If only anatomists were as familiar with the dissection of lower animals as with that of the human body, all these perplexing difficulties would, in my opinion, be cleared up. The situation is first of all clear enough in fishes where there is a single ventricle in the heart, and not lungs. The sac at the base of the heart, doubtless corresponding to the auricle, pushes blood into the heart, which plainly transmits it by a tube analogous to an artery. This may be confirmed by inspection, or section of the artery, the blood spurting with each beat of the heart. It is not hard to see the same thing in other animals with but a single ventricle, as toads, frogs, serpents, and lizards.

William Harvey, 1628

As noted by William Harvey over three and a half centuries ago, in vivo animal model systems are invaluable in clarifying the mechanisms of human disease. Although large animal models have long served as a gold standard, recent advances in transgenic and gene-targeting approaches, mouse genetics, and microsurgical technology are initiating a revolution in molecular medicine. Given the multifactorial, integrative, and acquired nature of the bulk of human diseases, the ability to fuse genetic-based approaches with the in vivo analysis of complex physiological traits is clearly one of the most important advances in the field of molecular medicine. In essence, the mouse now offers the genetic advantages of lower organisms, while having sufficient biological complexity to allow connections with human physiology and disease. To obtain a variety of viewpoints on future directions for *Molecular Medicine in Genetically Engineered Animals*, *The Journal* has commissioned a series of short perspectives from leaders in the field (see box below) which will run consecutively in issues of *The Journal* over the next several months. Of course, the use of the mouse as a model system for human physiology and disease is

not without inherent difficulties. In fact, as the increasing resources developed by the Human Genome Project continue to accelerate the pace of the identification of genes potentially involved in health and disease, and as tools available for genome engineering gain even greater precision and sophistication, the need for combining molecular manipulation with precise physiological analysis will become critical for exploiting the full potential of the mouse.

For the past two decades, the intersection of genetics and human disease has been confined largely to the analysis of monogenic disease, which has provided a wealth of information on the molecular determinants of development, physiology, and disease. With the advent of the new mouse genetics and the development of miniaturized technology to rapidly and quantitatively assess in vivo physiological phenotypes, it is now possible to use genetic approaches to identify the molecular determinants of complex acquired diseases which form the bulk of human clinical disorders. Finding these target genes for complex diseases is likely to spawn a new era of molecular medicine, as well as a renaissance in in vivo physiology, that will be similar to the current impact of mouse genetics on the field of developmental biology. In the coming years, molecular biologists and clinicians are likely to be spending considerably more time at the bedside of mice which display interesting human disease phenotypes, perhaps giving new meaning to the following adage by Sir William Osler:

Medicine is learned by the bedside and not in the classroom.

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"Molecular Medicine in Genetically Engineered Animals"

January 1	Gene modification via "plug and socket" gene targeting	Jada Lewis, Baoli Yang, Pete Detloff, and Oliver Smithies
January 15	Biological insights through genomics: mouse to man	Edward M. Rubin and Gregory S. Barsh
February 1	In vitro differentiation of murine embryonic stem cells: new approaches to old problems	Mitchell J. Weiss and Stuart H. Orkin
February 15	Genes and physiology: molecular physiology in genetically engineered animals.....	Kenneth R. Chien
March 1	Animal models of human disease for gene therapy	James M. Wilson
March 15	New methods for genetic alteration and phenotypic analysis in the mouse	Andras Nagy and Janet Rossant
April 1	Transgenesis in the rat and larger mammals.....	John Mullins and Linda Mullins
April 15	Zebrafish as a model system to find genetic determinants of vertebrate physiology and disease	Mark Fishman and Wolfgang Driever
May 1	Recent advances in conditional gene mutation by site-directed recombination	Jamey Marth and Klaus Rajewsky

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