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Letters to the Editor

The Rodent Quarantine Quagmire

Dear Editor,

We write today to discuss what we have termed the rodent 'quarantine quagmire,' a term reflective of the inertia in which we seem to be mired regarding quarantining live rodents versus the shipping of cryopreserved germplasm. As we know, modern genetic engineering practices have greatly increased the number of mutant mouse strains available for research.[19] Many of these strains are not available from standard vendors and so are 'traded' among investigators and between institutions. These valuable research animals are of varying health status and may possibly harbor pathogens that could interfere with research.[8] As novel pathogens, such as mouse norovirus,[16] appear on the scene, it may become increasingly difficult to exclude these common agents. Exemplifying the basis for such concerns, 5 articles from the last 2 issues of JAALAS (vol 48, issues 3 and 4, 2009) focus on the control or impact of microbial contaminants in rodents.[7,9,11-13]

Traditionally, the mechanism for such exclusion has been to maintain an onsite quarantine program into which unapproved or noncommercial mice are placed and extensively tested to determine their pathogen status.[15,18] The purpose of such programs is to ensure the quality of incoming animals, as well as maintain the quality of existing populations, by controlling microbiologic status. However, these programs also leave institutions vulnerable to the importation of excluded pathogens that, like mouse parvovirus, may be insidious and not always discernable by using standard techniques.[2,3] Our experience, for example, has been that fur mites can be acquired through nonvendor mice and that traditional quarantine with extensive parasitologic testing does not always identify infested mice.[14,17] In addition, in the not-too-distant past (2002), we were the unfortunate recipients of mouse hepatitis virus (MHV) into quarantine, having received founders that the source institution had not identified as at risk of infection. Despite the presence of a highly trained, technically capable animal caretaker on the scene, MHV spread throughout quarantine, with considerable associated costs and delays for investigators.

Microbiologic management is necessary to ensure animals of sufficient quality for research. Had our quarantine not been in place, for example, our MHV experience would have been shudderingly worse. Unfortunately, such programs are costly and labor-intensive for animal resource facilities and, just as unfortunately, can be a source of friction between veterinary staff and investigators. Most frequently, the conflict is due to the competing interests of quality control on the one hand (veterinary staff) and getting going with research on the other (investigative staff). It is commonly the case, and arguably has been the experience of most laboratory animal veterinarians, that some investigators just want their mice, and want them yesterday, because they are engaged in the competition that is science and are competing for publications and funds. For investigators, receiving mice through quarantine programs is perceived as, and often is, a time-consuming hassle.[4] Shipping and receiving institutions must share information, receiving institutions can be quite picky about microbiologic status (even when their own status is not pristine—no one wants to make an existing problem worse), hassles can be associated with shipping (for example, there can be shipping embargoes during very hot and cold months), and the whole process can be derailed by any of a myriad of problems along the way.

Quarantine programs are also a hassle from the perspective of animal resource programs. They require space, and sometimes an extensive amount of it. Most commonly, researchers cannot work with their animals while in quarantine, so in the case of academic institutions, the cost of the space is not recovered by indirect funds. The work is repetitive and tedious and must be done by incredibly meticulous, highly trained personnel. Such personnel are increasingly difficult to find.[5] And the programs remain risky for the introduction of agents to be excluded. Given the considerable difficulty, risks, costs, and time involved with the standard method of rodent quarantine, it is worth some effort to consider alternatives.

At Emory University, faced with staffing challenges, we made an attempt to ameliorate the burden placed on our program by outsourcing quarantine to a commercial contractor. Mice from shipping institutions sent their mice to the vendor, where they were housed in individual isolators. The vendor operated quarantine according to our instructions, sent us health report data, awaited our permission to release mice from quarantine, and shipped them directly into our housing rooms upon release. This situation was greatly appreciated by the animal resources program: a room became available to support investigators and for which indirect funds were received, quarantined animals were housed in a situation of greater biosecurity than we could provide (individual isolators a significant distance away), and we enjoyed the associated labor savings. However, it did not work from the perspective of the investigator, and an outcry ensued. Investigators felt there was even more hassle associated with this third party, more people with whom to interact, more possibilities for customer service to go astray (for example, research specimens proved difficult to obtain from animals that died unexpectedly). Unfortunately, analysis showed that the outsourced quarantine took longer than in-house (86 d at the contract location versus 69 d in-house, $P < 0.05$), and cost per cage more than doubled for mice to go through the process. Needless to say, after this analysis, quarantine, along with its associated risks and personnel and space requirements, returned to Emory.

It seems to us, however, that there is another way. Hassles, costs, and the potential for disease transmission could be mitigated by trafficking in 'mouse parts' in lieu of live mice. 'Mouse parts' here means embryonic stem cells, frozen sperm, embryos, and the like. The NIH has begun an initiative to increase the mouse part trade with the creation of the Knockout Mouse Project (KOMP). This project aims to create a public resource whereby embryonic stem cells can be ordered off the shelf. In the words of David Grimm, the project would create an "IKEA-like superstore: a place to buy easy-to-assemble furniture at reasonable prices."[4] Some assembly would be required: turning embryos into live mice.[4] But a resource of this type would be a far cry from today's hassle- and risk-laden mouse trade. An additional potential benefit of trading mice in this way is the naturally ensuing potential for cryopreservation of mouse lines. In the face of natural or other disaster resulting in loss of murine life or infection of valuable stocks, the benefits of cryopreserved lines in terms of cost and time are incalculable.[10]

At Emory, we have attempted to get a handle on prevailing attitudes regarding the mouse part trade in a couple of ways. In 2007, we began formally recommending shipping sperm or embryos instead of live mice and asked investigators shipping from other institutions whether their institution could do so. We also asked whether investigators were generally interested

in this option, regardless of their institution's ability. As of this writing, these questions have been posed 60 times, with 37 responses encompassing 33 different institutions. Of these 33 institutions, 20 are capable of shipping mouse parts. Amazingly, when simply asked whether investigators were interested in the option, only 5 replied in the affirmative. To keep our survey simple, we did not enquire into the rationale behind this lack of interest. However, some potential reasons we considered are presented following.

In another attempt to evaluate attitudes, a survey enquiring about the use of mouse parts versus whole mice was distributed to the animal resource program directors attending an annual meeting of the top 25 funded biomedical academic research institutions at the 2007 national AALAS meeting. Although the survey received poor response (7 of 20), the responses we did receive supported what we believed to be the case: folks out there continue to use quarantine as their primary importation mechanism and rarely, if at all, import mouse parts in lieu of whole mice. All 7 responders ran an in-house quarantine, and only 1 responder indicated that it had been more than 2 y since an agent on the excluded list had been admitted into quarantine. All other responders indicated an undesirable agent had been found within the past 6 mo (3 of 7) to 1.5 y (3 of 7). Undesirable agents included MHV, mouse parvovirus, fur mites, and *Aspicularus*. Four responders indicated that they were willing and able to receive embryos to rederive instead of live mice but indicated that this practice was, in actuality, vanishingly rare, on the order of 1% of the time. Analysis of costs at Emory suggest that rederivation costs are roughly similar to quarantine costs and that the rederivation process generally is faster. Costs, admittedly, vary according to the process used and mouse strain.[10] In addition, there are no shipping impediments caused by weather, and very few caused by infectious disease, so investigators can move forward whenever they are ready. We propose, then, that the process of shipping mouse parts and rederiving lines is associated with less hassle, less time, less risk of disease transmission, may cost about the same as quarantine, and, with the addition of cryopreservation and storage, provides valuable insurance. Why, then, as a community, do we not more often advocate or use resources such as this?

One possibility is that transgenic cores may be run separately from animal resources programs, providing no obvious avenue for streamlining of effort. In addition, there are admittedly some upfront costs for getting nonexistent programs up and running, and these are difficult to charge to grants because they are infrastructure-related. Among other things, space is needed for the work of rederivation and for storage of cryopreserved embryos. Different equipment and procedures are necessary for handling sperm versus embryos and the ability to handle both is ideal. Is it the responsibility of busy transgenic core directors to lobby the administration for resources that would assist the animal resources program? One might reasonably answer "no." Is it the responsibility of busy animal resources directors to lobby the administration for equipment and space that would then be operated by the transgenic core? Again, one might well answer "no." A conundrum ensues. We propose that those of us in animal resources programs must reach out to the transgenic cores and jointly lobby to generate this invaluable resource. Space to operate such resources needs to become a priority and such priority communicated to administration. Equipment must be made available to accomplish the goals. And the transgenic core and animal resources programs must develop closer working relationships to better support the research staff that are our clientele.

Rederivation, embryonic stem cell transfer, and the like are not a panacea, eliminating all possibility of infectious organisms[1,6] but certainly will eliminate some (ecto- and endoparasites, for example) with 100% effectiveness and greatly reduce the risk of others. Similar to live animal quarantine, the risk of infectious agents must be managed by a program of testing the biological material for contaminants; however, such analysis is likely to be less intense and less costly. In addition, there may be situations where shipment of live mice instead of mouse parts is necessary (some particularly fragile strains may not cryporeserve well, for example), so institutions would need to be prepared to handle both situations. Even with those caveats, however, the reduced risk associated with a program dealing primarily with mouse parts, along with an enhanced customer service experience, would seem to make the process a no-brainer. With the increasing use of genetically modified mice, the costs and hassles associated with quarantine, and the risk of disease transmission, the time is now to step up shipment of mouse parts, thereby helping ourselves and the investigators we support join the 'IKEA meets KOMP' era.

Sincerely,

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