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Ethics and refinement in animal research¹

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Based on a case study we conclude that scientists and journals could and should do more to secure the ethical standards of animal use in biomedical research: Scientists often justify animal use referring to the scientific value and biomedical importance (2). However, except from a purely anthropocentric perspective, ethical concern about compromised animal welfare cannot be justified by human benefits alone (1). It is equally important that the benefits are achieved with a minimum of negative effects to the animals involved. Thus scientists must apply 'refinement', the third R of the so-called 3Rs (3). But here scientists seem sometimes to do less than they should and journals fail in their duty to enforce high ethical standards.

We studied the use of animals as models for the neurodegenerative Huntington's Disease. Here refinement should focus on limiting the negative impact of declining sensorimotor function as the disease progresses: housing adaptations facilitating food and water intake and humane endpoints (using earlier, less severe clinical signs as endpoint parameters rather than awaiting spontaneous death) are two possible approaches (4). We asked to what extent animal welfare problems and refinements addressing them were reported in publications of the most common rodent models by analyzing 90 research reports published in international peer-reviewed journals during 2003-2004. These include quinolinic acid (5,6) and 3-nitropropionic acid (6,7) administration to rats and mice and R6/1, R6/2 and N171-82Q transgenic mice (8,9,10). Our results show that the majority of experiments (36+17) were in the two most severe categories, in which animals have sensorimotor deficits interfering with their capacity to eat and drink normally from the cage top (11, 12, 13).

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Very few papers reporting such severe experiments included information on refinement measures: Out of 14 survival studies of transgenic animals with a progressive neurodegenerative phenotype, only 6 referred to humane endpoints and only 2 to housing adaptations. Among the majority of studies referring to compliance with official regulations and / or efforts to reduce animal suffering, we also found experiments using far from best practice, such as administration of rising neurotoxin doses until high animal mortalities.

We believe that our study permits two main conclusions about the role of scientific journals in enhancing the ethical standards of research with animals. First, journals should ensure that referees seriously consider whether submitted studies were indeed carried out with the smallest achievable negative impact on the animals. Although important results might be found in a paper not complying with current refinement standards, a journal like *Science* should still reject such a paper, thereby sending an important signal to the research community, similar to what is common practice for studies involving human research subjects. Secondly, journals should give authors space to describe refinement and welfare precautions. We demonstrate that such descriptions are rare, which means that other researchers cannot benefit from refinement ideas (14), in turn implying a real danger that animals will have to suffer unnecessarily, and that animal welfare will be improved later than necessary.

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