SECOND EDITION

The Mouse in Biomedical Research

Diseases

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American College of Laboratory Animal Medicine Series

The Mouse in Biomedical Research, 2nd Edition

Volume I
History, Wild Mice, and Genetics

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Volume I
History, Wild Mice, and Genetics

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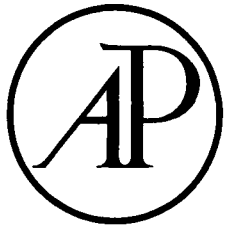

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Foreword for Volume I

Mice are centuries old as an interest of humans. Probably initially pets, eventually they became a research interest, even by Gregor Mendel in the 1800s. But it was the achievement of an inbred strain by Clarence Cook Little in 1909 that launched the mouse as a focus for understanding the biology and genetics of ourselves. The establishment of inbred strains nearly 100 years ago led the way to defined strains with animals of repeatable and also repeatably different genotypes for biomedical study. They soon offered the exciting initial understanding that genetics played a role in cancer.

With large mouse populations under observation, natural mutations of many varieties appeared, some morphological, some debilitating, others subtle with defined biochemical problems. And so it was recognized early that the mouse had similar (sometimes nearly identical) diseases to humans and that it could provide a powerful basis for a practical understanding of the human medical condition. For researchers it was obvious the mouse provided us as well with a tool for understanding the whole mammalian biology, including physiology, immunology, and development. Thus the mouse became essential for basic research. And the mouse was small, easily and economically maintained. It bred quickly and aged 30 times as fast as humans. It had everything.

A hope early on was that the powerful combination of genetics and chromosomal anatomy so well exploited in *Drosophila* would be found in the mouse. This hope was temporarily dashed when it was discovered that except for the X chromosome, all the chromosomes of the mouse were acrocentric. Except for their length, the mouse chromosomes were essentially indistinguishable. But soon after in the 1960s with the development of techniques for banding chromosomes, this drawback was fully overcome. The positioning of mouse genes on specific chromosomes and the studies of chromosomal aberrations and disease quickly advanced. We were all amazed at how many huge chunks of chromosomal segments were conserved between mouse and human since their separation some 65 million years ago. That finding alone has helped scientists to find genes controlling human disease, already found in the mouse. It cannot be understated that advancements in understanding of animal health and control of mouse diseases was essential for these wide ranging and exponential opportunities in research. Similarly, the parallel exponential advances in computer technology, capacity, and availability was essential.

The mouse has never since disappointed researchers as was evidenced by the first four volumes of The Mouse in Biomedical Research published in 1981-1983. In those volumes the word "exponential" was used many times. The success of the studies described there was a milestone for researchers to learn and reflect on the variety of scientific advancements and understanding the biology of the mouse. It provided as well a description of the fundamental guidelines and techniques for raising mice, essential for effective and humane experimentation.

"Exponential" continues to be the word for our times; it characterizes so many human endeavors and certainly research avenues, methodologies, and successes. Various new breeding schemes have revealed much about linkage and biological effects of specific genes, segments, and single chromosomes. A better understanding of mutagenesis has made the production and study of mutants an experimental science. Genes and other segments of chromosomes can now be moved around and exchanged among species. Gene therapy and stem cell research in the mouse have the promise of great immediate medical benefit. Every new research approach of course does not work, but the plasticity of biological systems and their seeming "willingness" to be maneuvered is surprising.

In the last two decades the rapid advances in DNA technology have made it now possible to study essentially complete known sequences of the genomes of mouse and human. It now does not surprise us that the human and mouse genomes each contain about 30,000 genes and that the DNA sequences are for the most part the same. Perhaps only a few hundred genes uniquely differentiate the species. Much non-protein coding DNA is also conserved, but for what reasons? Comparative genomics is providing awesome insights and raising revolutionary new questions.

It is timely now for this second edition of The Mouse in Biomedical Research where the state of the art in mouse research is captured again. Much has happened since the first edition. Much basic information has remained the same with modifications. The first volume entitled History, Wild Mice, and Genetics begins with three chapters by Morse, Tucker, Singleton, and Krebs on the background of the mouse in history, systematics, and natural environment. A researcher will find this fascinating background useful, because appropriate interpretation of laboratory findings may depend on it. Berry and Linder's chapter on Breeding Systems reveals the years of

development of such a variety of systematic mating schemes that manipulate the genome to better understand linkage and genetic effects. The following chapter by J. T. Eppig describes many years of thought given to systematic and agreed-upon nomenclature, essential to communication among us about genetically defined mice. The next four chapters by Adams, Davisson, Fox, Wiles, Petkov, and Handel provide a broad up to date understanding of present genetic knowledge of the mouse and methods for examining the genome. The exciting new approaches and prospects in mouse gamete and embryology are given by Kaufman and Lloyd. Then de Angeles, Michel, Wagner, Becker, Beckers, and Lloyd describe methodological advances and findings in the relatively new field of experimental mutagenesis. New developments in gene transfer and its value in mouse biology is given by Pergolizzi and Crystal. Lock's chapter shows how pluripotent embryonic stem cells have already provided many new avenues for research in mouse and human. The insights derived already are significant and the impact on medical science can be expected to be enormous. The last chapter by Jorge-Nebert, Derkenne, and Nebert shows the great advances in understanding the genetic nature of reaction and metabolism of drugs where information is desperately needed.

The breadth of topics and the depth of coverage, assures that The Mouse in Biomedical Research will continue to be a standard reference for investigators using mice in biological research.

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Preface

The American College of Laboratory Animal Medicine (ACLAM) was formed in 1957 in response to the need for specialists in laboratory animal medicine. The college has promoted high standards for laboratory animal medicine by providing a structured framework to achieve certification for professional competency and by stressing the need for scientific inquiry and exchange via progressive continuing education programs. The first edition of "The Mouse in Biomedical Research" consisting of four volumes, and published in 1981-1983 was a part of the College's effort to fulfill those goals. It is one of a series of comprehensive texts on laboratory animals developed by ACLAM over the past three decades: "The Biology of the Laboratory Rabbit" was published in 1974, "The Biology of The Guinea Pig" in 1976 and a two-volume work "Biology of The Laboratory Rat" in 1979 and 1980. Also, in 1979 the College published a two-volume text on "Spontaneous Animal Models of Human Disease". In 1984 the first edition of "Laboratory Animal Medicine" appeared in print followed by "Laboratory Hamsters" in 1987. The second edition of The Biology of the Laboratory Rabbit was published in 1994. A two-volume treatise on "Nonhuman Primates in Biomedical Research" was published in 1995 and 1998. A text "Anesthesia and Analgesia in Laboratory Animals" was published in 1997 followed by the second edition of "Laboratory Animal Medicine" in 2002. Most recently, the second edition of "The Laboratory Rat" was published in 2005.

The estimated annual use of 100 million-plus mice worldwide attests to the importance of the mouse in experimental research. The introduction of genetically engineered mice has only increased the usefulness of the mouse model in biomedical research. In no other species of animal has such a wealth of experimental data been utilized for scientific pursuits. Knowledge of the mouse that has been accumulated is, for the most part, scattered throughout a multitude of journals, monographs and symposia. It has been 25 years since the publication of the first edition of the "Mouse in Biomedical Research". The intent of this second edition is to build upon the framework of the first edition, rather than simply to update and duplicate the earlier effort.

The intended purpose of this text is to assemble established scientific data emphasizing recent information on the biology and use of the laboratory mouse. Separation of the material into multiple volumes was essential because of the number of subject areas covered. The four volumes consist of 80 chapters coauthored by 167 scientists.

The information in Volume 1 serves as a primer for scientists new to the field of mouse research. It provides information about the history, basic biology and genomics of the laboratory mouse (*Mus musculus*), as well as basic information on maintenance and use of mouse stocks. Mouse origins and relationships are covered in chapters on history, evolutionary taxonomy and wild mice. Genetics and genomics of the mouse are covered in chapters on genetic nomenclature, gene mapping, cytogenetics and the molecular organization of the mouse genome. Maintenance of laboratory mice is described in chapters on breeding systems for various types of strains and stocks and genetic monitoring. Use of the mouse as a model system for basic biomedical research is described in chapters on chemical mutagenesis, gene trapping, gene therapy, pharmacogenetics and embryo manipulation.

Volume 2 entitled Diseases departs from the first edition of the same title by discussing specific disease-causing microorganisms, whereas the first edition discussed infectious diseases affecting specific organs and tissues. This volume consists of 26 chapters subdivided into RNA viruses and DNA viruses, as well as bacterial, mycotic and parasitic infections. These chapters not only provide updates on pathogenesis, epidemiology and prevention of previously recognized murine pathogens, but also include chapters on newly recognized disease-causing organisms: mouse parvovirus, cilia-associated respiratory bacilli and *Helicobacter* spp. A separate category, consisting of 3 chapters, discusses zoonoses, tumor pathology of genetically engineered mice and spontaneous diseases in commonly used mouse strains.

Volume 3 encompasses 23 chapters whose contents provide a broad overview on the laboratory mouse's normative biology, husbandry and its use as a model in biomedical research. This consists of chapters on behavior, physiology, reproductive physiology, anatomy, endocrinology, hematology and clinical chemistry. Other chapters cover management, as well as nutrition, gnotobiotics and disease surveillance. Individual chapters describe the mouse as a model for the study of aging, eye research, neurodegenerative diseases, convulsive disorders, diabetes and cardiovascular and skin diseases. Chapters on imaging, surgical and other research techniques and the use of the mouse in assays of biological products also are included.

Volume 4 is a completely new addition to this series, dedicated to mouse immunology. It is based on the vast body of knowledge which has made the mouse the model of choice when studying immunity in human beings. Arguably more is known about the immune system in mice than any other species except human. In large part this is due to the power of genetic engineering to delineate molecular mechanisms. This volume includes an overview of mouse immunology, including both the innate and adaptive immune systems, followed by 15 chapters (mini-reviews), each dealing with a specific area of immunology. The overview addresses broad concepts concerning molecular and cellular immunology and cites both current references and the appropriate chapter, for more detailed information, from the mini-reviews which follow. The 15 chapters illustrate the power of genetic engineering in dissecting each component of the immune response from the development of lymphoid tissues to signal transduction pathways in activated cells. Individual chapters address: The Genomic Organization of the MHC, Toll-like Receptors, The Molecular Basis of Lymphoid Architecture, The Biology of Dendritic Cells, Somatic Hypermutation and Class Switching, Natural Killer Cell Function and Activation, Cytokine Mediated Signaling, Signal Transduction Events Regulating Integrin Function and T-Cell Migration, Central Tolerance in T-Cells, Peripheral Tolerance in T-cells, Inhibitory Receptors and Autoimmunity. The volume also includes the use of mice in studies of Systemic Autoimmunity, Immunodeficiency, Allergic Airway Inflammation and the Differences Between Mouse and Human Immunology.

This treatise was conceived with the intent to offer information suitable to a wide cross section of the scientific community. It is hoped that the four volumes will serve as a standard reference source for scientists using mice in biomedical research. Students embarking on scientific careers also will benefit from the broad coverage of material presented in compendium format. Certainly, specialists in laboratory animal science will benefit from these volumes; technicians in both animal care and research will find topics on surgical techniques, management and environmental monitoring of particular value.

The editors wish to extend special appreciation to the contributors to these volumes. Authors were selected because of knowledge and expertise in their respective fields. Each individual contributed his or her time, expertise and considerable effort to compile this resource treatise. In addition, the contributors and editors of this book, as with all volumes of the ACLAM series texts, have donated publication royalties to the American College of Laboratory Animal Medicine for the purpose of continuing education in laboratory animal science and comparative medicine. This book could not have been completed without the full support and resources of the editors' parent institutions which allowed us the time and freedom to assemble this text. A special thanks is also extended to the numerous reviewers of the edited work whose suggestions helped the authors and editors present the material in a meaningful and concise manner. We also thank the editorial staff of Elsevier for their assistance.

Finally, we especially acknowledge with deep appreciation the editorial assistance of Lucille Wilhelm, whose dedication and tireless commitment, as well as good humor, throughout this project were of immeasurable benefit to the editors in the completion of this text.

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Chapter 1

Building a Better Mouse: One Hundred Years of Genetics and Biology

Herbert C. Morse III

I. OVERVIEW

For the Mouse (Mus) prevails in the Latin.
For Edi-mus, bibi-mus, vivi-mus—ore-mus.

From *Jubilato Agno*
Christopher Smart (1722–1771)

I am the magical mouse
I don't eat cheese
I eat sunsets
And the tops of trees.

The Magical Mouse
Kenneth Patchen (1911–1972)

Thou wilt be as valiant as the wrathful dove, or most magnanimous mouse.

From *Henry IV*
William Shakespeare (1564–1616)

These quotes reveal the smallest portion of images of the mouse in mirth, myth, magic, and magnanimity to be found in literature and art covering a period of nearly 6,000 years. Aside from Disney's Mickey as the beloved centerpiece of that empire, our current affair with the mouse relates to its status as the model of choice for understanding mammalian biology in general and human biology in particular. Beginning with studies of mutations and naturally occurring polymorphisms that set the stage for the birth of mammalian genetics at the dawn of the twentieth century, research involving inbred mice has yielded profound insights into processes of critical importance to human health and disease. Mice have provided invaluable models of normal and aberrant processes affecting metabolism, aging, cancer, immunologic function, and many others. Recently developed gene-driven approaches that complement more established phenotype-driven studies have

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