

Chapter Seven

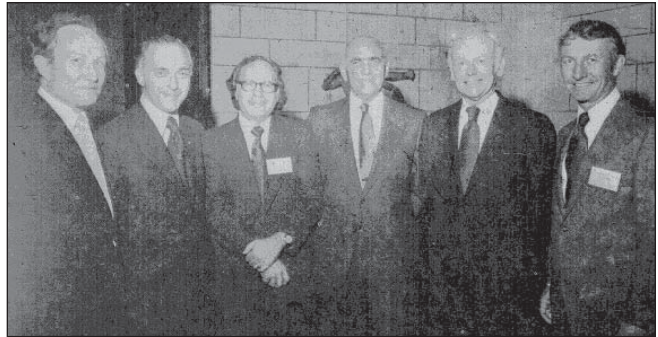
The History of the Institute of Laboratory Animal Resources 1953–1999

Thomas L. Wolfle, DVM, PhD

An editorial in the Institute of Laboratory Animal Resources' (ILAR) first newsletter, dated October 1957, stated that ILAR and augury have common roots. It suggested that the forefathers of ILAR served as prophets, a status similar to that which the legends of Homer ascribed to the priest of the god of mice, Apollo Smintheus (1). Just how well this analogy fits is left to other historians, but it is unmistakable that ILAR's forefathers' ability to plan wisely for the future, and their benevolence toward laboratory animals, continues to the present time as ILAR's legacy.

ILAR's early history blends indistinguishably with the rise of laboratory animal science as a discipline and portions of this history have been told (2, and in numerous issues of the *ILAR News* and its successor, the *ILAR Journal*). The overlap with other historical manuscripts in this volume, in terms of common forefathers and key events, are unavoidable and perhaps desirable, for it emphasizes the importance of the vision of a few individuals and their collegial relationships that fostered the development of laboratory animal science.

Zeitgeist perhaps best describes the origin of ILAR, for after World War II increased attention was being devoted to medicine and key players were congregated in a few research facilities of mid-western universities. In 1945, Nathan Brewer was hired by the University of Chicago to manage the laboratory animal facility and to develop plans for a new facility (Brewer, personal communication). As he proceeded with these chores, other veterinarians were hired by Chicago-area institutions: Bennett J. Cohen, Northwestern University; Elihu Bond, University of Illinois; W. F. Schroeder, Hektoen Institute of Medical Research at Cook County Hospital; and Robert J. Flynn, Argonne National



(Left to right) Cluff Hopla, Bennett Cohen, Tom Clarkson, Bob Yager, Howard Schneider and Ed Melby. Hopla, Cohen, Clarkson, Schneider and Melby have served as ILAR Council Chairs, and Yager was ILAR Director from 1965 to 1975.

Laboratory. These men are some of the giants of laboratory animal science; they, and their colleagues, are the history of ILAR.

On November 28th, 1950, at the initiative of these men, a meeting was convened at the University of Chicago, which brought together approximately 75 persons with an interest in laboratory animal care from Canada and the United States. This meeting resulted in the organization of the Animal Care Panel (ACP) with Nate Brewer, Chairman; Charlie A. Slanetz, Vice Chairman; and Ben Cohn, Secretary. Subsequently, annual meetings were held and minutes were published as *The Proceedings of the Animal Care Panel*.

In parallel with his work in creating the ACP, Nate Brewer was developing a quality laboratory animal program at the University of Chicago. Impressed with the opportunities and challenges that lay ahead of laboratory animal science, Paul Weiss (Chairman of the Division of Biology and Agriculture of the National Research Council (NRC), National Academy of Sciences) was motivated to convene a Conference on Animal Procurements on July 10, 1952. The conference was chaired by scientist-administrator Clarence Cook Little of the Jackson Memorial Laboratory. The result of this conference was to request that the NRC, establish a Committee on Animal Resources (CAR) "for the purpose of recommending a long-term procurement and supply mechanism of animals for biologic, medical, and agricultural research." The conference report specifically charged the CAR to take advantage of the expertise of existing organizations and individuals and to seek implementation of their recommendations by the NRC. In November 1952, the CAR recommended formation of the Institute of Animal Resources (IAR) within the NRC. In July 1953, the IAR was established under the NRC's Division of Biology and Agriculture. T. C. Byerly was Chairman of IAR this first year and was replaced by Dale W. Jenkins in 1954 (Table 1). Orson N. Eaton was hired as the first Executive Secretary in July 1954 (Table 2).

During the early years, the membership of the IAR advisory committee was a Who's Who of early laboratory animal science, with such distinguished veterinarians and investigators as Philip Armstrong, Cornell University; Jules Cass, University of Cincinnati; L. R. Christensen, New York University; C. N. W. Cumming, Carworth Farms; Nathan Brewer, University of Chicago; Paul Day, University of Arkansas; R. J. Flynn,



T.C. Byerly, first Chairman of Council

Table 1. ILAR Council Chairs

Dates	Name
1953–1954	T. C. Byerly
1954–1959	Dale W. Jenkins
1959–1962	George E. Jay, Jr.
1962–1966	Bennett J. Cohen
1966–1969	Howard A. Schneider
1969–1972	Thomas B. Clarkson
1972–1975	Cluff E. Hopla
1975–1978	Edward C. Melby, Jr.
1978–1981	Nicholas G. Bottiglieri
1981–1987	Franklin M. Loew
1987–1993	Steven P. Pakes
1993–Present	John L. VandeBerg

Table 2. ILAR Directors

1954–55	Orson N. Eaton
1955–65	Berton Hill
1965–75	Robert Yager
1975–87	Earl Wayne Grogan
1988–1997	Thomas L. Wolfle
1998–	Ralph Dell

Argonne National Laboratory; Benjamin Fremming, Balcones Research Center, U.S. Air Force; Harry Herrlein, Rockland Farms; George Jay, National Institutes of Health (NIH); George Kidder, Amherst College; Walter Landauer, University of Connecticut; C. C. Little and E. S. Russell, Jackson Memorial Laboratory; Raymond Randall, Walter Reed Army Institute of Research; Victor Schwentker, The West Foundation; Charles Slanetz, Columbia University; Paul Weiss, Rockefeller Institute; and many others.

Two years after IAR was established within the NRC, Chairman Byerly established a "Subcommittee on Health Standards", which appointed a Parasitism Committee chaired by Nate Brewer, who was also serving as a member of the IAR scientific advisory council. This committee produced the first IAR report titled, *Parasitic and Infectious Diseases of Laboratory Animals* (3). This timely report provided the first comprehensive information relative to "infections and infestations of laboratory animals, to the end that diseases of laboratory animals may be effectively controlled". It called for "a system of accreditation and certification of laboratory breeders..." and for "the elimination of certain diseases in animal colonies" in order for accreditation and certification to succeed.

In 1956, when the Diseases report was released, the National Cancer Institute's (NCI), Cancer Chemotherapy National Service Center (CCNSC) contracted with the newly renamed Institute of Laboratory Animal Resources (ILAR) to develop minimum standards for the commercial production of rando-bred and inbred mice. A conference on Animal Standardization and Accreditation, chaired by T. C. Byerly, initiated the development of the requested standards. Key to their development was the assignment of George Wolff, CCNSC, to ILAR. He inspected a number of commercial mouse production facilities and consulted with experts on a range of genetic, disease, and management issues. These site visits and discussions led to development of the Standards by which the CCNSC implemented the first accreditation of commercial mouse breeding facilities.

During the mid-50s, while Berton Hill was Director and Dale Jenkins was Chairman of Council, ILAR became deeply involved in issues relating to the availability of rhesus monkeys

for research and the transportation of laboratory animals. Transportation and Primate Committees¹ were formed, conferences were held, and reports developed, which directly impacted the manner in which laboratory animals were transported and led to the development of domestic rhesus monkey breeding colonies to ensure stable supplies of this valuable animal. Indirectly, the work of the ILAR Primate Committee led to the establishment of the NIH-sponsored National Primate Research Centers program, the first of which was the Oregon Primate Center, dedicated on May 6, 1962.



Berton Hill

In December 1956, ILAR joined with the United Nations Educational, Scientific, and Cultural Organization (UNESCO), the International Union of Biological Sciences (IUBS), the Committee on International Organization of Medical Sciences (CIOMS), and representatives from organizations in Great Britain and France to discuss international transport, supply, and quality of laboratory animals. An International Committee on Laboratory Animals (ICLA) was established to which ILAR appointed a representative. ICLA was conceived as a non-governmental organization to promote high standards of laboratory animal quality, care, and health. In 1979, the name was changed to the International Council of Laboratory

Animal Science (ICLAS). [Steven Pakes, former ILAR Chairman, was elected Secretary General of ICLAS in 1995.] ILAR continues to serve as the U.S. representative to ICLAS. It is an important link in ILAR's international programs, which are designed to provide assistance to investigators in developing countries through dissemination of ILAR reports. This international effort also seeks to harmonize policies under the General Agreement on Tariffs



Steven Pakes

and Trade (GATT) (World Trade Organization) and the North American Free Trade Agreement (NAFTA) in order to facilitate exchange of biological materials and animals used in research and for the marketing of biologicals and pharmaceuticals derived from their use.

Animal Models and Genetic Stocks

Throughout the 1950s, ILAR developed a reputation as a source of information for locating unique laboratory animals and for information regarding their care and use. ILAR began replying to approximately 2,000 requests annually for this information and, in October of 1957, published the first quarterly *Information on Laboratory Animals for Research* newsletter "to develop and distribute information for laboratory animal science."

Sensing the need for a scientific and reliable source of information, the Genetics Society of America and the NIH adopted a resolution that cited a need to establish a central agency to collect, maintain, and disseminate information on animal models and genetic stocks useful in biomedical research. In response, ILAR conducted surveys of inbred and hybrid mouse producers in cooperation with the National Cancer Institute, the results of which Bert Hill described as "an unparalleled treasury of data on

producers, users, stocks and characteristics." The data assembled from these surveys soon led to the popular publication, *Animals for Research* (4), which contained a compilation of commercial sources of laboratory animals. Periodic revisions of *Animals for Research*, and ILAR staff replies to thousands of queries for sources of biological resources and for appropriate models for disease, constituted ILAR's expanding Animal Models and Genetic Stocks (AMGS) program, which was directed by ILAR's AMGS Committee under the leadership of John VandeBerg, William Stone, and others. In 1988, the decision was made to also include investigator-held animals. This, and the enormously expanding sources of genetically engineered transgenic and "knock-out" animals, caused the number of listings to soar faster than *Animals for Research* could be revised. For the next 10 years, this database was housed on a Wang main frame computer in the NRC and was used by ILAR staff to answer telephone and written inquiries. With the coming of desk-top computers and the Internet, the logical answer was to place the entire AMGS database on-line. In 1998, *Animals for Research* was combined with the *International Index of Laboratory Animals* (5), which provides the location and status of over 7,000 stocks of laboratory animals throughout the world, and both were linked to ILAR's Home Page. These databases provide an extensive listing of sources of unique animals and enable direct on-line access eliminating the need to seek the information from the ILAR staff and permitting ILAR to more rapidly update the listings.

Another part of the AMGS database is the international listing of Laboratory Genetic Codes, established at the request of the International Committee on Standardized Genetic Nomenclature for Mice. This code is international in scope and provides instant recognition of the source of an animal. As stated in *Rodents: Laboratory Animal Management Series* (6), "each laboratory or institution that breeds rodents should obtain a laboratory code from ILAR.

Principles of Humane Care

In the late 1950s, ILAR's Committee on Animal Care began developing species-specific standards, including standards for Syrian hamsters, rabbits, guinea pigs, cats, and primates, which provided information for the care and use of these animals. As such, these reports—then and today—serve as valuable supplements to the *Guide for the Care and Use of Laboratory Animals* (7). These committees also developed *Principles of Animal Care*, and adopted *Guiding Principles in the Use of Animals by Secondary School Students and Science Clubs*. These Principles, revised by ILAR in 1989 as *Principles and Guidelines for the Use of Animals in Precollege Education* (8), are endorsed by the American Veterinary Medical Association, Science Service (parent organization of the International Science and Engineering Fairs and the Westinghouse Talent Search), National Association of Biology Teachers, National Science Teachers Association, and federal agencies of the Interagency Research Animal Committee.

The Origins of Microbiological Quality Control

An important series of meetings began in April 1959 at the Lobund Institute of the University of Notre Dame. Co-sponsored



John VandeBerg

by ILAR, the Lobund Institute, NIH, and the Office of Naval Research, this first of three annual meetings in South Bend, Indiana was designed "to show the individual scientist how he can adapt current techniques in germ-free technology to his own investigations" (9). The second "Gnotobiotic Workshop" was convened by ILAR and attended by representatives of eleven commercial rat and mouse breeders. This 4-day meeting demonstrated construction of flexible film isolators, cesarean section derivation of germ free animals, detection of microbial contamination, effect of microbial contamination upon the health of the animals, and methods for shipment of germfree animals. Upon completion of this workshop, collaboration continued for a year between commercial breeders and Professor P. C. Trexler of the Lobund Institute. By assessing the microbiological status of discarded breeders sent to him by the participating commercial breeders, Trexler issued certificates to those whose animals remained germfree for at least six months (10). This workshop was the first attempt by commercial breeders to produce germfree animals and led to the formation of the Association for Applied Gnotobiotics the following year.

ILAR Reports at Work—Comparative Medicine Training Programs

Eight years after the formation of ILAR great strides had been made in many aspects of laboratory animal science. The ACP was formed, the AVMA recognized laboratory animal medicine as a specialty, a gnotobiotic organization began to address the quality of research animals, and the concept of accreditation of animal care and use programs was about to be launched as a private, non-profit organization. While ILAR reports fueled growth of the discipline, this growth also continued to require guidance from ILAR. The time had come for consensus reports on laboratory animal facilities and care. The first of these resulted from a symposium on Research Animal Housing, sponsored by ILAR in November 1962 and attended by over 500 people. The proceedings (11), and those of a subsequent report, *Laboratory Animal Housing*, served as a standard for architects, budget and administrative personnel, and animal colony managers for many years.

Numerous reports were developed by ILAR that required professional judgement and implementation by veterinarians, colony managers, scientists, and animal technicians. Information and training was provided for some at national and regional meetings of the ACP. But, as veterinarians were added to the staff of many industrial laboratories, government research institutions, and academic institutions their value in these assignments increased the demand and soon exceeded the supply of available "laboratory animal" veterinarians. In 1960, in order to meet this demand Thomas Clarkson at Bowman Gray School of Medicine started the first program for Veterinary Postgraduate Training in Laboratory Animal Medicine. The following year, Colonel Robert Hummer of Brooks AFB, Texas, initiated a Laboratory Animal Residence program in conjunction with Texas A&M University. During his tenure as Chairman of ILAR, Ben Cohen initiated a similar program at the University of California at Los Angeles. The NIH assisted in the funding of these and other similar postgraduate laboratory animal medicine programs, and soon required guidance by which the excellence of these competitively awarded training grants could be assessed. The NIH Division of Research Resources (now the National Center for Research Resources) requested help from ILAR, which resulted in a *Workshop on*

Graduate Education in Laboratory Animal Medicine held in March 1965, in Washington, D.C. The usual people were leading the discussions—Cohen and Clarkson—but new names such as Kenneth Burns, Charles Cornelius, Al Edwards, Roger Estep, Hal Eyestone, Ed Melby, Charles Middleton, Al Moreland, L. J. Serrano, Sigmund Rich, and Orland Soave began to appear. Three study groups wrestled with such issues as the definition of laboratory animal medicine, manpower needs in laboratory animal medicine for the next 5, 10, and 20 years, and increasing need for graduate education and training in laboratory animal medicine. Later that year, ILAR held an animal technician training workshop, attended by over 100 people.

Following these meetings, ILAR completed *A Guide to Postdoctoral Training in Laboratory Animal Medicine*, revised it in 1971 and again in 1978, as *Laboratory Animal Medicine: Guidelines for Education and Training* (12). These reports served for over two decades as the standard for training and education of veterinarians in laboratory animal (“comparative”) medicine. Today, training programs in laboratory animal medicine not only provide clinical skills essential for support of the nation’s biomedical research enterprise, but also training for principal investigators. The combining of expertise in comparative medicine and research methodology enhances knowledge of diseases of laboratory animals and their use as models of diseases of humans. It should also be noted that training of veterinarians to recognize deviations from the normal condition in many species has provided some of the most valuable serendipitous discoveries of animal models of human diseases.

The Growth of a Young Discipline

Key events of the 1960s gave evidence of the strong future of laboratory animal science: publication of the guidelines for laboratory animal training, recognition of the American College of Laboratory Animal Medicine (ACLAM) by the AVMA, the hiring of Joseph J. Garvey as the first full-time Executive Secretary of the ACP, and publication of the *Guide*.

In 1962, the executive committees of ACP and ILAR met to establish a division of responsibilities. With ILAR serving as the liaison between the laboratory animal science community and the National Academy of Sciences, development of guidelines and standards fell to ILAR and education remained the purview of the ACP. There are many accounts during this period in which ILAR, ACP, ACLAM, AAALAC, and the National Society for Medical Research (NSMR) had productive meetings, which cross-fertilized the young discipline. This close interaction was considered essential for continued success of individual organizations and the laboratory animal science discipline. In addition to the collaborations among the various laboratory animal science organizations, collaboration within the NRC was also often effective in making contributions to this field. One such successful effort, was the role played by the NRC’s Board on Agriculture in producing a series of *Nutrient Requirements of Laboratory Animals* reports (18). By October 1961, these reports were available for poultry, swine, dairy and beef cattle, sheep, horses, foxes and minks, dogs, and rabbits. This series continues to be valuable and is updated frequently.

The Guide Sets New Standards and Responsibilities

The need by investigators and colony managers for well-defined parameters of animal care and use fueled the development of one of the most significant advancements yet to be made in

laboratory animal science: the 1963 *Guide for Laboratory Animal Facilities and Care* published by the ACP under contract from the Division of Research Resources, NIH. The names of its authors—Cohen, Clarkson, Flynn, Rabstein, Soave, Thorp, and Trum—are legends in laboratory animal science. As is so often the case, the most capable people wear many hats. Such it was for Bennett Cohen. In 1962, he was elected Chairman of ILAR and in 1963, President-elect of ACLAM. At that time, he was also chairman of the ACP’s Standards for Laboratory Animal Facilities and chairman of the authoring committee of the *Guide*. Through this cross-fertilization, ILAR collaborated with the ACP in developing this first issue and soon endorsed it, giving it the influential imprimatur of the National Academy of Sciences. After only two years, ILAR was asked by NIH to develop the second edition. This attests to the importance of the document and the rapidly changing state of laboratory animal science.

The importance of this new report cannot be overstated. The document provided the first yardstick against which facilities could judge their animal care facilities and programs. Also, an important but largely immeasurable outcome was the impact of the *Guide* on Congress, the Department of Agriculture, and the public. The *Guide* provided widely accepted guidance on laboratory animal care and use prior to any national animal welfare laws. Then, upon passage of the 1966 Animal Welfare Act, ILAR was commissioned by the Department of Agriculture to prepare “*Recommended Minimum Standards for the Humane Handling, Care, Treatment, and Transportation of the Animals Prescribed under the Act.*” Five subcommittees were appointed. The report, considered by USDA along with those submitted by humane groups and animal dealers, contributed to the content and “performance” tone of the *Guide* in the resulting USDA regulations.

As further evidence of the sincerity of biomedical scientists to use and care for laboratory animals properly, following publication of the *Guide* the ACP initiated the Animal Facilities Accreditation Board and successfully conducted a pilot visitation program to 24 institutions. Subsequently, in the fall of 1965, the leadership of ACP, who had participated in the writing of two editions of the *Guide* and a number of ILAR publications on species standards, diseases, and training, sought to validate the utility of these documents and to formalize the accreditation process. For this, they joined with a 15-member Board of Trustees to establish a volunteer accreditation program known as the American Association for Accreditation of Laboratory Animal Care (AAALAC). AAALAC’s announcement of this new venture stated “The U.S. Public Health Service’s *Guide for Laboratory Animal Facilities and Care* serves as the basic guide used in evaluating institutional animal care facilities” (13).

A review of the first *Guide* reminds one of the changes made in our field. The largest section was an extensive treatment of the physical plant, whereas that honor in the 1996 edition goes to the chapter titled: Animal Environment, Housing, and Management [See Clark et al. for a review of the 1996 *Guide* (14)]. This transition, from an emphasis on the engineering details of the facility to the performance goals of the animal environment, from a concentration on bricks and mortar to an emphasis on the living environment of the animals, is, in itself, a story of the progress of laboratory animal science. The story is still being written.

With an uncanny bit of prophecy, the authoring committees of early editions stated that *permissive* language of the *Guide* was intended to “encourage investigators to seek new and better methods of laboratory animal care and apply professional judgment in the interpretation of these recommendations” (15). By

“permissive” they meant that the *Guide* provided end-points or goals, but not details for achieving the goal. Although *performance* language had not yet evolved, it is clear from the beginning that the authoring committees felt that prescribing the exact methods by which to achieve the goals of laboratory animal care and use, as known then, was counterproductive. Most important, from a humane standpoint, is that performance standards require that judgement be made *from the animals’ perspective*, rather than from conditions or descriptions of the facility as was the common practice of engineering or prescriptive standards. Even with an emphasis on prescriptive details of the facility, each edition of the *Guide* also emphasized that practices should change as information and expertise changed, not just when a new edition of the *Guide* was published, as long as the goals were achieved. This encouraged institutions to develop new and improved methods in each programmatic area of the *Guide*, and was to have a profound effect not only on subsequent editions of the *Guide* but for the eventual *Public Health Service Policy on Humane Care and Use of Laboratory Animals* (16) and the Animal Welfare Regulations (17). Subsequent to the initial 1963 ACP edition, the *Guide* was revised by ILAR in 1965, 1968, 1978, 1985, 1996. The Government Printing Office published all but the 1996 editions, and users were free to copy or translate it into other languages, as there were no copyright restrictions. The 1996 edition, however, was published by the National Academy Press, which holds the copyright. This change was made to give it the full imprimatur of the National Academy of Sciences.

ILAR Continuing to Grow

In the spring of 1965, Bert Hill left ILAR to become Director-General of Charles River France. He had served as Director of ILAR for ten years and was responsible for much of the growth in laboratory animal science during that period. He was replaced by Robert Yager, who soon brought Francis (Sam) Judge aboard as his Assistant Director.

In 1966, Howard Schneider replaced Ben Cohen as Chair of ILAR; the *ILAR Newsletter* became *ILAR News* with a colorful eagle, cat, and dog announcing the passage of the Animal Welfare Act; and the Laboratory Aids Branch of NIH became the first federal animal facility to be accredited by AAALAC. In 1967, the ACP became the American Association for Laboratory Animal Science (AALAS), ILAR assisted the NRC’s Board on Agriculture in the evaluation of the effectiveness of 1100 veterinary drugs at the request of the Food and Drug Administration, and Max Lang sought ways to utilize newly evolving computer technology that would ease the laborious search of the literature. As a result of Lang’s efforts, the National Library of Medicine and the National Agricultural Library commissioned ILAR to assist in the development of a vocabulary in veterinary medicine to overcome deficiencies that existed when applying *Index Medicus* to veterinary and animal terms. Max Lang chaired the study and a Public Health Service veterinarian, Fritz Gluckstein, was assigned to the Library of Medicine to head this task for NIH. This task resulted in the publication of *Laboratory Animal Medical Subject Headings*, commonly shortened to “LAMESH” (19), which is an outgrowth of the National Library of Medicine’s Medical Subject Headings (MESH).

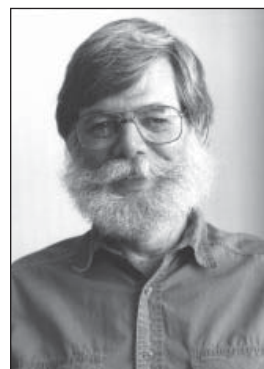
An Early Warning—Emerging Viruses

On September 14, 1967, Joe Held, then at the Centers of Disease Control (CDC) wrote to Bob Yager of ILAR that 7 persons had died in Germany from “a disease of unknown etiology” while

working with African monkeys or their tissues (20). This etiologic agent was ultimately identified as Marburg virus (21), a filovirus that is structurally identical with, but antigenically distinct from, Ebola virus. While there have been no human deaths in the U.S. to either the Marburg or Ebola viruses, B-virus infection (Cercopithecine herpesvirus 1, CHV1) present in macaque monkeys has resulted in the death of several animal workers in the US. The importance of each of these viruses is that they represent “emerging viruses” about which we know very little. The CDC issued a “Requirement for a Special Permit to Import Cynomolgus, African Green, or Rhesus monkeys into the United States” (22) and guidelines for transit and quarantine (23). Concern for such emerging viruses has also been addressed in numerous forums, one of the first of which was in the *ILAR Journal* (24) in association with the risk of xenotransplantation using organs from nonhuman primates. Subsequently, the Institute of Medicine (IOM) prepared a report on *Emerging Infections: Microbial Threats to Health in the United States* (25). This report alerted Ralph



Joe Held



Ralph Dell

Dell, then on sabbatical at ILAR, of the potential importance of introducing pathogens in patients receiving organ transplants from animals. At this time, the IOM was planning a workshop on the science and ethics of xenotransplantation. With Dell’s leadership, the resulting publication, *Xenotransplantation: Science, Ethics, and Public Policy* (26), included a significant and timely section on the risk of introducing disease in human xenotransplantation trials. This issue clearly places great responsibility on those breeding, importing, handling,

and using nonhuman primates to obtain animals free of viruses known to be hazardous to humans and to employ appropriate safeguards for personnel who handle them. This concern for human health and safety led the Interagency Research Animal Committee (IRAC) to ask ILAR to prepare comprehensive recommendations on Occupational Health and Safety in the Care and Use of Research Animals (27).”

The Decade of the 70s

Throughout its history, ILAR has produced reports through the time and energy of its volunteer committee members. ILAR reports are prepared in response to requests by federal agencies and others for advice on specific topics. In response, the NRC appoints committees composed of members with a wide range of expertise on the subject and who serve without fee. Upon completion of a committee’s manuscript, it is submitted to a similarly constituted review panel, who must approve it before it can be published. Members of the National Academy of Sciences serve as the final arbitrators in case of dispute. The 1970s were a busy time for laboratory animal science and for ILAR. An example of the extent and influence of ILAR’s activities during this time can be appreciated by the number of



Earl Wayne Grogan

projects with which it was involved in a single year. In 1976, ILAR had a new Chairman, Edward C. Melby, Jr. and Earl Wayne Grogan had replaced Robert Yager as Director only the year before. Under their leadership over 100 volunteers (chairs in parentheses) worked on the following reports: *Animal Models and Genetic Stocks* (Dante Scarpelli); *Animal Models for Thrombosis and Hemorrhagic Diseases* (Jean Dodds); *Care and Management of Rodents* (Max Lang); *Care and Use of the "Nude" Mouse* (Pietro Gullino); *Care*

and Use of Spontaneously Hypertensive Rats (Sidney Udenfriend); *Conservation of Nonhuman Primates* (Charles Southwick); *Genetic Standards* (John Ainsworth); *Guide for the Care and Use of Laboratory Animals* (Al Moreland); *Histologic Classification of Laboratory Animal Tumors* (Richard Griesemer); *Laboratory Animal Diets* (Paul Newbern); *Laboratory Animal Housing* (Emerson Besch); *Long-Term Holding of Laboratory Rodents* (Albert Jonas); *Standards for Birds* (James King); *Standards for Cats* (Richard Griesemer); and *The Future of Animals, Cells, Models, and Systems in Research, Development, and Education* (George Harrell).²

In addition, other ILAR committees completed reviews of the Interagency Research Animal Committee's *National Primate Plan* (28) and initiated studies on *Laboratory Animal Records* and other reports. Of course, *ILAR News* continued to be published, staff responded to many questions regarding sources of animals and models, and grant requests to support each of these projects and activities were written. ILAR's calendar for 1976 lists 31 committee meetings, workshops, and symposia, and the publication of six reports and proceedings of three symposia, all making for a mighty busy period for ILAR. Also during this period, ILAR co-sponsored a symposium with its parent organization, the National Academy of Sciences, on *Defining the Laboratory Animal in the Search for Health*. This symposium grew, in part, from concerns arising from the Marburg virus deaths and was the first ICLA symposium in the New World. Bill Gay, Tom Clarkson, and Henry Foster were session chairman from the United States. A tour of the White House and viewing of the Hope Diamond was a part of this 4-day international gathering!

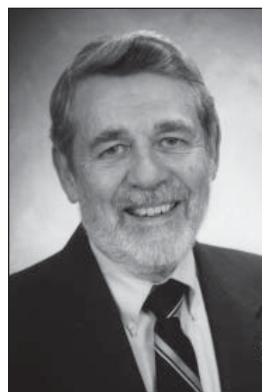
ILAR's history would not be complete without mention of the role key people at NIH have played in ILAR's programs. Most specifically, ILAR has worked closely with the NIH Division of Research Resources' (currently the National Center for Research Resources, NCRR) under the leadership of Roger Estep, Joe R.



Charles McPherson



Leo Whitehair



Thomas Wolfe

Held, Robert A. Whitney, and Judith Vaitukaitis. ILAR's benefits from the intellectual and financial support of the Animal Resources Branch (currently the Comparative Medicine Program) of NCRR, under the leadership of William I. Gay, Charles McPherson and Leo Whitehair, is inestimable. Also, the Primate Steering Committee (becoming the Interagency Primate Steering Committee in 1983) under the leadership of Joe Held, Bob Whitney, Tom Wolfe, and James Taylor

sought assistance and collaboration from ILAR on numerous occasions and provided ILAR with a valuable access to the other federal agencies involved in laboratory animal science.

Over the next several years, with Nicholas Bottiglieri and Franklin M. Loew serving as ILAR Chairmen, ILAR completed the review of the *Laboratory Animal Databank*, another in a series of *National Surveys of Laboratory Animal Facilities and Resources* (29), and cooperated with the Registry of Comparative Pathology in development of an exhibit on *Animal Models of Human Diseases*, which was displayed by ILAR staff members at numerous scientific meetings. Following a report on *The Future of Animals, Cells, Models, and Systems in Research, Development, and Education*, ILAR began a series of initiatives in non-traditional animal models and conservation, including a report on *Marine Invertebrates*.

ILAR Changing Its Image

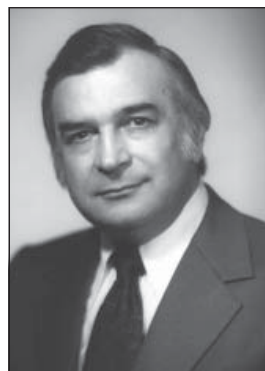
ILAR experienced a rather tumultuous change in 1987. Frank Lowe completed his term as ILAR Chairman and Wayne Gro-



Robert A. Whitney



William I. Gay



Nicholas Bottiglieri



Franklin M. Loew

gan retired after 12 years as ILAR's Director. Lowe was aptly replaced by Steven Pakes, but no Director was to be recruited until the following year when this author retired from the Commissioned Corps of the U. S. Public Health Service, NIH, to become Director. In addition to these changes, there were about to be other changes, which would affect ILAR for years to come. For approximately 30 years, federal agencies and other sponsors requested ILAR to convene conferences and workshops and produce reports on basic topics of care, husbandry, and microbiologic and genetic standardization of laboratory animals essential to the support of the rapidly growing fields within laboratory animal science. Many of these reports focused on veterinary medical themes and husbandry, and the composition of the ILAR Council was heavily represented by veterinarians. Sensing a need to broaden this perspective, and the resultant reports produced by ILAR committees, ILAR's parent division within the NRC, the Commission on Life Sciences, initiated an internal and external review of ILAR. This review charged ILAR to diversify its portfolio and to recruit scientists, including members of the Academy, for the ILAR Council and committees. Also, at this time, other organizations were convening meetings and publishing valuable proceedings that addressed many of the topics traditionally contained in ILAR reports. Most notable were those of the Scientist Center for Animal Welfare (SCAW), Public Responsibility In Medicine and Research (PRIM&R), Association of Primate Veterinarians, AALAS, AVMA, and ACLAM. With few exceptions, these reports sought to clarify and garner consensus for "best practices" by which to implement policies, standards, and regulations developed by ILAR, the Public Health Service, the Department of Agriculture, and others. These changes encouraged sponsors to seek reports from ILAR with an increasingly greater focus on emerging issues not likely to be a topic for other organizations, and for recommendations regarding federal policies affecting biological sciences for which the imprimatur of the Academy was felt important. At the end of the 1980s, committees of volunteers were working on several reports that exemplified this transition. One focused on important issues of immunodeficient rodents (30) and another addressed the important problem associated with the loss of unique animal models in recognition that many colonies of unique animal models were being disbanded for such reasons as lack of funding, changes in research focus, or death of investigators. It recommended strategies by which the NIH, and other sponsors of animal models, might address this issue (31). *Education and Training in the Care and Use of Laboratory Animals* (32) and *Recognition and Alleviation of Pain and Distress in Laboratory Animals* (33) were prepared in response to specific requirements within the Animal Welfare Regulations that these subjects be addressed by each institution. The report on pain was notable for its treatment of distress as an entity often existing in the absence of pain. After a monumental effort, lasting several years, by a committee chaired by Russell Lindsey, two-volumes on *Infectious Diseases of Mice and Rats* (34–35) was produced. These documents provide students of infectious disease, or investigators who only want to understand the cause of the signs they are observing in their animals, with a comprehensive treatment of infectious disease in mice and rats. The importance of this work will stand for many years.

In 1993, Pakes was replaced as Chairman by John VandeBerg who was to serve in that position to the end of the decade. As a population geneticist, VandeBerg broke the recent tradition

of having a veterinarian serve as Chairman of Council and he infused new breadth into both the composition of Council and the diversity of the ILAR reports and activities. Three rodent reports were produced, each with a different focus. In recognition of the increasing use of laboratory rats in research, ILAR convened a committee of international scientists to develop *Definition, Nomenclature, and Conservation of Rat Strains* (36). This report encourages standard nomenclature and stresses high genetic quality for rats. The report was adopted by ICLAS and serves as guidance for ICLAS Monitoring Centers for genetic and microbiological quality for rats world wide. With the development of transgenic animals came a requirement for ways to identify and catalog them. This need led to the report, *Standardized Nomenclature for Transgenic Animals* (37). The third report, *Rodents: Laboratory Animal Management Series* (6), a companion report to ILAR's *Dogs: Laboratory Animal Management Series* (38), supplements the *Guide* with species-specific details. Both laboratory animal management documents include a chapter, which provides detailed information on the care and use of rodent- and dog-models of disease that require special consideration.

The conservation and humane use of animals, as succinctly presented in the *U. S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training* (39) and the 3 R's (Reduction, Replacement, and Refinement) (40), has not been greatly emphasized in this history because ILAR has embraced these as integral goals of each meeting and report, rather than topics for independent attention. The lack of ability to catalog the tens of thousands of new transgenic animals so other investigators might know of their existence was the motivation behind ILAR's reports on transgenic nomenclature (37) and is an example of the focus on conservation and concern for animal welfare while supporting scientific advancement. The development of a nomenclature was needed to accurately catalog and report details of the transgene. Such a nomenclature would reduce duplication of effort by investigators in different laboratories, encourage a wider sharing of unique and valuable transgenic animals that might otherwise be lost to science, and guard against loss of information (requiring additional studies and additional animals) caused by the inability to do comparative studies. Through the cooperative efforts of investigators, the Jackson Laboratory, and the Medical Research Council in the United Kingdom the nomenclature is achieving these goals, and provides the ability to include transgenic animals in the The Transgenic/Targeted Mutation Database managed by The Jackson Laboratory.

In the mid to late 90s, ILAR convened numerous workshops and public forums, and committees produced reports published by the National Academy Press. The report on occupational health and safety (27), chaired by Emmett Barkley, brought together for the first time in a single document comprehensive guidelines for use by laboratory animal scientists. Key to this document is the use of risk assessment in developing occupational health and safety programs, as required by the PHS Policy and the *Guide*. The document was eagerly received by the scientific community and has greatly assisted in understanding the important difference between risk *management*—as formerly practiced by many institutions at considerable financial cost without commensurate gains in human health and safety—and risk *assessment*.

Because chimpanzees are the closest genetic relatives to humans, they have been thought to be important for research in critical human health situations where other species are not

effective. As such, chimpanzees have been instrumental in the development of a hepatitis B vaccine and are being used for study of malaria, viral respiratory disease, the metabolism of new human drugs, cognition, and most recently for study of acquired immunodeficiency syndrome (AIDS). Because of their endangered status in the wild, none have been imported into the United States since 1975, when the United States became signatory to the Convention on International Trade of Endangered Species of Wild Fauna and Flora (CITES). This has required captive breeding and careful management of the United States' population of approximately 1,700 animals. In 1986, the NIH initiated a National Breeding and Research Program to ensure future generations of breeders and to provide animals anticipated to be needed in the study of AIDS. This effort has been very successful, but the use of chimpanzees in AIDS research has been less than anticipated, resulting in a rather large population of animals not being used in research, but with an ongoing annual total cost of approximately \$9 million for their support. At the request of NIH, ILAR initiated a study chaired by Dani Bolognesi of the long-term care of these animals with a goal of providing cost effective, humane recommendations. Following release of the report in 1997 (41), the Director, NIH, assigned the National Center for Research Resources (NCRR) with responsibility for implementing the recommendations. Paralleling the development of the NRC report and implementation of the recommendations by NIH, animal protectionists were lobbying Congress for legislation to establish sanctuaries for chimpanzees no longer needed for research or breeding. In November 1998, H.R. 4777, the *Postresearch Chimpanzee Care Act*, was introduced in the House of Representatives to amend the Public Health Service Act to provide for a system of sanctuaries. This is the latest in a long list of ILAR reports that have been incorporated into federal policy, adopted by medical research institutions, or otherwise had broad impact on the biomedical science.

In 1998, Ralph Dell replaced Tom Wolfle as Director of ILAR. With this replacement, Dell brought the experience of chairing the IACUC at Columbia University for many years and being involved with laboratory animal science from many perspectives. Dell is a pediatric physician with strength in mathematics and a strong interest in infectious disease and hit the ground running with a series of high visibility studies. *Approaches to Cost Recovery for Animal Research: Implications for Science, Animals, Research Competitiveness, and Regulatory Compliance* (42), a study conducted for NIH, developed recommendations by which federal auditors and research institutions can establish what cost components of research animal facilities should be charged to an institution's indirect cost pool, and what animal research facility cost components should be included in the per diem charges to investigators. At issue in this study was the worrisome Office of Management and Budget (OMB) Circular A-21 that was placing severe restrictions on the use of institutions' indirect cost pools for animal research facilities.

Another timely report, *Methods of Producing Monoclonal Antibodies* (43), also prepared at the request of NIH, looked at the broad issue of monoclonal antibody production, both *in vivo* and *in vitro*. The report provided recommendations in six broad areas, which will be useful to investigators, regulators, and protectionists alike.

The rapidly changing nature of biological models used in research, the vast number of mammalian and non-mammalian models, and the emerging *in vitro* models are increasingly

competing for limited resources with which to support them. Because of this, NIH asked the NRC to study this problem and an assessment of opportunities and needs for model development consistent with available resources. A committee, chaired by Muriel Davisson, issued *Biomedical Models and Resources* in 1998 (44). The report provides 6 recommendations by which the NIH might address these issues.

The Psychological Well-Being of Nonhuman Primates (45), chaired by Irwin S. Bernstein, was completed at the end of Wolfle's tenure in 1998 and provides the NIH and the USDA sponsors, and others agencies and users of nonhuman primates in research, with extensive information by which to comply with the Animal Welfare Regulation's requirement for programs to ensure the psychological well-being of the animals. Building on this study, and a previous one on Occupational Health and Safety in the Care and Use of Research Animals (27), ILAR is currently forming a study on occupational health and safety when using nonhuman primates. This study originates from the death of a laboratory worker from CHV1. The follow up to this death led to a review by the National Institute of Occupational Safety and Health (NIOSH) of the protection of those who work with nonhuman primates. A conference held at the CDC in early 1999 reviewed the NIOSH findings and led to a request for ILAR to conduct a study to review engineering controls and personnel protective equipment and provide recommendations for the safety of those who work with primates. Many primate facilities (most of which are located in warm southern climates) are concerned, that adopted policies not contribute to additional accidents. As an example, while a "space suit" might offer maximum protection, it can also increase the risk of other accidents, injuries, and heat stroke. The importance of this issue is seen by the fact that of the 54 persons infected with CHV-1 since 1932, 74% have died.

The ILAR Journal

The Institute of Animal Resources' (later changed to Institute of Laboratory Animal Resources and then to Institute for Laboratory Animal Research) *Quarterly Newsletter* was founded in 1957 to communicate important publications, meetings, and events relating to laboratory animal science to a growing constituency. It has changed over the years, much as laboratory animal science has changed and matured. In 1966, it became *ILAR News* and in 1995 the *ILAR Journal*. Today, it is a peer-reviewed journal of current interest to biomedical scientists, animal care and use committees, and animal care personnel. It is managed by an NRC-appointed (ILAR) Editorial Board, which oversees all phases of planning and publication. Because each issue is devoted to a single topic, unsolicited manuscripts are typically not accepted. Recent issues have been devoted to such diverse topics as xenotransplantation (24), animal well-being (47), comparative gene mapping (48) and opportunistic infections (49). *Comparative Gene Mapping*, published as a 2-volume edition, includes large multi-color posters of the Comparative Genome Maps of Vertebrates and Comparative Chromosome Painting. This is the first time this material has been published and promises to be a source of reference for molecular geneticists for years to come.

The People and Places That Make ILAR's Work Possible and the ILAR Associates Program

As a component of the National Research Council of the National Academy of Sciences, ILAR receives no funding

from its parent institution nor does it receive line-item funding from Congress or any federal or private agency. Funding for all activities, including staff support, is achieved through competitive grant proposals submitted to federal, private, and public agencies. The operating charter of the Academy requires that 51% of funds for each project must come from federal agencies or private foundations. Other funds may come from commercial organizations such as pharmaceutical companies, and from academic organizations. No funds can be provided by non-government entities that might have a conflict of interest with the outcomes of the report. Without the support of ILAR's core sponsors and the sponsors of each study, ILAR's work would not have been possible. There have been hundreds of sponsors over the years; too many to list here. A few must be mentioned due to their long-time association with and support of ILAR especially at critical times in ILAR's history. These are the National Center for Research Resources, Comparative Medicine Program, and the National Cancer Institute, NIH; U.S. Department of Defense and the biomedical research laboratories of each of the military services; Department of Agriculture; National Science Foundation; Howard Hughes Medical Institute; Department of Veterans Affairs; the American Cancer Society, and numerous pharmaceutical companies. Sincere gratitude is extended to each of them, and to the individual and professional organizations that have sent checks, small and large, to ILAR over the years. This manuscript was prepared by the author after retiring from ILAR and did not use sponsor funding in its preparation.

ILAR's core sponsors have enabled the *Newsletter*, *News*, and *Journal* to be distributed without charge. However, effective in mid-1997, this was no longer possible. In that year, the issue on *Unusual Mammalian Models* included "An important Notice to Readers: Our quarterly has been published without charge to the international animal research community since it was first published in 1957. We are proud of that tradition, and it is with regret that we bring you the news that the ILAR Journal will no longer be free." With that announcement, ILAR launched the ILAR Associates program, in which individual and corporate subscribers receive the Journal, free or discounted NRC reports, and other benefits. Information about this program and all of ILAR reports can be located on the ILAR home page (<http://www2.nas.edu.ilarhome>) or by e-mail to ilar@nas.edu.

The Future

Because ILAR belongs to a dynamic and changing discipline of laboratory animal science, its history is far from complete. Appreciation is extended to everyone named in this history and to the many others, unnamed but not forgotten, who have volunteered their time and talents on ILAR committees, and to those who will continue to shape its future. A very special sense of gratitude is extended to John VandeBerg, current ILAR Chairman, and to the past, present, and future members of the ILAR Council and committees, for it is these people who will shape and direct ILAR into the future. My projection of ILAR's future suggests that much work is yet to be done and the nature of that work will continue to change. Much of this work will recognize the increasing role of the nonscientific public who care about how research animals are used and cared for. It will also recognize, to an increasing degree, the importance

of working with scientists and organizations similar to ILAR in other countries of the world. This global scientific exchange will ensure compatible standards that will permit free trade of animals, biologic materials, and pharmaceutical products derived from animal research. This work is necessary not only to permit research to progress, but to ensure that the highest humane standards of animal care and use are recognized and accepted.

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- 1 The authors of ILAR reports are scientists, veterinarians, philosophers and others who are appointed by the Chairman of the National Research Council, who also is the President of the National Academy of Sciences, and serve without compensation. Though these are NRC committees, with staff support provided by ILAR, they are sometimes referred to in this history as ILAR committees.
 - 2 Many of the publications mentioned in this report are out of print and only selected ones are referenced. For information, contact ILAR, or the National Academy Press web site found at (<http://www.nap.edu>).