Commentary

Laboratory animals as veterinary patients

Steven M. Niemi, DVM, DACLAM

> "I believe a leaf of grass is no less than the journeywork of the stars, ... And a mouse is miracle enough to stagger sextillions of infidels."
> Walt Whitman, Leaves of Grass

The history of organized laboratory animal medicine in the United States may be described in two major phases (although laboratory animal medicine is also tightly linked with identification and development of animal models of human diseases, this facet is more accurately categorized as comparative pathology and therefore omitted from this discussion). Its first phase, roughly between 1950 and 1985, focused on colony medicine in tandem with optimization of husbandry practices.[1] During this period, common natural pathogens were identified and reliable and cost-effective means were developed to detect and contain or eliminate those microbes and reduce their impact on research data.[2] In addition, species-specific standards were established for nutrition, caging, bedding, and environmental parameters such as temperature, humidity, ambient light, and noise.[3] These standards were implemented to avoid unintended animal disease or injury and to permit more accurate comparisons between similar experiments performed at different times or in different locations that otherwise could have been confounded by differences in the animal subjects' care and immediate environment.

While progress in colony medicine continues, this initial focus was supplanted in the mid-1980s as a result of new federal laws and regulations in the United States. At that time, amendments to the federal Animal Welfare Act[4] concurrent with the Health Research Extension Act of 1985 and resultant Public Health Service policy[5] mandated the establishment of an institutional animal care and use committee (IACUC) at each site where specified species of animals were used in research, testing, or education. Under these new directives, every IACUC had three primary responsibilities: review and approve the intended use of all applicable animals before those animals were used, inspect all areas where animals were housed and used and assess the institution's entire program of animal care and use at least once every six months, and investigate concerns regarding improper care and use of animals in the institution. In addition, for the first time, IACUC voting members had to include nonscientists and so-called nonaffiliated members from the community, in addition to scientists and veterinarians.

From the Department of Research Management, Massachusetts General Hospital, Boston, MA 02114, and the Department of Pathology, Harvard Medical School, Boston, MA 02115.
Address correspondence to Dr. Niemi (sniemi@partners.org).

This more formal and inclusive process by which laboratory animal care was overseen by IACUCs, coupled with external regulatory scrutiny of the effectiveness of those IACUCs, resulted in more attention devoted to avoiding, minimizing, and alleviating animal pain and distress. This, in turn, resulted in more consideration being given to postoperative analgesia, nonlethal endpoints, social housing for naturally social species, environmental enrichment, and other components of laboratory animal care and use.[6]

Consequently, animal welfare became even more embedded in laboratory animal medicine, involving rodents and a few higher order invertebrates to a greater degree than previously practiced.[7–9] This shift in emphasis from animals as groups to animals as individuals led to the second major phase of laboratory animal medicine: palliative medicine (defined as "reducing the severity of [disease]; denoting the alleviation of symptoms without curing the underlying disease"[10]). In essence, laboratory animal medicine adopted a version of hospice care, such that animals anticipated to become moribund as a result of a given experiment were more intensively monitored so they could be euthanized sooner to avoid unnecessary pain or distress and spontaneous death. This newer phase required scientific and regulatory confirmation of moribund and more benign endpoints as valid surrogates for death[11–13] and relied on IACUC cooperation.[14]

As science and our understanding of animals continue to evolve, it is reasonable to expect that laboratory animal medicine will change, too. What will this field look like in the future? I envision yet another new phase for laboratory animal medicine in which individual animals are managed simultaneously as research subjects and veterinary patients without compromising the scientific aims of their use. This phase may be labeled restorative medicine and will involve managing selected components of induced illness or injury with the intention of restoring organ or tissue function to a more normal state, thus mirroring a fundamental aim of clinical practice in other veterinary specialties, such as companion animal practice and equine medicine and surgery.

This may, at first glance, seem a radical change from the long-standing culture in animal-based research and testing, which to this time has typically discouraged clinical intervention so as to not disturb experimental parameters, thereby permitting the disease or injury being modeled to follow its natural course. Allowing any interventions, as the argument goes, would create too much variation and render comparisons between animals and between experiments unnecessarily difficult if not impossible.

But restorative interventions are already commonplace in some mainstream animal models of human diseases. Consider insulin-dependent diabetes mellitus, a condition that can be induced in healthy animals for the purpose of evaluating pancreatic islet or stem cell implants or programmed insulin-delivery pumps as a replacement for lifetime insulin injections. Following chemical ablation of pancreatic islet cells, sometimes combined with partial pancreatectomy, blood glucose concentrations are routinely monitored at least twice daily and insulin is administered as required in these animals until the grafted cells or implanted device alone can maintain normoglycemia.[15,16] A diligent IACUC would not approve withholding insulin injections in these experiments unless the purpose of the research protocol was specifically to study complications of diabetes-associated hyperglycemia.

If scenarios like this are the exception rather than the rule, are there changes afoot to encourage restorative medicine for laboratory animals on a larger scale? And what benefits would ensue besides improved animal welfare? I suggest that there are three related needs in biomedical research and preclinical testing today that are compatible with and would profit from an expanded restorative medicine ethos.

The first need is a consequence of the use of increasingly sophisticated experimental endpoints. As our knowledge grows about the molecular bases of disease and healing, new and more complex questions arise as the simpler ones get answered. More complex questions about the mechanisms of disease and cell death require more detailed answers, such as which genes are involved in enhancing or resisting infection versus simply whether animals will succumb to a particular pathogen. Similarly, how a specific receptor on a cancer cell influences metastasis is a more contemporary question than simply whether a particular tumor spreads. Which specific cocktail of growth factor proteins will allow regrowth of severed nerves is a more contemporary question than simply whether animals will regain the ability to walk. Answers to detailed questions like these are difficult to obtain if the experimental system (ie, the experimental animal) comes with multiple disparate variables that may mask or counteract the cellular or biochemical phenomena of interest. Consider, for example, congestive heart failure, a leading cause of hospitalization for elderly patients and for which there is no cure.[17] The personal and economic impacts of congestive heart failure drive considerable animal-based research on effective treatments, including gene therapy and stem cell therapy.[18,19] A common complication of congestive heart failure is fluid buildup in the lungs, resulting in fatigue and eventually death from hypoxia or secondary pneumonia. Standard supportive treatment for congestive heart failure in people and animals is a diuretic, such as furosemide, to increase the elimination of body fluid as urine and thereby improve gas exchange in the lungs. If mice with experimentally induced heart failure are used to study only the effects of reduced cardiac muscle contractility associated with the disease, the presence of excessive fluid in the lungs may not be scientifically relevant for the study and could interfere with the study aims by necessitating euthanasia of animals before the potentially most valuable data can be obtained. If pulmonary congestion is not the target of scientific inquiry, diuretics and perhaps even additional oxygen should be administered to improve breathing and extend survival time. Even better, a low-salt diet could be provided from the beginning of the study as a prophylactic measure, given that this is routinely recommended for older dogs and cats with congestive heart failure. Good research should focus on biological specifics at the appropriate scale and avoid interference from peripheral influences that are not pertinent to the scientific question at hand. Importantly, avoiding unwanted or unnecessary influences on research data applies to behavioral conditions as well as physiologic states. Laboratory animals should be made to feel less anxious, fearful, or depressed if these emotional states interfere with the research question being asked. Fortunately, in this regard, we are getting closer to identifying and managing some psychological states in animals that until now were considered applicable only to people.[20,21]

The second need that would benefit from restorative laboratory animal medicine is the growing financial cost of animal models, something that is becoming ever more important in an era of tightening research funding. More complex scientific questions and more subtle experimental endpoints often equate to more expensive animal-based research. A given experiment may involve multiple costly procedures such as MRI or positron emission tomography to track fluorescent cancer cells in the brain or serial colonoscopies on mice to follow progression or resolution of ulcerative colitis. Other research expenses arise from genetically engineered mice that require special husbandry, consuming tens of thousands of dollars annually merely to maintain breeding colonies. Major investments in labor, supplies, and instrumentation like these make many of today's animal models more costly than ever before. If experimental animals could be kept alive and in better health longer, a bigger intellectual return on those financial investments could be realized.

A third need served by restorative laboratory animal medicine pertains to the clinical homology between animals used as models of human disease and the human patients with those same diseases, especially in a regulatory context. Testing of new drugs, biologics, and medical devices intended for human patients requires evaluation in laboratory animals first, for both efficacy and safety[22]; efficacy is determined in animals with the pertinent disease or injury, and preclinical toxicological evaluation uses animals initially in good health. In both situations, the circumstances under which animal testing is performed should mirror human patients as closely as possible to obtain the most accurate prediction of therapeutic benefit or safety risk. Restorative medicine for human patients always includes supportive care in addition to prescribed drugs or devices. Such supportive care may vary, depending on the circumstances, but usually comprises basic elements such as maintaining vital signs and minimizing pain or distress. If supportive care is withheld from an animal test subject with the same disease or injury, that animal may not accurately model the actual clinical progression seen in its human counterpart.

But such supportive care conventionally is withheld in preclinical efficacy testing today. If the animal dies during experimental treatment, that candidate product is considered a failure even though the animal's death may have had little to do with failure of the product or a lack of efficacy. In these cases, promising new products may have been abandoned prematurely because they were not given a fair chance to succeed during animal testing. Similarly, preclinical drug and device safety testing should be performed in the appropriate clinical milieu so that only those toxicoses relevant to the product will be detected in a comprehensive medical context, rather than tracking moribund or lethal outcomes that may be due to nonspecific causes. To expand this point, safety testing of new drugs intended for young or old immunodeficient patients should be performed in young or old immunodeficient animals, respectively, and consumer products should use healthy animals of an age corresponding to the intended consumer market. But manufacturers understandably are reluctant to change established practices to increase the complexity of already expensive animal studies without clear direction from regulatory agencies. Encouragingly, there is recent evidence that US regulators are beginning to appreciate the greater predictive value of supportive (ie, restorative) care in pivotal animal efficacy studies and may even expect it for candidate drugs and vaccines against potentially lethal emerging pathogens and select agents.[23]

In conclusion, laboratory animal veterinarians have been conditioned to not intervene until animal subjects are either in extremis or have crossed an established threshold that mandates euthanasia; common examples of such thresholds include tumors that ulcerate, excessive (eg, > 15% to 20%) weight loss, and reluctance or inability to move. But, by maintaining a hands-off approach, laboratory animal veterinarians fail to leverage the full spectrum of their knowledge and skills that could improve both the welfare of the animal subjects and the quality and cost-effectiveness of the research involved. Laboratory animal medicine has provided scientists, medical professionals, patients, and consumers with great advances in research animal quality and welfare for more than 60 years. The future can be even more fruitful if we expand our repertoire by practicing restorative medicine to a greater degree.

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