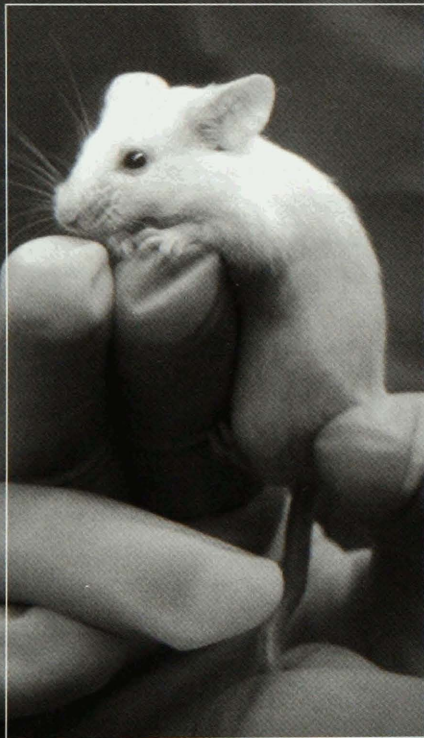


# 'THE LEAST OF THE SENTIENT BEINGS'



AND THE  
QUESTION OF  
REDUCTION,  
REFINEMENT, AND  
REPLACEMENT

BY JOSEPH VINING

The following essay is based on the keynote address the author delivered at the annual meeting of the Michigan Society for Medical Research last April in Lansing. It appears here with permission of the author, © Joseph Vining.

The subject I was asked to think about with you today is raised by a very large change in the focus of biomedical research. In raw percentage terms, the animals involved in experimentation are now overwhelmingly rats and mice, and, perhaps because they are rats and mice, they are used in large numbers, numbers in thousands and tens of thousands at some institutions.

Legal, ethical, and practical accommodation to this fact on the ground presents a host of questions. There are questions of the cost of care. There are questions of the training of veterinarians, principal investigators, and laboratory personnel. With mice particularly, there are questions about the creation of conditions in an animal that do not yet exist, a future animal, by knocking out a gene and, as we say, “seeing what happens”: new questions, really, that move us away from the traditional focus on the details of how an investigator treats a living animal.

Then there are the central questions of weighing costs and benefits, of justification and the application of the three R’s of reduction, refinement, and replacement, where it is not dogs or primates or marine mammals that are concerned, but rats and mice — for many, the least on the scale of concern for animals. Rats, mice, and birds have of course been recently exempted from the Animal Welfare Act. But that may be viewed as making the questions only that much more difficult, thrown back into the laps of researchers themselves and review boards, veterinarians, laboratory assistants, and university and corporate administrators, who for the moment can expect to have that much less outside guidance or mandate in deciding what to do. And I think it is fair to say that lying behind particular responses to questions and resolutions of issues is a newly pressing, overarching problem, which is how to *think* about rats and mice, not a new problem at all, but newly pressing.

Now I speak of the “least,” and my title is “The Least of the Sentient Beings.” But I am a lawyer, and I know that in this audience and in general view there is something vertebrate and warm-blooded that is beneath rats and mice. My colleague Mark Gallanter at Wisconsin follows the relative popularity of lawyer jokes, and has reported that the most popular lawyer jokes are lab rat jokes, such as, Why have laboratories starting using lawyers instead of rats in experiments? One: There are more of them. Two: The lab assistants don’t get attached to them. And three: There are some things a rat just won’t do.

But that opens the positive things that are said about rats and mice, as sentient beings in the world with us. Jokes aside, some of us may know of cases where a lab rat became a favorite and was adopted as a pet by a member of the lab. Rats are pets in classrooms around the country. I remember my surprise when I was in the waiting room at the vet’s and I picked up a copy of the *Rat and Mouse Gazette*, with its departments and features, the “Medical Corner,” the “Mouse of the Month” (named “Moo”), the articles on upcoming shows and rat and mouse events. You can go to the Web and read memorial testimonials: “Skin was my favorite rat. I adopted Skin in November 1998 right after my 40th birthday — a wonderful birthday present indeed! . . . Skin was a very cuddly rat and loved to nestle in my arms or lay on my lap to be petted. He was also very playful and enjoyed wrestling with my hand.” All this makes me think of the patron saint of Peru, and of the Dominican Order in the southern United States, the 16th century St. Martin de Porres, who doctored and healed slaves, Indians, and Viceroy’s and also established the first animal hospital. He was known for his way with mice, whom he could persuade to disinfest a building on his promise that he would feed them outside, which he did. His picture often has a mouse at his feet or in his hand. Indeed, a very distinguished biopsychologist, Barbara Smuts, came to a class of mine last year to talk about her work with primates and dolphins and the possibility of true mutual relationships between human beings and these animals viewed as whole beings. A student asked whether she thought a human being could have a true relationship with a mouse. She finally answered, Yes, she thought that was possible.

What then to consider, what to look at, what context to be aware of in thinking responsibly about the future of experimentation on these creatures? I would suggest four things to keep an eye on.

- **First** is that developments in experimentation on humans parallel and are connected with developments in experimentation on animals. Animal experimentation is not isolated off and a field of activity unto itself.
- **Second** is that there are developments in the science of animals beyond the biomedical field, in other subdisciplines, that will have an impact. Science advances on more than one front.

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- **Third** is that in the legal treatment of animals there are large movements, general movements, which are not the outcome of tactical battles between animal activists and research institutions, and which may affect, and properly so, the thinking of responsible decision makers in research.
- **Fourth** is that what we might call attitude is a critically important focus in any regulation of experimentation, animal as well as human.

## HISTORICAL AND CONTEMPORARY PARALLELS WITH HUMAN EXPERIMENTATION

As to the first, research on humans, it is useful to note the historical work being done now, pointing to an emergence of concern about human experimentation from concern about animal experimentation, rather than the other way around. Comparing human and animal research, people working with animals today frequently say that animals, unlike humans, cannot give or withhold their consent, and that this in a way puts a greater burden on animal researchers.

But official commission reports have increasingly revealed that consent was not much involved in human experimentation either, in the United States, up to and after the Second World War. Even today, the conceptual possibility of free and fully informed consent in human experimentation does not produce a real gulf between human and animal experimentation. A large part of human experimentation still cannot be and is not justified by the consent of the subject — experimentation on children, on the retarded or the mentally ill, in the military, on the very poor. The dilemmas and decisions end up being thought about in much the same way as in animal experimentation, weighing costs, which are deemed “ethical costs,” against hoped-for benefits, and asking at what point utilitarian thinking, justification of means by ends, of suffering by some to prevent suffering by many, comes up against a substantive limit, where there are some things that are just not done.

There is a category of experimental procedures that under the Animal Welfare Act are “unacceptable regardless of anticipated results,” to quote one research institution’s expression of it. The statute itself refers to the use of paralytics without anesthesia. I think we may find that at some point true and exquisite pain or deep distress that remains as part of a stress experiment on a rat

or a mouse after reduction, refinement, and replacement have been thoroughly explored, or genetic manipulation that produces something of the same, may not be ours to inflict deliberately. We can imagine some point where no hopes about the future can justify present reality, and I want to suggest, to those who must decide, that thinking about substantive limits or the limit to cost-benefit analysis is going on in consideration of experiments on children, the mentally ill, and others, and is there to be both drawn on and affected by in thinking about animal experimentation.

## THE DEVELOPMENTS IN SCIENCE OUTSIDE THE BIOMEDICAL FIELD

Second, in looking for guidance and context for thinking about the treatment of and the resources devoted to rats and mice, I suggest it will be increasingly important to stay open to and abreast of what is going on in the whole range of scientific research on animals.

I have been surprised, for instance, to see what scientists who work closely with fish, not as a medium of experimentation but as whole beings, say about common attitudes toward fish and their degree and kind of sentience, really questioning our general conception of fish. Oncologists, endocrinologists, and neuroscientists may need to stay abreast of scientific work in fields they might have thought distant from their own in method and even presupposition.

Twenty or thirty years ago cognitive ethology was really just beginning as a field and biopsychology would not have been found in the university phonebook. Today the situation is quite different. One telling recent product, I think, is the federal CHIMP (Chimpanzee Health Improvement, Maintenance, and Protection) Act of 2000, which rejected euthanasia for chimpanzees no longer needed for research and set up a sanctuary for them where no experimentation can be done on them, they cannot be transferred out, and (I quote) none can be “subjected to euthanasia except as in the best interests of the chimpanzee involved.” Congress adopted the majority report of a National Research Council study commission which had noted “the close similarities between chimpanzees and humans,” a conclusion the legislative history pulled out and repeated.

A large part of human experimentation still cannot be and is not justified by the consent of the subject — experimentation on children, on the retarded, the mentally ill, on prisoners, in the military, on the very poor.

Chimpanzees are not rats and mice, but much of scientific work proceeds on the presupposition and even with the motivation of showing that there is no qualitative difference between human beings and the rest of animate nature. Biomedical science is judicious in selecting its systemic similarities between animal and human models. But the default position, which determines the burden of proof, is reflected in Principle #4 of the U.S. Government Principles: “Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals.”

Going back to the first point, the parallels in human and animal experimentation and the relevance of one to the other, we should not wonder that careful scientific observation draws animals and human beings together. An unfolding general question is going to be inevitably with us, whether to treat human research subjects more like animals, or to treat animal research subjects more like humans — even animal research subjects we may presently rank lower than the primate, dog, and cat of yesteryear’s research focus.

#### THE BACKGROUND DEVELOPMENTS IN THE LEGAL LANDSCAPE

The third point, the large and general movements in the legal treatment of animals, I can only mention. It is wise counsel, of course, to stay consciously aware that we are almost never in a position where “no law” applies to animal experimentation. In human experimentation people sometimes say that this or that aspect remains to be regulated, and they forget the background, which is the ordinary law of assault, battery, mayhem, and homicide including reckless and negligent homicide, that applies to what any individual does to any other human being. Similarly, the ordinary criminal laws of animal cruelty, animal fighting, animal neglect, and so forth, now over a century old, are the background to all animal experimentation. Charges have been brought when — we might say even when — the animal is a mouse.

Cruelty to animals has been moving in the recent past from a misdemeanor to a felony, which is significant, and new laws are mandating psychiatric treatment for cruelty to animals. The latter, moving beyond the criminal law, has an obvious wider significance. We live and work within an exemption from what otherwise would apply, an exemption that is not always explicit;

and wherever you find an exemption in the law, it indicates where the burden of justification lies.

But the legal context is wider than these specifics, and it is changes in the background as a whole that I think responsible decision makers throughout the biomedical research community can helpfully take into account. Some of them are what we call common law developments, shifts in the way judges and juries think about cases. Some of them are legislative and build on mainstream study commissions and ongoing law reform drafting at the state and local level.

In tort law — the law of civil recovery for harm that is not criminal or contractual — measures of damages have changed and animals are already beginning to move from their traditional property status to quasi-property and even something *sui generis* in both the United States and Europe.

That trend can also be seen in the law of international trade, where recent World Trade Organization litigation is producing a sense of animals as something other than the ordinary objects of trade and commerce and therefore exempt from a purely economic analysis. Even in the staid law of wills and trusts, law reform commissions as well as common law courts are moving to allow wills to be broken that require the destruction of animals, and to allow animals to be the beneficiaries of trusts where only human beings could be before.

The same is to be seen in the law of divorce, which you might think far afield, but really is not. Disputes over animals can move from being disputes over property to being disputes over custody, and as in custodial arrangements for children, concern for the animal as such enters legal consideration. These disparate developments are mutually reinforcing, in that seeing an animal as an independent being comes to settle more deeply and comfortably in the legal mind, so that a phrase such as that in the CHIMP Act, “the best interests” of the individual animal involved, becomes legally meaningful.

But the most important changes may be constitutional, not giving animals “rights” but changing the way they are perceived and how they are weighed in cost-benefit thinking, and fixing the values associated with them somewhat beyond the vagaries of the legislative process. Europe’s constitution, the Treaty of Rome, was amended six years ago to change the definition of animal from agricultural product or property to “sentient being” — that is the term used — for purposes of interpreting the whole range

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of European law. Just last summer Germany amended its constitution to allow courts to weigh the effect on animals against constitutional rights including freedom of religion and freedom to pursue scientific research. Last fall an agricultural provision was added to the Florida constitution, quite specific, but with a quite general constitutional preamble to it, "Inhumane treatment of animals is a concern of Florida citizens."

These developments cannot fail to have an ultimate effect on the treatment of the least of the sentient beings. Again, some of these developments outside the world of science that are pertinent to the world of science may be taken to be reflections of what science itself has learned about animals.

## THE REGULATORY FOCUS ON ATTITUDE

On the fourth matter to which decision makers might be attentive, I can be more definite. On the first three I can only suggest: the relevance here of thinking about human experimentation, which is conceptually divided from thinking about animals only by the questionable notion of free and informed consent; the relevance of scientific work on animals outside the subspecialties of biomedical research; the large developments in the legal conceptualization of animate life that both reflect and mold the conceptualizations of investigators who of course are citizen participants in civic life themselves. But I can be more than suggestive about the importance of attention to what, for want a better word, we call attitude.

There is the matter of attitude toward regulation and the requirements of regulation, such as it will turn out to be where rats and mice are concerned. The just-past Director of the Federal Office of Human Research Protections, Greg Koski, an anesthesiologist from the Harvard Medical School, traveled to a research institution about once a week, saying "It's a great opportunity to get a feel for the *culture* of the institution." Against skeptics who argued that accreditation and self-assessments may merely lead universities to do the "minimum necessary" to keep themselves off the radar screen, Koski argued that they will help research institutions switch, in his words, "from a culture of compliance to one of conscience and responsibility."

It is a strong and moral word, conscience, and it assumes a certain attitude toward the research subject. Indeed, the attitude toward regulatory requirement and oversight is hooked to attitude

toward the research subject, and this is as true in animal research as it is in human research.

I count myself very fortunate to have observed as a nonscientist what I think to be a culture of conscience and responsibility among scientists reviewing each other's work, which is largely, as anywhere, work on rats and mice. But as numbers rise and questions of time, effort, budget, and training become more pressing, a constant awareness of the attitude toward the research subject that is being expressed, accepted, or fostered will act to steady and protect those who have to make hard decisions.

What was it that led to the shutdown a few years ago of the entire program of human experimentation at a great institution like Duke? "The bottom line," as we are fond of saying when trying to be hard-nosed and no-nonsense in getting on with a task, was not that Duke failed to follow this or that procedure or violated this or that rule.

The reason wasn't what they *did*. The reason for the shutdown was the conclusion of the investigation that from top to bottom there was an attitude of uncaringness and indifference. Again in the history of experimentation on human beings, the more that is revealed about what went on in the United States prior to World War II, the more troubling is the comparison with what went on in Germany and was condemned at Nuremberg. German scientists used as a defense American practice as they understood it of experimentation on prisoners and children, and American testimony at Nuremberg refuting them is now widely viewed as perjury.

The best that contemporary historical researchers and commentators can do, the real distinction in historical judgment of "us" and "them," rests now on the ultimate difference in attitude toward the human research subjects used in the United States and those used in Germany.

Of course, standard questions from animal use and care committees that an investigator answers about his or her protocol are designed to bring out, and the questions explicitly say they are designed to bring out, the "ethical cost" of the experiment. The ethical cost of the experiment is flagged and detailed not just so the committee [members] can weigh it for themselves, but so that the investigator will face it and weigh it.

But it is not an ethical cost and will not really be weighed unless it is felt, inside, really, as a true cost. It will not be felt as a true cost if the attitude toward the research subject is not one of

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respect or even sympathy, *some* respect at least, *some* sympathy at least, which one cannot have at all for something viewed as mere tissue or a mobile metabolism.

I realize there is a contention in this, and that someone can say that how he or she views a rat or mouse is not anyone else's business, and that the only question, the bottom line as it were, is what is done or not done. But this is precisely what I would want not just to question but to deny.

Let me illustrate from the regulation of experimentation on children. This is a matter of considerable current comment in and out of courts because of recent insistence that drugs administered to children be tested on children. Current child research regulations draw the traditional distinction between therapeutic research and non-therapeutic research, non-therapeutic meaning that the individual research subject does not receive a benefit from it — the general situation in animal research. For such non-therapeutic research on children, increasing levels of risk, or what we here would call ethical cost, are spelled out — minimal risk, a minor increase over minimal risk, more than a minor increase over minimal risk — and cost-benefit analysis is specified. But subjecting a child to a considerable risk, a “more than minor increase over minimal risk” that has no upper limit, is not ruled out if the general gain is large enough. Instead, there are increasing procedural protections, layers of approval, leading up to decision by the Secretary of Health and Human Services.

We ask in animal research whether there is any substantive limit on what can be done to an animal by chemical or physical intervention or by genetic manipulation to produce a condition, if the hope for human benefit is great enough. The same general question can be asked in research on children: Are there things that you just do not do? In the case of children, when the Secretary [of Health and Human Services] has finished a period of public comment and consultation with a special review board, and looks for substantive guidance in making a decision, you will see that the standard the regulation provides and the finding the secretary must make is this, that the particular research will be conducted “in accordance with sound ethical principles.”

This is the regulatory standard for risky research on a non-consenting human being who receives no benefit from it. If this final test is not to be simply empty, and I don't think it was meant to be empty, the limit it produces is the limit that arises from a live sense of respect and sympathy for the research subject.

Research conducted with any other attitude toward the child, that the child is a physiological mechanism, a mobile metabolism, would not pass this final test.

On the animal side, we might say that there is no such implicit limit, that anything can be done if the human benefit is great enough, any degree or kind of suffering induced in a present creature or a future creature genetically altered. “Ethical” means weighing cost and benefit and nothing more than that.

But consider the three R's, reduction, refinement, and replacement, and whether the requirement of something other than a cold or wholly objectified view of an animal research subject is not really built into them. If there were no acute sense of ethical cost, of tension that cannot be escaped, reduction, refinement, and replacement would make no sense. There would be no real motivation to achieve them.

Consider also that there is something substantive, not just procedural, in the universal requirement that the investigator be a “qualified investigator.” A chemist's attitude or conception of the materials with which he works may not go to his qualifications — he may have a lively and romantic vision of the chemical world or a bleak and sad one, or one that has no affect to it at all. But where the materials being worked with are animals, an investigator's conception of an animal as a living and feeling being may go to his qualifications. This is no new observation; research administrators I know, who are as solicitous for research as any, are sensitive to this connection between attitude and qualifications, and it is implicit I think in standard training programs.

One of the very great pioneers in physiology, Claude Bernard in France, is well known for his attitude toward the living subjects of his experimental work. “Life,” he said, “is nothing but a word that means ignorance,” and he wrote of the ideal physiologist: “He is a man of science, absorbed by the scientific idea which he pursues. He no longer hears the cry of animals, he no longer sees the blood that flows, he sees only his idea and perceives only organisms concealing problems which he intends to solve.” Historically this was just at the beginning of the modern Western controversy over the actual treatment of living things in the pursuit of knowledge and general good, and we can certainly ask, now a century later, whether for all his genius and all the good he did, this great figure would be qualified today to engage in research even on rats and mice.

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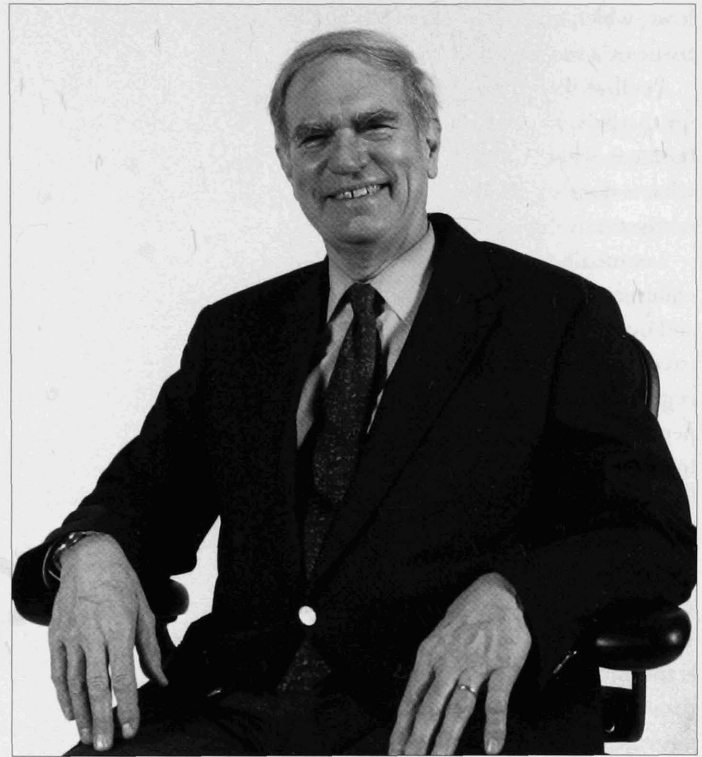
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I suppose we should end by acknowledging again that the animals that are becoming our principal research subjects are vermin to many or most, other than a saint like St. Martin de Porres or children in classrooms or the relative few who seek out a companion relation with them. Outside the laboratory mice and rats are hunted and poisoned, are inconvenient and threatening.

But we should remember that lovely deer are too, and sea lions or whales that eat fish. Other human beings are competitors or threats also. Human beings are neglected, abused, and indeed sacrificed for the greater good. But that has never changed one's own responsibility for what one does oneself. Rats and mice may live lives of terror and violence outside the laboratory, but that again does not take away one's own responsibility. A field mouse looking up at you in a field, not moving because she is beside her pups, is no less a presence because she may be pounced upon by a fox the moment you move on.

If unprovoked you lifted your boot and crushed the field mouse under foot I think you later might have doubts about your own humanity. These creatures are within the fold of human concern. I know they are now for distinguished and effective scientists, and I hope not just for these creatures' sake that they will continue to be within the fold of concern in the future.



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