

# Should a primate pair put asunder be reunited?

Many animal facilities have experienced the problems that arise when needed drugs or supplies become delayed or unavailable.

## A WORD FROM USDA AND OLAW

In response to the issues posed in this scenario, the U.S. Department of Agriculture Animal and Plant Health Inspection Service (USDA-APHIS) and the National Institutes of Health Office of Laboratory Animal Welfare (NIH-OLAW) provide the following clarifications.

In this scenario, nonhuman primates that were originally paired became singly housed for a study that was unexpectedly cancelled after several weeks of anticipation. The facility questions whether the animals should be reunited with cohorts after weeks of being unpaired and under the possibility of being placed on another study requiring single housing.

### Response from USDA-APHIS

Under the Animal Welfare Act (AWA) regulations, a facility is required to develop, document, and follow an appropriate plan for environmental enhancement to promote the psychological well-being of nonhuman primates<sup>1</sup>. A plan addresses four elements where applicable, namely: social grouping, environment enrichment, special considerations, and restraint devices<sup>2</sup>. Exemptions to the plan can be made by the Attending Veterinarian due to adverse effects to health or well-being; or made by the IACUC for scientific reasons as set forth in an approved animal study proposal<sup>3</sup>. Exemptions made by the Attending Veterinarian are to be reviewed every 30 days unless they are permanent; and exemptions approved by the IACUC are to be reviewed at appropriate intervals as determined by the IACUC but not less than annually<sup>3</sup>.

The AWA regulations are silent on the amount of time animals should remain individually housed. In this scenario, the decision on whether to re-pair the animals requires taking into consideration factors such as health, behavior, compatibility, and the environmental enhancement plan already in place. In light of this, a plan of action to re-pair the NHPs should be as specific as possible, providing some type of time frame that can be monitored and documented along the way. It would be ideal for the Attending Veterinarian, the IACUC, and

The impact on an animal's physical health or a study's continuation can easily be envisioned, but an incident at Great Eastern University illustrated how questions of

the Principal Investigator (PI) to work together in determining the best course of action that balances research needs with the promotion of psychological well-being. Exemptions to social grouping made by the Attending Veterinarian or the IACUC should be reviewed as required under the regulations, documented, and made available for inspection<sup>3</sup>.

### Response from NIH-OLAW

The *Guide* requires that single housing of social animals be justified based on experimental requirements or veterinary-related concerns, and if animals are housed singly it should be for the shortest duration possible<sup>4</sup>. In this scenario, a communication failure about the research status allowed the animals to remain singly housed for an unnecessary period. To prevent similar situations, the IACUC and the animal care team should enhance communications with PIs and establish a more frequent schedule for re-evaluating whether single housing should continue. The evaluations should include subject matter experts (e.g. behaviorists) to assess the individual animals and whether prolonged separation is more distressing than re-pairing. Research has shown that social housing reduces stress and assists animals in coping with stressful stimuli<sup>5</sup>. With rare exception, the default should be to socially house. □

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psychological wellbeing should also be taken into consideration.

U-2484 was a drug under development by American West Pharmaceuticals in collaboration with Great Eastern University. Dr. Kenneth Reisman, a cardiac physiologist, was beginning to study the effect of U-2484 on various aspects of heart rhythm and contractibility. Reisman's initial test subjects were two male rhesus macaques. Each animal was to receive weekly injections of U-2484 and monthly electrocardiograms for one year. The monkeys had been successfully pair housed for over a year before the study started but now were housed separately yet within eyesight of each other due to the need for Reisman's lab to collect and analyze fecal and urinary excretions from each animal. Nearly eight weeks into the study, American West discovered that there was a contaminant in the excipients (inert ingredients) that went into the U-2484 injections being given to the monkeys. The study was immediately halted, but with the expectation that it would start anew in about two weeks, using the same animals. To avoid stressing the animals from putting them together and separating them again, the school's IACUC approved keeping the monkeys in their separate cages, but closer to each other than they had been. Unfortunately, the two weeks stretched into four, then six, and then the study was discontinued by American West. During all this time, the two monkeys remained in their separate cages.

In considering what transpired, the Great Eastern IACUC began asking itself some questions. For example, when the macaques were allowed to remain separated after the contamination was found, how often should that separation have been reviewed? A related question was, do we set limits on how long an animal can be kept housed for new or renewed use if a study falls through? Also, the IACUC questioned if it would be ethical to reunite the two monkeys and then repurpose them for another study which may again require separate caging? How would you or your IACUC resolve these questions? □

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# Old World monkeys need their new world reviewed

Expecting the unexpected is a challenge when planning any scientific research study. Although standard adverse outcomes can be anticipated based on the nature of the protocol, a keen IACUC and veterinary care program will have a fluid process for handling unexpected scenarios such as the one described at Great Eastern.

The Animal Welfare Act outlines requirements for review of nonhuman primates exempted from an environmental enhancement plan. In the case of scientific exemption, it is up to the IACUC to review these exemptions at least annually<sup>1</sup>. Dr. Reisman's proposal was for a study with duration of one year; did the approved protocol adequately address enrichment considerations for long-term single housing? Did it describe a plan in the event that one animal died while on study, leaving the remaining animal socially isolated? These questions should be thoroughly assessed during protocol review, particularly for PHS-assured institutions<sup>2</sup>. Although short term separation of animals may be an acute stressor, long term separation or permanent social removal may cause distress and alter social behavior<sup>3-5</sup>. The physiologic and behavioral stress associated with singly housing social species is well documented in literature and careful pre-planning should exist to minimize detrimental effects<sup>5</sup>. Unless there is scientific or veterinary

justification to keep the animals separated, careful reintroduction by a trained care team should be pursued and guidance is readily available on this process<sup>1,6</sup>. If social housing proves to be unattainable, daily positive socialization with caregivers may be an adequate alternative to reduce distress<sup>1</sup>.

This scenario also demonstrates the importance of endpoints, timelines, and final disposition details when reviewing research proposals, which is especially important for species with long lifespans or conservation concerns<sup>2,6</sup>. Protocol review should be conducted with input from the Attending Veterinarian (AV) to ensure the facility is capable of meeting the species-specific needs and regulatory requirements for housing prior to approval. IACUC members should be properly educated on the ethical use of animals in multiple studies, particularly nonhuman primates<sup>6</sup>. Regulatory guidance is provided by multiple agencies on the use of animals in multiple major operative procedures<sup>1,2</sup>. In the case of Reisman's protocol, the study was non-surgical, and we assume the animals remained in normal physical health after U-2484 was discontinued.

If the study was no longer in compliance with the approved protocol timeline, or if these details were not described, an immediate discussion should have taken place between the PI, AV, and

IACUC to devise an action plan. Even with unanticipated study termination, a preexisting contingency or disposition plan for these animals should have been in place. This may have described re-pairing, transfer to another institution, or diversion to another study. Once the experiment was halted, the AV and IACUC should have been promptly informed to implement the contingency plan as described in the protocol or collaborate on an alternative strategy to optimize the wellbeing of the animals and conservation of animal resources. □

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## After further review...

While there seems to be an ever-increasing degree of regulation (both internal and external) on animal research, we should always bear in mind that things will happen for which we are not trained or prepared. This scenario is one of those instances where further review is needed in an effort to address unforeseen concerns. Notable facts include that prior to the start of the study, the animals were pair-housed for a considerable length of time and while on study the animals remained within eyesight. Soon after the study was initially halted, the animals were moved closer together but were still singly housed. Lastly, the animals

were approved for single housing until the study was ended by America West. This raises the following three questions:

First, how often should the separation of the animals be reviewed after the study, seemingly temporarily, stopped? Although the *Animal Welfare Regulations (AWR)*, the *Public Health Service Policy on Humane Care and Use of Laboratory Animals*, or the *Guide for the Care and Use of Laboratory Animals (The Guide)* don't address the specifics of this scenario. The AWA requires the Attending Veterinarian (AV) to review exemptions from social programs; if single housing is for the benefit of the animals' health or wellbeing, that is to

be reviewed every 30 days<sup>1</sup>. The IACUC can review and approve single housing or abstention from social programs for research projects as long as these conditions are reviewed at least yearly<sup>2</sup>. Importantly, the animal care staff has been monitoring these animals daily for the duration of the project and beyond. As such, monitoring of the animal's wellbeing is ever ongoing.

Second, how long can an animal remain 'single' housed for a new or renewed study if the study falls through? This question is intertwined with the first and third questions. One would assume studies falling through would be very uncommon

and it seems obvious that once a study ‘officially’ ended, that would be the trigger for further action.

And third, is it ethical to reunite the two animals, even though they might be separated again at a later date? Frankly, there is no right or wrong answer without further information about the two individual animals. We really do not know whether the animals were less stressed together or if they would prefer to be neighbors. For clarity, this question should be broken down into two parts. First, is it ethical to reunite the animals considering the stress that might involve? Since the animals were once buddies, one could anthropomorphically conclude they would be buddies again, especially considering they never lost sight of one another for the duration of the study. Additionally, *The Guide* endorses social housing as the default for nonhuman primates (NHPs)<sup>3</sup>; thus, from a regulatory aspect Great

Eastern should work towards reuniting the animals, assuming they are still compatible. Second, would it be ethical to separate the two animals again down the road after reunification for some other unknown project? I suspect, after much consternation regarding this question, the answer would be ‘it depends.’

In my opinion, the following should be implemented: Once a study ‘officially’ ends or falls through, the clock should start for regular 30-day AV reviews regarding socialization and wellbeing. Resocialization of animals after a study, when a study falls through, or during an unforeseen study break should be addressed as part of the institution’s required environmental enhancement plan<sup>4</sup>. If sufficient numbers of NHPs are held at the Great Eastern University, employment of a behaviorist or contracting a behaviorist would be helpful for the university to address our anthropomorphic best intentions. □

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