THE MOUSE IN BIOMEDICAL RESEARCH

VOLUME I

HISTORY, GENETICS, AND WILD MICE

EDITORS:

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American College of Laboratory Animal Medicine Series

The Mouse in Biomedical Research

Volume I
History, Genetics, and Wild Mice

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The Mouse in Biomedical Research

Volume I

History, Genetics, and Wild Mice

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The Biology of the Laboratory Rabbit, 1974

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Foreword

The unique utility of the mouse in biomedical research has made it both a major contributor to and object of the information explosion of the last few decades. No other mammal has been used in such numbers or in so many experimental contexts. This, combined with the growth of research in general and the rapid progress in techniques and instrumentation, has made it the subject of an enormous accumulation of data. There are no precise figures for the annual use of mice in research, but estimates place the number for the United States at 20 million or more in 1979 and worldwide at perhaps 50 million. Fifty years earlier, the number worldwide might have been of the order of one million. The list of papers based on experiments using inbred mice, which appears semiannually in conjunction with the *Mouse News Letter,* has grown from 212 in the original six-month summary of October, 1953, to 2147 in the corresponding summary of April, 1980, an expansion of tenfold in 26½ years. Between the April 1979 and the April 1980 lists, there was a growth of 90 papers, a rate of 180 per year. There is no sign that the growth is slowing. I find it reassuring that a biologist can still comprehend the principles of biology over a wide range of areas. In fact, as the details in any one area fall into place the fundamentals become clearer and easier to grasp. There is a continuing need, however, for updating the expositions of these principles. The mass of details, moreover, from which the principles are derived has reached such encyclopedic proportions that it is beyond the mastery of anyone, even in the single areas of study. The result is a great need for compendia in which this information is gathered and made conveniently available for all users of the laboratory mouse.

This volume of "The Mouse in Biomedical Research" is a major step toward filling this need. The editors have enlisted an outstanding group of contributors to prepare the fourteen chapters presented. Several forthcoming volumes will further expand the coverage.

Three chapters give background information about mice of the genus *Mus*. Anyone making extensive use of mice will find them fascinating. The chapters by Marshall on Taxonomy and by Sage on Wild Mice are likely to surprise by the extent of speciation revealed by recent studies. The "house mouse" is not a simple entity. The Laboratory Mouse—A Historical Perspective by Morse brings us closer to the experimental area. Data revealing exponential growth in the number of mapped loci document the information explosion in one specific area, and charts showing the origins of widely used strains help to explain the genetic similarities which some strains manifest.

Six chapters deal specifically with inbred strains in one way or another. Chapter 9 by Staats updates the invaluable listing and description of inbred strains that have appeared periodically since 1952. Chapter 11 by Bailey contains lists of recombinant inbred and congenic resistant strains. Besides listings, there is also in this group of six chapters extensive coverage of methods of constructing, testing, and monitoring strains. These appear in Bailey's chapter, E. L. Green's Chapter 5 on Breeding Systems, Flaherty's Chapter 10 on Congenic Strains, and Hedrich's Chapter 8 on Genetic Monitoring. All these chapters reflect the wealth, diversity, and wide-ranging utility of inbred strains now available in mice. They also will serve to warn the unwary experimentalist of the pitfalls that beset him if he uses these strains without adequate precautions or awareness of their limitations. Important background material for users, and even more for developers, of inbred strains is contained in Lyon's Chapter 3 on Nomenclature. It is interesting to note how much more complex the rules of strain nomenclature are than they were at the time of a 1966 listing in "The Biology of the Laboratory Mouse," second edition, edited by E. L.

Green. This is, of course, just one more reflection of the growing diversity of the strains.

Lyon's chapter also covers gene nomenclature. This nomenclature reflects the complexity of the mouse genome, even as seen in the light of our still grossly imperfect understanding, just as the inbred strain nomenclature reflects the multiplicity of inbred stains. As Lyon notes, the well-ordered nomenclature developed by the Committee on Standardized Genetic Nomenclature for Mice is an important aid to the mouse user trying to cope with these complications.

M. Green's Chapter 6 on Gene Mapping considers the gene in the context of the chromosome as demonstrated by various linkage tests, and Miller and Miller's Chapter 12 on Cytogenetics examines the chromosome as demonstrated cytologically. Both chapters put considerable emphasis on methods. And how these methods have grown in diversity and ingenuity since I used to do linkage studies! Examples of the new methods are the use of recombinant inbred strains, of chromosome deletion from hybrid cells in linkage studies, and of the hybridization of radiolabeled RNA to localize individual loci on the cytological map. One fruit of the new technologies is a remarkable degree of unification of the originally separate genetically demonstrated and cytologically demonstrated maps. An interesting finding of the cytological studies is the surprisingly high frequency of visable chromosomal variants.

Finally, there are three chapters devoted to murine experimental studies. Klein covers the Histocompatibility-2 (*H-2*) Complex; Selby, Radiation Genetics; Nebert, Selected Aspects of Pharmacogenetics. Selby devotes some attention to methods, but the emphasis throughout is on experimental data and their interpretation. Taken together, these chapters are a striking testimonial to the value of the mouse as the cutting edge in studies of mammalian biology. The same is true of chapters by M. Green and by Miller and Miller. The *H-2* complex, the subject of Klein's chapter, has been at the very center of the information explosion and is the source of much of what we know about the major histocompatibility complex common to all mammals and perhaps all vertebrates. Studies of radiation genetics carried out with the mouse have illuminated the difficult subject of the genetic hazards of radiation. And pharmacogenetic studies, even though the mouse seems to have been underexploited in this area of research, have revealed yet another manifestation of genetic diversity and one that certainly deserves the close attention of drug manufacturers and physicians.

''The Mouse in Biomedical Research'' should establish itself as a major adjunct to future biomedical studies. The emphasis of this volume is on genetics, but it will become a standard reference for investigators using mice in many areas of 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 multivolume treatise, "The Mouse in Biomedical Research," is 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 decade: "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."

The annual use of approximately 50 million mice worldwide attests to the importance of the mouse in experimental 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 fifteen years since the publication of the second edition of "The Biology of the Laboratory Mouse" edited by E. L. Green and the scientific staff of the Jackson Laboratories. It is not the intent of this work simply to update and duplicate this earlier effort, but to build upon its framework. We are indeed fortunate to have Dr. Green and many of his colleagues at the Jackson Laboratory as contributors to this treatise. It is the intended purpose of this text 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 contents of Volume I are presented in fourteen chapters and provide information on taxonomy, nomenclature, breeding systems, and a historical perspective on the development and origins of the laboratory and wild mouse. Six chapters deal specifically with the ever-increasing diversity of inbred strains of mice, including coverage of methods of developing and the genetic monitoring and testing of these strains. The emphasis of this volume on genetics is also manifested by chapters discussing the *H-2* complex, cytogenetics, radiation genetics, and pharmacogenetics.

Because of the impact of spontaneous diseases on interpretation of, and potential for, complicating experimental research, it is of paramount importance for investigators to recognize these diseases and their effect on the mouse. Volume II, for the first time, compiles in one format a narrative detailing infectious diseases of the mouse; the chapters cover bacterial, mycotic, viral, protozoal, rickettseal, and parasitic diseases. Also, non-neoplastic and metabolic diseases are covered as well as the topic of zoonoses.

Volume III provides comprehensive coverage of selected material related to normative biology and management and care of the laboratory mouse. Developmental, anatomical, nutritional, physiological, and biochemical paramters of the mouse are compiled in several chapters and will be of great interest and an important resource for normal biological profiles. A review of the histologic features was not included because of space constraints and the availability of this information in previous texts. Environmental monitoring and disease surveillance as well as management and design of animal facilities will be particularly useful for those individuals responsible for the management of mouse colonies. The chapters on gnotobiotics and gastrointestinal flora represent the state of the art in gnotobiology. The three chapters on selected aspects of immunology in the mouse serve to highlight the explosive progress being made in immunologic techniques and instrumentation and the underlying importance of genetic differentiation.

The fourth volume includes selected applications of the mouse in research. Several chapters discuss the use of the mouse in infectious disease research, while others range from eye research to the use of the mouse in experimental embryology. The chapters devoted to the use of the mouse in oncological research follow a body system format. Research topics in other disciplines have not been included, but hopefully will be included in future editions.

This treatise was conceived with the intent to offer information suitable to a wide cross section of the scientific community. It is hoped that it will serve as a standard reference source. Students embarking on scientific careers will benefit from the broad coverage of material presented in compendia 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. This book could not have been completed without the full support and resources of the editors' parent institutions which allowed 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 acknowledge and thank Rosanne Brown and Sara Spanos for their secretarial assistance. Also, the assistance provided to us by the staff of Academic Press was greatly appreciated.

Finally, we especially acknowledge with deep appreciation the editorial assistance of Patricia Bergenheim, whose dedication and tireless commitment to this project were of immeasurable benefit to the editors in the completion of this text.

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Contents

Chapter 1

The Laboratory Mouse—A Historical Perspective

Herbert C. Morse, III

Mus musculus, the house mouse of North America and Europe, is the experimental animal, par excellence, of modern biomedical research. By virtue of its manifold variations, convenient size, fertility, short gestation period, ease of maintenance, variable susceptibility and resistance to different infections, and exemplification of many diseases that afflict mankind, it has found a major place in the laboratories of geneticists, developmental biologists, immunologists, cell biologists, and oncologists. In spite of the current "most favored" status of this remarkable mammal in laboratories throughout the world, the relationship between man and mouse has not always been so cordial.

As noted by Keeler (1931),* the word *mouse,* and its variations in Latin-based languages, comes originally from the Sanskrit *mush* derived from a verb meaning *to steal.* Mankind, thus, was well-acquainted with the predatory habits of this creature by at least 4000 years before Chirst. Mice and rats, through their voracious activities in grain larders and as carriers of disease, inflicted considerable losses in food and lives upon ancient civilizations (Moulton, 1901). Examples of the mistrust and hatred that mice engendered in ancient societies can be seen in the deification of the Egyptian cat goddess, Bastet, during the Third Dynasty (circa 2800 BC, and the vilification in the Hebrew "Book of Leviticus" (11:29): "And these are unclean to you among the swarming things that swarm upon the earth: the weasel, the mouse, the great lizard according to its kind."

In spite of their distasteful reputation throughout most of the western ancient world, mice were protected, if not worshipped, in parts of the Middle East and the Orient. Around 1500 BC, a Greek contingent from Crete warred against the Troad of Asia Minor and were victorious. As myth would have it, their success was due to mice having chewed the leather from the shields of their adversaries (Gesner, 1551). In gratitude, the Greeks built a temple to Apollo smintheus, the mouse god, on the island of Tenedos. Mice raised under the altar of the temple were used for prophecy and employed in the art of healing. The mouse cult soon spread throughout Asia Minor and parts of Egypt, and Apollo smintheus and his mice were frequently represented on coins minted in these areas. Two such coins are shown in Fig. 1. The one on the top, showing Apollo smintheus crowned by the gates of the city of Alexandria and with a mouse at the nape of his neck, may be unique to the collection of Clyde E. Keller. No similar coins have been located in the extensive collections of the American Numismatic Society or the British Museum. The coin on the bottom shows a much more common representation of Apollo smintheus. Worship of this god and his mice probably continued in some form until the conquest of the area by the Turks in 1453.

A modern parallel to the battle of the Cretins against the

*This history of the mouse as reviewed in this chapter has many gaps. Some are intentional in that certain eras and people important in the development of mice have already been covered in depth. Keeler's (1931) monograph is replete with information on the ancient history of the mouse. The book, "Origins of Inbred Mice," deals more extensively with the personal histories of W. E. Castle, A. E. C. Lathrop, C. C. Little, L. C. Strong, J. Furth, W. E. Heston, H. B. Andervont, G. D. Snell, M. C. Green, and E. L. Green. The complete history of The Jackson Laboratory has recently been published (Holstein, 1979).

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Fig. 1. Two coins representing Apollo smintheus. (A) This cast comes from the personal collection of Dr. Clyde Keeler. (B) This cast is from the collection of the British Museum. (Courtesy of the Department of Coins and Medals, The British Museum, London, England.)

Troad is found in the history of World War II. During the seige of Stalingrad, German tanks, waiting in reserve to support the flanks of the attacking army, were stored in pits and camouflaged with straw from surrounding fields. When a Russian counterattack seemed imminent, orders were given to mobilize the tanks. Surprisingly, only a third of the tanks could be started, and of those that did, many failed or even caught fire on their way to the front. The reason for this calamity was soon apparent. During storage, field mice had made their way into the tanks in search of food and had nibbled away the insulation on the wiring. As a result, faults developed in the electrical equipment, and the tanks were out of commission from short circuits and sparking (Carell, 1964). In spite of the ensuing turn of events at Stalingrad and the rest of World War II, there is no history of a mouse cult developing in Russia.

The Chinese and Japanese also have a long recorded history of amicable relations with the mouse. The Buddhist belief that the spirit of Buddha is present in man and all living creatures is probably basic to this history. Thus, in paintings dating from as early as 1300 AD, all forms of animals (including animals abhorred in the West, such as, mice, snakes, and toads) were depicted in writhing agony at the death of Buddha. The Chinese word for white mouse is an ancient one, dating back at least to the time of the printing of the first Chinese lexicon in 1100 BC when albinos were used by Chinese priests in auguries. Throughout the Orient, the mouse has found recognition in that (a) one of every 12 years is known as the year of the mouse; (b) the day, being divided into twelve 2-hour periods, has the hours between 11:00 AM and 1:00 PM designated as the hour of the mouse, and (c) multiplications by serial 2s are known as *mouse numbers*.

In Japan, the mouse was given the elevated status of the messenger of the God of Wealth, Daikoku (Keeler and Fumi, 1937). A sure sign of financial stability in both Japan and China was symbolized by a well-stocked rice supply; Daikoku is usually shown reclining on bales of rice with mice nearby. Hokusai's painting of mice on rice bales (Fig. 2) was therefore probably prompted by religious and not economic persuasions. This black and white representation of his work does not do justice to his painting of a mutant black nonagouti mouse (top), four albinos bearing the ruby mutation (lower portion), or the two mice of wild type (dark eyes) carrying chinchilla (c^{ch}) or extreme albino (c^{ce}) mutations. The Japanese were probably also the first to maintain unusual (fancy) mice, for mutant waltzing mice were recorded as early as 80 BC.

During the late Greco–Roman and early Christian era, mice found their next place in the history of medicine, and then as part of a flourishing "pharmaceutical industry." Whole mice (or their various parts) were regularly included in potions designed to cure any of a number of maladies. One such concoction, composed of 10 newborn mice dissolved in olive oil and mixed with yellow and white Artemisia flowers, was still being produced for export to New York Greeks when Keeler visited the Island of Tenedos in the early 1930s (Keeler, 1932, and personal communication). Apparently, debate still rages as to whether yellow or white flowers are required for this brew, and the therapeutic nihilists have even suggested that the value of newborn mice is questionable.

However, until the early years of the seventeenth century, mice were not employed in experimental studies. This era marked a major transition point in the history of biology. From the age of Aristotle until the seventeenth century, biology had been a classic science with its primary goal being the descrip-

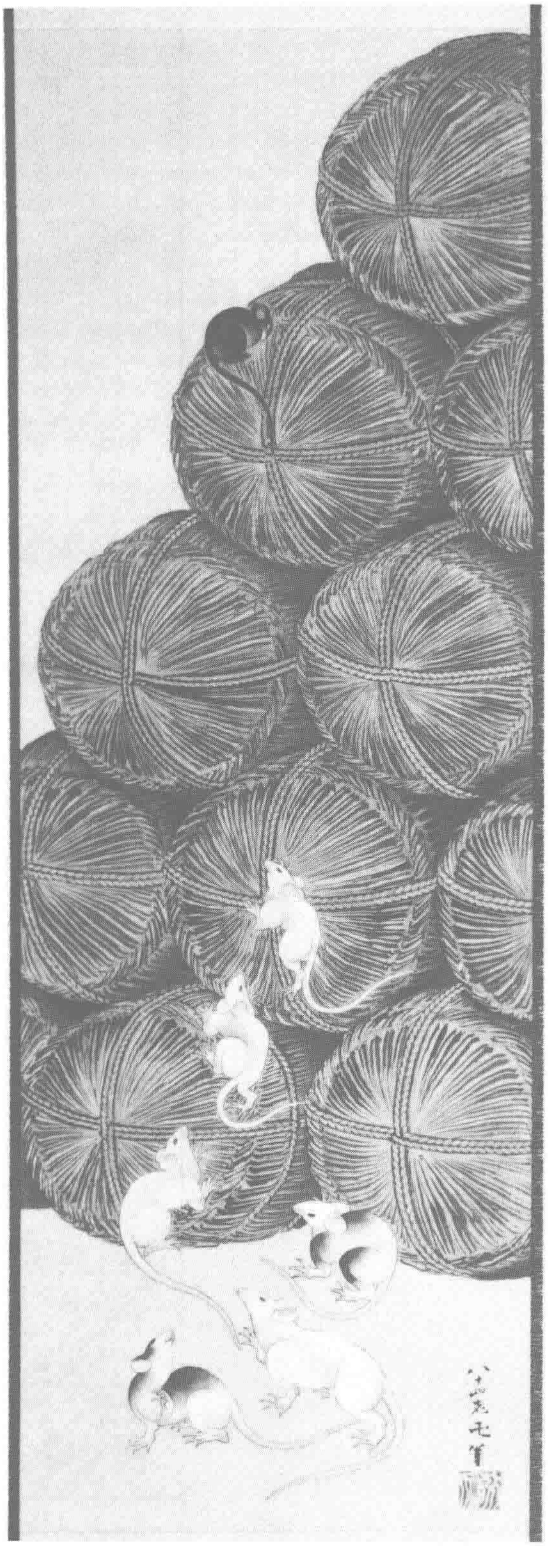

Fig. 2. Japanese painting of the Edo period (Ukiyoe school) attributed to Hokusai (1760–1849). Mice (symbolic of Daikoku) and rice bales (indicative of wealth). (Courtesy of the Smithsonian Institution, Freer Gallery of Art, Washington, D.C.)

tion and classification of natural phenomena. The new biology became an experimental science, one predicated on man's ability to frame questions about the living state and then to devise ways of answering such questions. This fundamental shift in emphasis was heralded by the brilliant studies of William Harvey (1578–1657; Fig. 3) on animal reproduction and blood circulation. Inasmuch as mice were repeatedly employed in the detailed comparative anatomic studies of vertebrates and invertebrates that formed the foundation of Harvey's (1616) work, the house mouse has been part and parcel of the experimental method since its inception.

Whereas Harvey led a long and rewarding life as scholar, physician to Kings James I and Charles I, and President of the Royal College of Physicians, others who successfully employed the mouse in early experimental studies met with less kindly ends. Joseph Priestly (1733–1804), a nonconformist English clergyman credited with the discovery of oxygen, used

Fig. 3. Portrait of William Harvey, founder of the experimental method, after a portrait in the British Museum. (Courtesy of the History of Medicine Section, National Library of Medicine, Bethesda, Maryland.)

mice extensively in his studies of the phlogiston theory. In his treatise, "Experiments and Observations, Vol. 1," Priestly describes an experiment designed to test if plants might purify air "polluted" by animals. (The experimental apparatus and the animals and plants used in this work are shown in Fig. 4.)

> In order to ascertain this, I took a quantity of air made thoroughly noxious by mice breathing and dying in it, and divided it into two parts; one of which I put into a phial immersed in water, and to the other (which was contained in a glass jar standing in water) I put a sprig of mint. That was about the beginning of August 1771, and after eight or nine days, I found that a mouse lived perfectly well in that part of the air, in which the sprig of mint had grown, but died the moment it was put into the other part of the same original quantity of air, and which I had kept in the very same exposure, but without any plant growing in it (Priestly, 1775).

Twenty years after this experiment, Priestly was hounded from his residence by a Birmingham mob incensed with his unorthodox theology (not his science) and fled to the United States. He died there in 1804.

The hand of fate dealt even more severely with Priestly's intellecutal successor, Antoine Lavoisier (1743–1794; Fig. 5). Although widely recognized as the father of modern chemistry, Lavoisier also made major contributions to our understanding of the physiology of respiration. He used mice repeatedly in the studies detailed in "Experiments on the Respiration of Animals," published in 1777. Like Priestly, Lavoisier did not find complete fulfillment in his life as a scientist and engaged himself in the workings of the royal tax system. As a result of

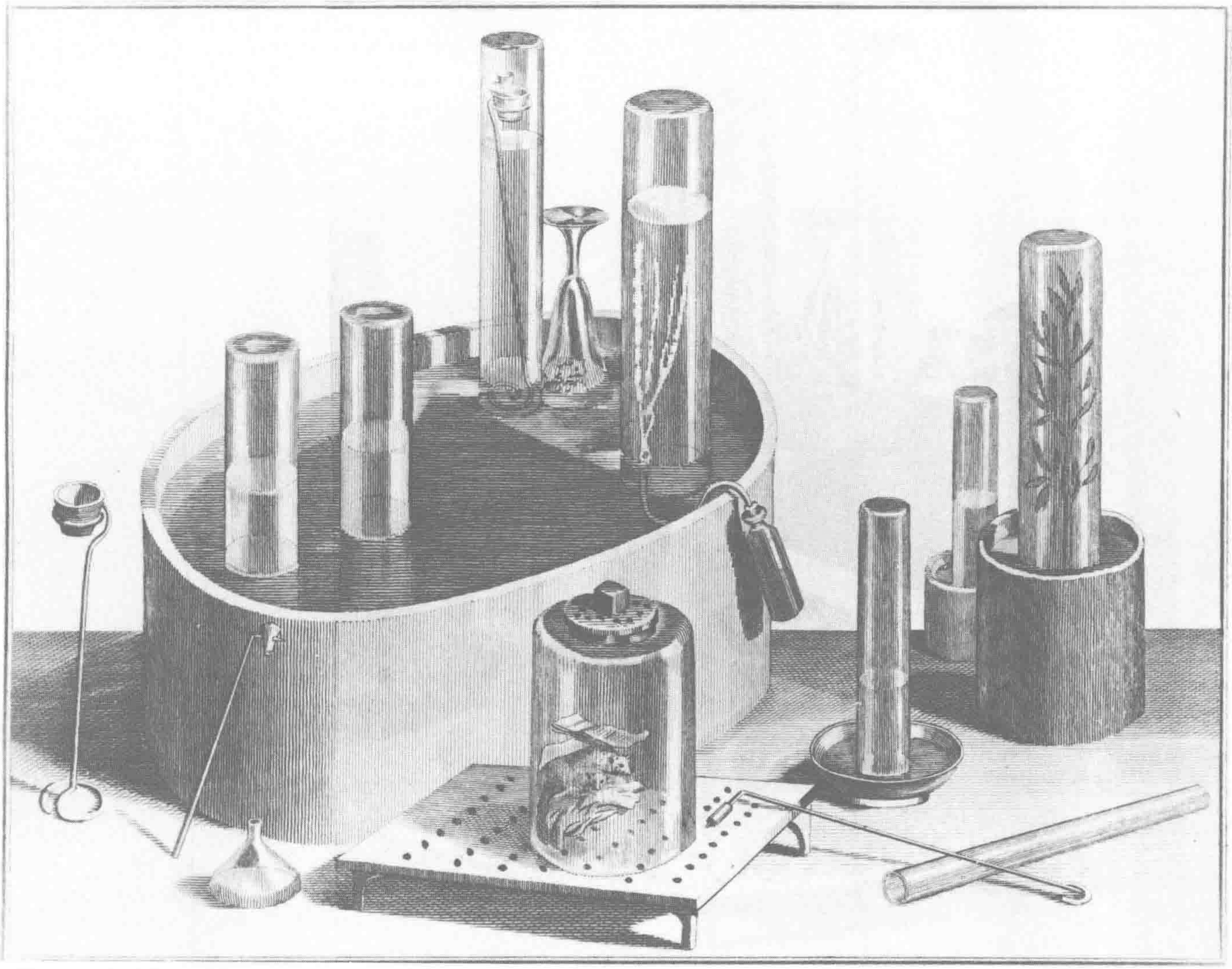

Fig. 4. Materials used by Joseph Priestly in his experiments on the phlogiston theory. Note the two mice in the foreground cage and one in the immersed phial. (From the frontispiece of "Experiments and Observations. Vol. 1" courtesy of the History of Medicine Section, National Library of Medicine, Bethesda, Maryland.)