

tion may actually have been the best course of action. The animal care staff would have been correct to question her judgment in leaving an ongoing breeding colony if there was no anticipated use of the animals.

IACUCs direct most of their attention to potential animal pain and distress and their alleviation. Federal regulations and guidelines stipulate that euthanasia should be done humanely (in accord with AVMA recommendations) and that euthanasia should be employed as an alternative to ongoing untreatable pain; there is, however, much less consensus about when and whether to euthanize healthy animals. Still, McNulty's plans to depopulate an entire colony are well within the purview of the IACUC's responsibility to review the approximate number of animals to be used in a research project (and by implication, to be maintained for breeding for such use).

Had McNulty explained her plans in advance to the IACUC and the facility staff, they might have had suggestions or requests regarding what action to take with the animals. They may even have asked her to follow precisely the course she took, so that resources would be available for other investigators' projects. Having failed to communicate proactively, McNulty certainly should address people's concerns before she expects to receive more animals. Although one hopes she has better sense than to continue starting up breeding programs and then depopulating them, in this case she should nevertheless detail her plans for disposition of the animals were she once again to encounter problems.

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## Review the Game Plan

**Paul H. Nicolaysen, VMD**

The primary issue is whether an investigator can continue to use animals in an

approved protocol when the project has not yet produced suitable results. Anyone involved in experimental science knows that usable results are not easily obtained, and there is no regulative restraint on such continued use of animals, as long as there is proper oversight of the project. That oversight is in place here, from the IACUC and from the agency funding the research. Because McNulty is an experienced investigator with a previously productive record, it appears that the funding agency was satisfied with her accomplishments before approving this project.

There is no distinct mandate for the IACUC to be involved in this situation, had the issues not been brought to them. However, the IACUC is required to carry out continuing review of her approved protocol, and this would be an appropriate occasion for them to review the activities in greater depth than an annual report provides. First, the IACUC should confirm that the project is still in compliance, that McNulty has followed the protocol as approved, that any substantial modifications have been approved, and that any new policies have been transmitted to the investigator. The Committee should also recognize that this situation is an opportunity to fulfill other IACUC roles and responsibilities, which include ensuring that personnel are appropriately trained, that animals have appropriate husbandry and use, and that there is proper interaction among the members of the animal research program.

An obvious issue for IACUC review is McNulty's commitment to a reduction of animal use and her justification for the number of animals used. The Committee should discuss with McNulty whether her depopulation of the breeding colony had been necessary or wise. Rather than eliminate the colony entirely for a short sabbatical, she could have reduced it to a size that would just maintain itself by producing enough offspring to replace retired breeders. The animal care personnel raise a legitimate question about whether the depopulated colony might have had other uses. This transgenic strain might have been

specifically useful to another laboratory, or the mice might have served some purpose such as training in mouse handling techniques. Another question concerns the fate of the male pups that will be produced by her colony in approximately equal numbers to the females that she will use in her experiments.

It is also the IACUC's responsibility to ensure that personnel are trained about the biology and care of their animals, and to oversee the design and operation of breeding colonies at their institution. For each of McNulty's studies requiring 25 females, the breeder mice will need on average to produce 50 pups, and (depending on litter size and viability) this will require about five to ten litters, each from a mating that must occur at least six to eight weeks before the study uses them. If, for example, she wants to use them at a rate of one study per week, she will need about eight cohorts of five to ten breeding females, each cohort fertilized a week apart. Given her plan of starting with only two pairs, it will require more than six months for them to produce several generations of breeders and expand the new breeding colony to a size that can produce enough offspring for her research use. The investigator should be aware of such logistics, should plan and schedule the breeding program in coordination with the animal facility, and should describe it briefly in her animal protocols.

McNulty should also be aware that importing breeding pairs of transgenic mice from a colleague may be delayed by their health status. Her veterinarian will need accurate information showing that the colleague's animals are free of all microbes that Great Eastern excludes. If there are problems, she will need to find a better source, or tolerate the time and cost involved in having them re-derived for elimination of pathogens. Thus, her research may be even further delayed by her elimination of the breeding colony.

McNulty has told the Committee that she plans not "to do anything different" with the resumption of her work; however, in view of her previous problems the IACUC could call for a comprehensive

review of all the variables that may have contributed to her failures. Use of consultants could provide a fresh view as well as expertise in various areas in which she may be lacking. The Committee should ensure that she is aware that "the same" transgenic mice are not necessarily the same in different situations. First, she may need to have a genomic reassessment of the animals and confirmation that the specific transgenic line is the same one used elsewhere successfully. Although they have the same nucleic acid construct inserted, transgenic lines descending from different founder individuals will often differ in phenotype because of the insertion site of the construct, which can alter the expression of the transferred gene or mutate another gene. Second, there should be an in-depth search for infectious agents that may be present in her animal facility, especially those that are not included in routine surveillance panels or that are not easily detected. Transgenic mice may not express the expected phenotype if infected by inapparent pathogens, and, conversely, gene alterations can cause atypical expressions of infections, which may still be subclinical but affect the phenotype. Also, subtle differences in environmental conditions or nutrition at her facility might alter the phenotype from that seen in the same transgenic line under ostensibly similar conditions elsewhere.

Finally, this scenario discloses apparent mistrust, tension, and lack of cooperation among the various players—investigators, animal caretakers, IACUC—who need to work together for an effective animal program. Several mistakes in this situation could have been avoided or ameliorated with better communication and better planning. The IACUC should make efforts to analyze and correct the reasons for these deficiencies in interaction among their personnel.

**Nicolaysen is Animal Facilities Director at the National Institute for Occupational Safety and Health, Morgantown, WV. The opinions expressed are solely those of the author and not of any government agency.**

## Follow the Rules of the Game

Lynn Matsumiya, DVM

The details of this situation are somewhat unclear, making it difficult to draw a fair and sound decision. Was this project funded by a peer-reviewed granting agency? If yes, the IACUC is not responsible for reviewing the protocol's scientific merit. The use of the term "failure" to describe McNulty's experiments is ambiguous and unclear. If they "failed" because McNulty was unable to generate data that support an experimental hypothesis, she should remember that unexpected results are not necessarily meaningless. On the other hand, if the term "failure" alludes to increased rates of morbidity and/or mortality within the experimental animal population, consultation with the Attending Veterinarian (AV) is in order. Are technically competent individuals using standard and published methods? A complete protocol review, ranging from the laboratory methods employed to the technical proficiency of the research personnel, may shed additional light on the situation. Rodent health surveillance and animal husbandry programs vary considerably among institutions, and even within a single organization. To what extent does Great Eastern screen for pathogens capable of causing subclinical infections? Subclinical disease, which often goes undetected or is simply overlooked, can be a potentially important confounding experimental variable. Similarly, there is a wide variation of both the implementation and execution of husbandry practices among facilities. Therefore, given the paucity of information, a comparison of rodent health between Great Eastern and other institutions is inconclusive at best.

McNulty should not suffer penalties for her pre-sabbatical actions. Investigators are not obliged to give advance notice for an impending colony depopulation. Not only are the animals often unique to a single study, but experimental manipulations may also make them of little use to others.

She is currently requesting a reasonable number of animals. Although the facility supervisor's concerns are understandable in light of the historical problems with this protocol, given the nature of the work and the specific candidate criteria, culling of unsuitable animals remains inevitable.

Before resuming the work, McNulty should consult with the AV and facility supervisor to clarify information concerning the University's rodent health monitoring and animal care programs. The IACUC might recommend that an objective third party assist McNulty in reviewing the entire experimental protocol. If unresolved problems surface, implementation of necessary changes can commence immediately. If McNulty initiates any new measures, these should be highlighted in a report to the IACUC. Following resumption of the work, the IACUC can request regular updates until such time that the Committee is fully satisfied with the implemented amendments and current status of the protocol.

Most importantly, at no time did the investigator ever violate her protocol. Given that she will act cooperatively with the IACUC to strive for optimal animal care and use, the approval should be neither revisited nor rescinded.

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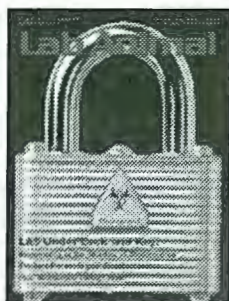
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