

## Introduction

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Rodents, specifically rats and mice, comprise more than 80% of the animals used in biomedical research, teaching, and testing. Estimates vary as to the exact numbers used (NABR 1999); however, it is clear that the use of rodents in biomedical research will increase with the use of knockout technology, advances in genomics, and advances in surgical and anesthetic techniques, coupled with technological advances in the fields of electronics. More importantly, as advances in these fields and in genomics and embryo stem cell technology occur (Drews 1996), the mouse and perhaps the rat may re-emerge as the most versatile and valuable tools for scientists in the next several decades. As the number of identifiable disease targets becomes clear as these fields mature, scientists will require relevant animal models and *in vivo* systems to validate the scientific advances realized in the areas of molecular biology, genomics, and stem cell research.

Unfortunately, because the rigorous discipline of science dictates that new scientific discoveries be reproduced and the data validated, the use of rats and mice may actually increase until such time as these new scientific disciplines and targets are validated sufficiently to allow us to achieve another set of objectives—the reduction or replacement of animals in research. Although the goals of reduction and replacement may not be realized immediately, advances in these fields permit us to refine our rodent animal models and gain far more meaningful scientific information from even one mouse in real time. The advances in noninvasive imaging techniques (e.g., nuclear magnetic resonance, positron emission tomography, and magnetic resonance imaging) have allowed us to do just that (Landi 2001).

Conventional animal models that are now commonly developed in species such as the dog and nonhuman primate can now be refined or replaced through miniaturization of these models using rats or mice. Miniaturization of these animal models becomes possible in the mouse and rat as the technology of advanced physiological monitoring (Goode and Klein 2002) is coupled to advances in mammalian genetics (Paigen 2002). Miniaturization of the animal model in the mouse or rat becomes an important strategy for use in

the laboratory to accelerate the translation of new scientific knowledge into breakthroughs in medicine and surgery for humans and animals. Miniaturization allows us yet another animal alternative through reduction or refinement. The articles in this issue describe this approach as follows.

Kenneth Paigen (2002) eloquently describes how mutants and natural polymorphisms of the mouse have been identified, cloned, and sequenced, revealing exciting information about genes that are involved in diseases of both mice and humans. His review of the field of gene discovery using the mouse describes two complementary and integrated approaches to genetic research: phenotype- and genotype-driven approaches. The examples he cites provide strong argument for the great value the mouse model has had and will have in the future as a predictor of the genetic basis of many human diseases. Because of their genetic similarities to humans, Paigen illustrates how important the mouse will be in the area of stem cell research in light of the governmental, political, and ethical constraints placed on studies of human embryonic stem cells. His conclusion is that the future is very promising for the development of new human therapeutic and preventive medical treatment modalities because of the knowledge gained from a better understanding of the mouse genome.

The article on miniaturization of physiological systems monitoring in rodents (Goode and Klein 2002) provides an overview of several technologies such as laser Doppler flowmetry, digital sonomicrometry, bioelectrical impedance, and microdialysis, which may be used to better understand the phenotypic expression of the mouse genome. The review of these technologies as applied to the mouse and rat illustrates how the conventional animal model can be miniaturized to gather reliable data from a variety of physiological systems in various rodent species.

In the article titled “Noninvasive Cardiovascular Phenotyping in Mice,” Hartley and colleagues (2002) elucidate how more traditional techniques used formerly to assess the cardiovascular system of mice (e.g., dissection and microscopy) have limited the utility of the mouse as a cardiovascular model of human disease. Their description of advances in anesthesia techniques for the mouse, noninvasive physiological monitoring methods for the murine electrocardiogram, pulsed Doppler for measuring blood flow, and nuclear angiography to measure cardiac volume parameters is unique, extraordinary, and exciting. Their review of these methods, which define normal mouse values for pressure, velocity, and ejection fraction, illustrates that the ge-

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netically engineered mouse has clearly become an excellent model system for comparative study of the cardiac cycle of humans.

Hedlund and Johnson (2002) review the challenges and benefits of imaging the rodent lung and illustrate research opportunities and applications. Their description of proper techniques in rats and guinea pigs to achieve optimal image quality and data is very helpful. The principles described are useful to anyone considering imaging of a specific organ system in small animals, and particularly the use of hyperpolarized gas imaging for the lung.

The issue concludes with Nolan and Klein's (2002) overview of animal welfare considerations and a description of biotechnologies for vascular infusion as well as retrieval of samples from small rodent animal models. The commercially available vascular infusion technology is evaluated so that a user can select the optimal system or infusion devices such as catheters and pumps to ensure a successful study outcome when vascular delivery or collection of a sample via the vascular route is desirable.

We have sought to provide a baseline on current and future prospects of the exciting field of genomics and specifically mouse genetics. In the articles that follow, authors review the technologies available for monitoring rodent physiological systems and for monitoring and characterizing specific organ systems such as the cardiovascular and respiratory systems, and they describe state-of-the art methods for vascular access in rodents. We believe these reviews

provide the scientist with an exciting array of opportunities to redefine and further characterize the phenotypic expression of the genetically modified mouse. The synergy resulting from the use of genomics and technology to miniaturize animal models is a highly attractive option for the scientist. This combination of new opportunities to characterize rodents phenotypically coupled with the use of genetically modified rodents is intended to allow the scientist to refine or reduce animals and, more importantly, lead to exciting medical breakthroughs that will benefit our global community.

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