

Opinion

Focus on Animal Welfare

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The study of transgenic animal models is increasing our knowledge of gene function in physiologic and pathologic processes. However, the phenotypic effect of a transgene largely depends on the genetic background on which it is expressed, and is, therefore, still often unpredictable. This makes transgenesis often a rather inefficient procedure for creating animal models of human disorders. In an attempt to overcome this problem, other approaches are being explored. One of these is based on the chemical induction of mutations. N-Ethyl-N-nitrosourea (ENU) is a potent mutagen that causes random, single base pair mutations (1). This chemical is increasingly used to create new models of human diseases in the mouse. In several countries, scientists are establishing ENU mutagenesis centers. Their aim is to obtain better insight into the genetic networks that are involved in pathophysiologic processes. This requires careful phenotyping of the altered animals and subsequent dissection of the mutations that are involved. Indeed, this approach has the power to identify genes that control complex diseases. A recent special issue of *Mammalian Genome* covers this topic extensively (2). In the editorial of that issue, an action plan for mouse genomics is announced, for "exploiting the mouse as a model for studying the pathogenesis of human diseases."

Exciting as they are, these developments exemplify a potential for relegating animal welfare aspects to the background. Thus, neither the editorial nor any of the 25 reports in the special issue mentioned the possible negative effect of mutagenesis on the well-being of the animals that are being used for this purpose.

In the United States, mice, rats, and birds presently are not protected by the Animal Welfare Act. Last September, the U.S. Department of Agriculture (USDA) decided to take steps to include these species in the Act. This decision, which can have major consequences for research on transgenic animals and ENU-mediated mutagenesis research, has been criticized by the Association of American Medical Colleges (AAMC), the National Association of Biomedical Research (NABR) and the Federation of American Societies for Experimental Biology (FASEB) (3, 4). Yet the USDA is determined to implement their decision and is planning to make this rule effective by October 1, 2001.

Opposition to changes in the Act is not supported by the American Association for Laboratory Animal Science (AALAS), and contrasts with current European perspectives on the issue of animal use in research. Similar to those in the United States, the main European legislative regulations (which include rats, mice and birds) date from the mid-1980s (5, 6). National laws of European Union member states must meet the requirements of the 1986 Council Directive 86/609/EEC (6).

Last September, the European Science Foundation (ESF) published a position paper on the use of animals in research (7; <http://www.esf.org/ftp/pdf/SciencePolicy/ESPB9.pdf>). The ESF is an association of major national organizations for science in Europe. Member organizations of the foundation are 67 leading science-funding agencies, research councils, and academies of science, from 23 European countries. Its role is to advance science by stimulating co-operation between national organizations and individual scientists from different countries and to advise on science policy.

The position paper was prepared to set out views on conditions that must be met to make use of animals for research purposes morally acceptable. It is explicitly stated that the paper refers to all vertebrate species (and invertebrates with comparable neurophysiologic development). The ESF encourages member organizations and individuals involved in animal experimentation to follow guidelines formulated in the position paper. These can be summarized as follows:

- The ESF recognizes that laboratory animals not only have an instrumental value, but also an intrinsic value (value in themselves) which must be respected.
- While accepting the need for animals to be used to advance scientific knowledge and to promote human and animal health and well-being, the ESF strongly endorses the *reduction, replacement, and refinement* principles (three Rs).
- Research to improve the welfare of animals should be encouraged and actively supported by ESF Member Organizations.
- Prior to the performance of a program of research, the proposed animal use should be subjected to independent expert review, for both scientific and animal welfare considerations. The assessment and weighing of the likely benefit and likely animal suffering should be an essential part of the review process.
- Investigators should assume that procedures that would cause pain in humans also cause pain in other vertebrates, unless there is evidence to the contrary.
- Investigators and other personnel involved in the design and performance of animal-based experiments should be adequately educated and trained. The ESF member organizations should encourage development and organization of accredited courses on laboratory animal science, including information on animal alternatives, welfare, and ethics.
- The ESF encourages the editorial board of journals publishing the results of animal-based research to include in the "instruction to authors" a policy statement on the ethical use of animals.

These guidelines were adopted by the ESF assembly in Strasbourg last November. The guidelines can be considered as a reinforcement of developments that have already been started in several countries, but did not always receive full support of the scientific community.

The editorial published in *Nature*, October 12, 2000, stated that "the conduct of animal research needs continual reassessment, as scientific knowledge grows and ethical and social perspectives evolve"(3). The guidelines formulated by the ESF is a sign that this message is taken seriously and that (at least part of) the scientific community is developing a less defensive attitude, and becoming more proactive in expressing standards for the use of animals in research. This should provide benefits for animals and science.

Part of this Opinion paper is also published elsewhere (van Zutphen, L. F. M. 2001. European researchers encourage improvement of lab animal welfare. Nature 409:452.).

References

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