sentient being is established, and since Parliament shares decision making power with the Council of Ministers in protection of animals, the voice of the people will be heard. For example, with one million signatures from citizens of member states of the European Union, the Commission has a duty to examine the issue raised and if appropriate to recommend action. But those practices are integral to the EU and there is still the question of standards in other nations. We have a high regard and respect for differences in cultures within and outside the European Union, yet we can only try to educate, inform and influence those outside our jurisdiction to embrace higher standards of animal welfare and invest in efforts to progress the 3R’s. Of course, we will need to pay close attention to negotiation in order to avoid misunderstanding”.

### NON-ANIMAL MODELS

Perhaps as a result of the focus on sentience and perhaps as a natural next step, biomedical science is taking ever longer looks at non-animal models of research. I am grateful to Tim Watson at the UK’s National Centre for the 3R’s for pointing me to the research and technology that might one day make replacement in some research arenas a reality.

“Lab on a chip (LOC), which may be only millimeters to a few square centimeters,” Tim explained, “handles extremely small fluid volumes, and so can represent human metabolism, and measure metabolic pathway development—on a chip”.

*LOC Journal* Editor Harp Minhas says the research is applicable to animal models, and he provided some background. “Lab on a Chip is the term used to refer to (usually) thumbnail size chips, made of a variety of materials, including glass, silicon, or polymers, into which micro or nanoscale channels and chambers are accurately etched, stamped, or fabricated in varying degrees of complexity. By flowing liquids through these channels, a variety of chemical and biological functions can be carried out ranging from a simple chromatographic separation, through the growth and measurement of metabolites from single cells and tissues to the identification of DNA sequences. All these measurements have previously



been carried out on large devices that form the traditional bench laboratory; hence the term Lab on a Chip.

"With respect to animal testing, Lab on a Chip technologies have the potential to replace a great proportion of testing on live animals altogether by mimicking the various biological compartments on chip. For example, through the culture of artificial oral, stomach, liver, kidney, and digestive tract compartments on the chip and then flowing drugs and potential toxicants through these compartments to determine relevant metabolism and metabolites".

Tim Watson also pointed me to the Dennis Noble, who is developing computer models of biological organs and organ systems aiming to simulate the living organism from the cellular level. With collaborators, Dennis Noble created the first virtual organ, the virtual heart, and helped launch the Physiome Project, aiming to create computer simulations of human physiology that could ultimately be used to develop more patient-specific healthcare. "The project has created a heart so lifelike it has been used to identify new targets for drug development". Tim says. "This is a good point in time for technology—an exciting time".

## THE MIDDLE GROUND

The status of sentient being has inspired thinking anew about how to improve animal welfare without hampering the fight against diseases, and many agree that the way forward will be sensitivity, respect, and collaboration. "If people can leave entrenched polarised positions behind in order to talk about reality and compromise", Tim Watson observed, "and if we could create an environment within which scientists can talk openly about their work, we could learn from what works and what doesn't. We would make good progress while bringing everyone along. It's a middle ground we're after—a place that's usually pretty hard for people to find".

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