Chapter Eleven

Development and Major Contributions of the Extramural Comparative Medicine Area, NIH (1962-1999)

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Background of Comparative Medicine Area Programs

The Animal Resources Branch (ARB) of the Division of Research Facilities and Resources (DRFR), National Institutes of Health (NIH) was formally established in July 1962. The DRFR was created to develop and provide various types of essential resources (laboratory animals, bio-instrumentation, clinical research centers, construction of biomedical research facilities, and other types of infrastructure) to support the needs of the NIH extramural community (1). Laboratory animal resources were recognized to be an important part of the overall infrastructure required to support numerous NIH-sponsored biomedical research programs at hundreds of institutions throughout the United States.

In 1956, Dr. James Watt, director of the National Heart Institute (NHI) of NIH and Dr. Paul Dudley White, a noted heart specialist, visited the world's first and only primate research center at Sukhumi (Georgia) in the Soviet Union. Discussions were held in 1957 by a planning committee of the NHI Advisory Council concerning the potential value of nonhuman primates for use in cardiovascular research and the concept of establishing a single, large national primate research station for such use. Later discussions by that committee in 1958–59 broadened this novel concept and the NHI Advisory Council recommended the establishment of seven nonhuman primate centers in the U.S. to serve regional and national needs in a variety of biomedical research areas where it was believed that the primate model would be useful. These important early events have been well documented (2–5).

The Regional Primate Research Centers (RPRCs) Program was transferred from the NHI to the newly-created DRFR on July 15, 1962 (1). After receiving appropriations from Congress in fiscal years 1960, 1961, and 1962, plans proceeded rapidly in the selection of sites and construction of facilities at the seven centers during the period of 1961–66 (2). Dr. Willard H. Eyestone, a veterinary pathologist and former chief of the NIH (Intramural) Laboratory Aids Branch, joined DRFR to assume overall responsibilities for the formulation of plans to establish the RPRC Program. The seven Centers were selected on a competitive, peer-reviewed basis from applications submitted by major academic institutions. A total of approximately $18 million, a modest sum by today's standards, was awarded by ARB, DRFR on a non-matching basis for construction of facilities at the seven RPRCs (2). The RPRCs and their host academic institutions are: California RPRC (University of California, Davis); Tulane (formerly Delta) RPRC (Tulane University); New England RPRC (Harvard University); Oregon RPRC (Oregon Health Sciences University); Washington RPRC (University of Washington); Wisconsin RPRC (University of Wisconsin); and Yerkes RPRC (Emory University). Following the construction grants, support for the Centers' base operations has been provided through grants administered by ARB - now termed Comparative Medicine (CM) Area of the National Center for Research Resources, (NCRR), NIH.

The Early Years (1962–70)

During the first several years of ARB's existence (1962–65), major efforts by Dr. Eyestone, initially assisted by Dr. Raymond Zinn, and later by Dr. Joe R. Held, were devoted to the selection of the RPRC sites, initial staffing of the centers, and construction of facilities. In 1963, Dr. William I. Gay initiated the development of the Laboratory Animal Sciences Program (LASP). Dr. Charles W. McPherson, a veterinary officer in the NIH (Intramural) Laboratory Aids Branch, succeeded Dr. Gay in 1966 to direct the further development of LASP activities. The early LASP efforts were focused toward the establishment of institutional programs for postdoctoral training of veterinarians in laboratory animal medicine; support for institutional animal resources; and animal model development. Meanwhile, the construction of facilities, acquisition of species of nonhuman primates from feral sources, and staffing with scientific and support personnel at the seven RPRC's proceeded between 1962–66. Facilities at the Oregon RPRC were completed in 1962, followed by those at the University of Washington RPRC shortly thereafter. By 1966, construction had been completed at all seven regional centers, which were in operation and at least partially staffed with research and support personnel. The RPRCs were initially assigned mission areas of biomedical investigations on nonhuman primates that were related, but not duplicative, of research efforts to be undertaken at the other RPRCs. Their initial basic research missions included reproductive biology, neurophysiology and gastrointestinal physiology, behavioral sciences, cardiovascular diseases, and infectious diseases (2). Many nonhuman primate species were still available at that time from their native feral sources, and it was necessary to study the biological profiles of the individual species in order to select the most appropriate models for particular types of biomedical and biobehavioral studies. It was also necessary to determine the husbandry and housing requirements of each species. The University of California-Davis RPRC was initially assigned these tasks as the "National Center for Primate Biology." It was later determined that these studies should more appropriately be conducted on selected species at all seven RPRCs, and the

FIG. 1. Early Regional Primate Research Centers Directors' Meeting (April 2, 1965): Left to Right (sitting) William Montagna, Geoffrey H. Bourne, Lloyd Neurauter (NIH), Leon H. Schmidt, Harry F. Harlow, Bernard F. Trum (Standing) Theodore H. Ruch, Arthur J. Riopelle, and Willard H. Eyestone (NIH).

California RPRC was assigned its own research missions, in a similar manner to that of the other RPRCs (2).

By 1970, the RPRCs had become reasonably well staffed and were productively engaged in many studies of human health disorders using nonhuman primate models. Some of the most important contributions during their early years were in demonstrating the extreme value of nonhuman primate models for a broad range of biomedical research areas. These areas included cardiovascular disease, reproductive biology, various types of infectious diseases, neuroscience, behavioral sciences, nutrition, drug abuse, visual disorders, and mental retardation (6, 7). The RPRCs also had a national leadership role in the development of efficient housing, husbandry methods, domestic breeding, and veterinary medical care for various species of nonhuman primates. Its companion program, the LASP, was also functioning well by 1970 and provided grant support for postdoctoral training, diagnostic laboratories, animal model development, and institutional laboratory animal resources. Both the RPRC and LASP were then poised to advance rapidly and make significant contributions to many areas of biomedical research. They were to be joined in later years (mid-1980s) by two additional programs (AIDS Animal Models and Biological Models and Materials Research) to comprise the CM Area of the organization known since 1990 as the National Center for Research Resources (NCRR) of NIH. Some of the significant events related to each of these programs are summarized below.

The Regional Primate Research Centers (RPRCs) Program

Since their very beginning, (described above), the RPRCs have provided highly specialized resources, experienced personnel, and appropriate environments for basic and applied research on nonhuman primates, which are designed to improve our understanding of a variety of important human health disorders and social problems. In addition to the research programs which are conducted by core scientists at each center, the RPRCs' resources are also utilized by numerous collaborators, affiliates, and visiting scientists from institutions outside of the centers, as well as by graduate students who conduct investigations for their doctoral dissertations. More than 1,200 investigators currently conduct biomedical studies at the RPRCs. In this manner, the seven RPRCs have served as unique biomedical research resources on a regional, national, and international basis. The RPRCs were the first biomedical research centers program to be established by NIH, thus serving as a model for many other types of center programs which have been initiated by NIH and other federal agencies in later years (8).

One of the greatest challenges facing the seven RPRCs during their rapid growth period in the 1970s was the threat of a severe shortage of feral nonhuman primates. Domestic breeding programs were already underway at several of the centers by 1975 (9); however, about 50 percent of their nonhuman primate requirements were still dependant on feral sources. This problem was particularly serious in the case of feral rhesus monkeys (*Macaca mulatta*), due to export embargos on nonhuman primates which were imposed by the government of India and made totally effective in 1978. Collectively, the seven RPRCs had approximately 45 species of primates on hand at that time. However, the rhesus monkey predominated as the most commonly used research model at most Centers. A notable exception was the RPRC at the University of Washington which was heavily dependent on supplies of cynomolgus (*Macaca fasicularis*) and pig-tailed macaques (*Macaca nemestrina*) from Indonesia. The RPRCs successfully met these challenges by rapidly initiating domestic rhesus breeding programs and an island breeding program on Tinjil Island, Indonesia for cynomolgus macaques. In 1975, the RPRC Program set a goal of reaching near self-sufficiency in their supply of nonhuman primates. By 1985, approximately 80 percent of that goal had been achieved and by 1990, 90 percent of the goal was reached. In 1998, the seven Centers bred approximately 95 percent of their overall annual primate needs. Collectively, the seven RPRCs now house approximately 18,000 nonhuman primates of 30 species. Rhesus monkeys (more than 12,000) comprise about 2/3 of the total inventory. The RPRCs have had a national leadership role in the development of efficient captive housing systems, husbandry methods, domestic breeding, and veterinary medical care for the various primate species.

Some of the RPRCs' most significant scientific contributions have related to their studies on acquired immunodeficiency syndrome (AIDS). A form of immuno-dysfunction in macaque species was detected at several RPRCs prior to 1980 (10, 11). Investigators at the New England and California RPRCs were the first to successfully isolate and identify the simian immunodeficiency virus (SIV) in macaques. The biological characteristics of SIV are strikingly similar to those of the human immunodeficiency virus (HIV). The SIV macaque model is now universally recognized as the animal model of choice for basic pathogenesis and other AIDS-related investigations. Important advances have also been made by several RPRCs toward developing effective vaccines to prevent this devastating disease (8).

Many other outstanding biomedical contributions have been made by the RPRCs. These include the Nobel prize findings of Dr. Torston Wiesel, a professor at Harvard University, at the New

FIG. 2. Dedication Ceremony at Yerkes Regional Primate Research Center, Atlanta, GA, on October 27, 1965: Left to Right—Henry Bowden, chairman of Emory University Board of Trustees; Sanford S. Atwood, president of Emory University; Geoffrey H. Bourne, director of Yerkes RPRC; Ernest M. Allen, director of Division of Research Grants, NIH; George Haslerud, Yerkes RPRC scientist; David Yerkes and Roberta Yerkes, (son and daughter of Robert M. Yerkes); Orie Myers, vice president for business affairs, Emory University; Willard H. Eyestone, NIH; Lloyd J. Neurauter, NIH.

England RPRC, which elucidated the development of visual pathways in neonatal rhesus and stumptailed macaques (12); the classical behavioral deprivation studies conducted by Dr. Harry Harlow at the Wisconsin RPRC on separation of macaque mothers from their infants; the language development studies by Drs. Duane and Sue Rumbaugh with chimpanzees which were first conducted at the Yerkes RPRC in the 1970s; and the recent pioneering work on embryonic stem cells of nonhuman primates by Dr. James Thompson (Wisconsin RPRC), which may have enormous medical applications in the future. These and numerous other studies on nonhuman primates at the RPRCs have contributed greatly to the basic knowledge of a large number of important human diseases and health disorders.

Laboratory Animal Sciences Program (LASP)

Since its beginning in the 1960s, the LASP has provided support for a broad range of activities which have contributed greatly to the advancement of laboratory animal science (13). Activities have included training programs in laboratory animal medicine; establishment of institutional and national shared resources of special animal colonies; diagnostic laboratories to detect and characterize intercurrent diseases in colonies that may compromise research results and animal welfare; and the development and characterization of numerous natural and induced animal models for studies on a variety of human health disorders. These types of activities were expanded in the 1970s and 1980s, and continue to represent important components of the LASP. Resource-related research projects, designed to enhance the value of laboratory animal resources and to assist in the development of new and improved animal models have also been supported since the early 1970s (14). Because of a recognized national need to upgrade many seriously deficient laboratory animal facilities, the LASP initiated a facility improvement program in 1971. Grants-in-aid for renovations and major animal resource equipment were continued through the mid-1970s. Additional funds (up to $12 million annually) were allocated for these purposes starting in 1987. The laboratory animal facility improvement program continued as part of the LASP until 1995 when it was transferred to the newly organized Research Infrastructure Area of NCRR. Grants-in-aid from the facility improvement program have assisted numerous institutions in their efforts to upgrade their laboratory animal care programs to comply with federal regulations and gain accreditation status. The NCRR (including the CM Area) gained authority to support basic types of investigations through the R01 research project grant mechanism in 1990, and the LASP has sponsored projects related to biotechnology, genetic engineering, normative biology, animal diseases and animal models. Many other types of activities supported by the LASP can be cited throughout its 35 year history. Several examples are described below:

- Support for the core functions and many special projects conducted by the Institute for Laboratory Animal Research (ILAR) of the National Research Council (NRC), National Academy of Sciences (NAS). These activities have included periodic revisions since 1965 of the *Guide for Care and Use of Laboratory Animals*, preparation of standards related to nutritional requirements and care of various laboratory animal species, surveys of feral populations of New World primates in their countries of origin, national surveys of laboratory animal facilities, recommendations concerning occupational hazards for personnel working with laboratory animals, a report on psychological well-being of nonhuman primates, and studies related to animal care costs.
- Support to aid in the establishment of an island free-ranging commercial breeding operation for Herpes-B virus free rhesus macaques at Key Lois, Fla. (Charles River Laboratories, Inc.) in the early 1970s. This was a relatively new concept for commercial breeding and had been preceded by the successful breeding of a colony of semi-free ranging rhesus monkeys which was established on Cayo Santiago Island, Puerto Rico, in 1939 (15, 16). As part of the Caribbean Primate Center, the Cayo Santiago Island research resource has been supported by the LASP since 1973.

FIG. 3. Visitors at Key Lois Island, FL (L to R - Drs. George Pucak, Dennis O. Johnsen, Albert E. New, Henry L. Foster, and Charles W. McPherson (Circa 1974).

Comparative Medicine Area
(formerly Animal Resources Branch)
Professional Staff Listings (1962–1999)

Directors of Animal Resources Branch/Comparative Medicine Area

1)	Willard H. Eyestone, DVM, PhD	1962–70
2)	Charles W. McPherson, DVM, MPH	1970–80
3)	William I. Gay, DVM	1980–90
4)	Leo A. Whitehair, DVM, PhD	1990–99
5)	John D. Strandberg, DVM, PhD	1999–

Directors of Regional Primate Research Centers Program

1)	Raymond Zinn, DVM	1962
2)	Joe R. Held, DVM	1962–65
3)	Lloyd J. Neurauter, DVM	1965–66
4)	Robert Courter, DVM	1966–67
5)	William J. Goodwin, PhD	1967–75
6)	Leo A. Whitehair, DVM, PhD	1975–85
7)	Dennis O. Johnsen, DVM, MS	1985–88
8)	Leo A. Whitehair, DVM. PhD (interim director)	1988–90
9)	Don C. Gibson, DVM, MPH	1990–93
10)	W Richard Dukelow, PhD	1993–95
11)	Jerry A. Robinson, PhD	1995–

Directors of Laboratory Animal Sciences Program

1)	William I. Gay, DVM	1963–66
2)	Charles W. McPherson, DVM, MPH	1966–70
3)	John E. Holman, Jr., DVM, PhD	1970–87
4)	Leo A. Whitehair, DVM, PhD	1987–88
5)	Leslie P. Bullock, DVM	1988–90
6)	Allan Lock, DVM	1990–91
7)	Leo A. Whitehair, DVM, PhD, (interim director)	1991–92
8)	Cynthia L. Pond, DVM, MS	1992–95
9)	Leo A. Whitehair, DVM, PhD (interim director)	1995–97
10)	Neal B. West, PhD	1997–99

Directors of AIDS Animal Models Program

1)	William I. Gay, DVM	1985–87
2)	David L. Madden, DVM, PhD	1987–88
3)	Leo A. Whitehair, DVM, PhD (interim director)	1989–90
4)	Milton April, DVM	1990–95
5)	W Richard Dukelow, PhD	1995
6)	Jerry A. Robinson, PhD	1995–

Directors of Biological Models and Materials Research Program (BMMRP)

1)	James Willet, PhD (BMMR became separate NCRR Program in 1988)	1985–90
2)	Louise E. Ramm, PhD	1990–95
3)	Elaine Young, PhD (BMMR Program was reunited with Comparative Medicine Area in 1996)	1995–97
4)	Jill L. Carrington, PhD	1998–

Professional Staff Assigned to Other Activities in ARB/CM Area

1)	William Cissel (engineer/architect for regional primate research centers' construction)	1962–66
2)	Robert A. Whitney, Jr., DVM, MS (project officer, Animal Resources Branch)	1971–72
3)	Dennis O. Johnsen, DVM, MS, (executive secretary, Animal Resources Review Committee)	1976–81
4)	Carl E. Miller, DVM (executive secretary, Animal Resources Review Committee)	1981–87
5)	Arthur D. Schaerdal, DVM (executive secretary, Animal Resources Review Committee)	1987–90

Note: All Comparative Medicine Area scientific review activities were consolidated into the newly established NCRR Office of Review in 1990.

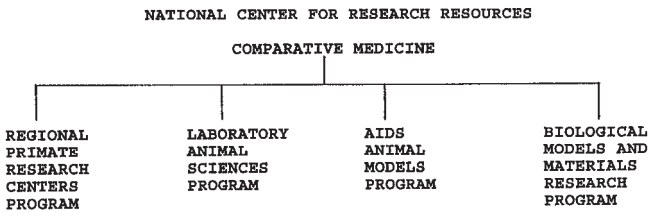

FIG. 4. Organizational Chart (1996 - Present) for Comparative Medicine Area, National Center for Research Resources

- Partial support to aid in the early establishment and formative years of the American Association for the Accreditation of Laboratory Animal Care (AAALAC, a private organization which is now known as Association for Assessment and Accreditation of Laboratory Animal Care, International).
- Preparation and publication of the Cost Analysis and Rate Setting Manual for Animal Resource Facilities in 1973 (revised in 1979). The Manual was prepared by a committee established by ARB to provide the NIH grantee community with recommendations for the sound financial management of animal resources, as well as standard guidelines for a cost analysis and rate setting system. The 1979 revision incorporated changes in the Office of Management and Budget (OMB) cost principles for federal grants and contracts and other changes related to equipment depreciation and use charges (17). In 1995, the CM Area established a committee of financial and laboratory animal care specialists to revise and update the manual and its recommendations. A draft of this extensive revision has been completed by the Committee on Revision of the Cost Analysis and Rate Setting Manual and its release as an approved working document is pending (18). Following the committee's completion of this draft, the NCRR sponsored an animal cost study which was conducted by ILAR of the NRC, NAS. The ILAR committee has made additional recommendations relating to the extensive changes made in OMB Circular A-21 for allocations of animal costs (direct costs vs. indirect costs). Further discussions on this important matter are currently ongoing with officials of the cognizant institutional indirect cost rate setting agencies (Department of Health and Human Services and Office of Naval Research) and OMB (20).

Postdoctoral training in laboratory animal medicine for graduate veterinarians (normally three-year programs) has been a hallmark of the LASP since 1963 when the first training grant was awarded to the Bowman-Gray School of Medicine (principal investigator Thomas B. Clarkson, DVM), followed shortly thereafter by an award to the University of Michigan (principal investigator Bennett Cohen, DVM, PhD). Additional institutional awards, as well as individual research fellowships, were made in the late 1960s and early 1970s (21, 22). A total of nine institutional awards, with approximately 40 to 42 training positions, remained fairly constant until 1988 when funds were increased by approximately $1 million to allow for a total of approximately 80 training positions. Seven additional institutional awards were made (total of 16) at that time and this number has remained relatively constant to date. The National Research Service Awards (NRSA) Program (established in the mid-1970s) provided for various types of health-related training, including institutional training grants, individual research fellowships, and grants for short-term research training of veterinary students. Five Colleges of Veterinary Medicine currently receive the latter type of awards from the LASP.

Since 1965, approximately 500 veterinarians have completed postgraduate training in comparative medicine and/or comparative pathology through support from the LASP.

AIDS Animal Models Program (AAMP)

The National Chimpanzee Breeding and Research Program (now known as the National Chimpanzee Biomedical Research Program) was initiated in 1986 to develop urgently needed animal models for AIDS-related studies (23). Based on their genetic and physiological similarities to humans, as well as their earlier successful role in the development of the viral hepatitis A vaccine for humans, it was believed that the chimpanzee might be an ideal animal model for studies on human immunodeficiency virus (HIV) studies and the development of preventive and/or therapeutic measures for AIDS. A program of five breeding colonies (total of approximately 315 chimpanzees of all ages) was established in 1986. These colonies are located at the Yerkes RPRC in Atlanta; the University of Southwestern Louisiana at New Iberia; the University of Texas at Bastrop; the Primate Foundation of Arizona near Tempe; and New Mexico State University (now the Coulston Foundation) in Alamogordo. Auxiliary research support projects were also initiated within the total AAMP to provide important information on genetics, reproductive biology, immunology, demography, and behavior to enhance the resource.

Since very little experience had previously existed in the colony breeding of captive chimpanzees, there was considerable initial skepticism among certain groups regarding the potential success of this project. By 1996, after some 400 live births and with a total population of about 545 animals, the breeding was considered so successful that it was necessarily curtailed to tailor production more closely to actual and anticipated biomedical research needs. Although the chimpanzee can be infected with HIV, it has not proven to be an ideal AIDS animal model, with only one case of full-blown AIDS in a chimpanzee recorded to date (24). However, it is believed that the chimpanzee may still play an important role in the testing of candidate AIDS vaccines for safety and efficiency. The very success of this breeding program has assured the biomedical community that an adequate resource of healthy chimpanzees now exists for current and future research needs in the United States. Following a study by an ILAR committee on long-term care of chimpanzees, NCRR is currently planning a national chimpanzee management program (25).

With the successful development of simian immunodeficiency virus (SIV) macaque models by the Regional Primate Research Centers, the need for adequate resources of specific-pathogen-free (SPF) macaques for AIDS-related research became apparent. Six SPF breeding colonies, with the support of a Simian retrovirus reference laboratory, a Herpes B diagnostic resource, genetics typing laboratory, and behavioral management research were established by ARB as part of the AAMP efforts in 1988. The major objectives of the SPF macaque breeding colonies are to produce and maintain animals that are seronegative and virus negative for *Herpesvirus Simiae* (Herpes B virus), a fatal pathogenic virus in humans, and free of specific retroviruses (SIV, SRV and STLV-1) which may interfere with research results. The offspring are made available to the biomedical research community, with priority given to NIH-sponsored AIDS-related studies. Production of both SPF rhesus and pig-tailed macaques has been highly successful. Since these well-established colonies are expected to become self-supporting through sale of the animals for biomedical research use, support from the CM Area for these projects is currently declining.

Biomedical Models and Materials Research Program (BMMRP)

The BMMRP was initially established within ARB in 1985. Although the LASP had supported some types of marine invertebrate resources since 1973, the BMMRP was initiated to greatly expand the development of a wide-range of non-mammalian models and resources, as well as mathematical and computer systems which are useful in biomedical research. These non-mammalian animals include aquatic invertebrates, lower vertebrates, and an array of other important biological materials, including zebrafish, cell cultures, genetic stocks of *Caenorhabditis elegans*, viruses, bacteria, yeasts, fungi, and fruit flies. Basic research to improve our understanding of these biological organisms and increase their usefulness in biomedical research is also supported. National resource centers for biological models which are of multi-categorical research interest (e.g. zebrafish; *Drosophila spp.*, and *C. elegans*) are supported by the BMMRP and made available to investigators.

The small, free living nematode *C. elegans* is an excellent example of the genetic model organism resources which are supported by the BMMRP. The Caenorhabditis Genetics Center acquires, maintains, and distributes genetic stocks and information concerning its collection of more than 2,650 strains. The collection includes one allele of each mapped gene, all available chromosome rearrangements, and selected multiple mutant stocks for genetic mapping (26). After 10 years of tedious studies, British and American scientists recently announced that all of the 97 million genetic "letters" that spell out the instructions for making the multicellular, complex *C. elegans* organism have been identified and placed in exact order. This remarkable accomplishment provides the first complete genetic blueprint of any animal and offers new insights into human development and disease (27).

The BMMRP became a separate, free-standing program within NCRR in 1989. In 1996, NCRR's extramural functions were reorganized and the BMMRP activities were re-incorporated into the CM Area.

Summary

The extramural ARB/CM Area of NCRR, NIH has made many significant contributions to the advancement of laboratory animal science during the past 36 years. Its programs of regional primate centers, diagnostic and investigative laboratories, animal facility improvement, research on intercurrent diseases and professional training in comparative medicine and pathology have greatly improved the health status and overall welfare of laboratory animals. Many new and improved animal models- mammalian and non-mammalian-have been developed by these programs. Technological methods are now available to create transgenic animal models which are well-defined in their genetic, microbiological, and physiological traits. Regional and national animal resources are supported and made available to the biomedical research community.

The four programs within the extramural CM Area currently support approximately 200 projects through 17 types of grant mechanisms. These projects include a broad spectrum of research and resource activities which range from cell systems to nonhuman primate models.

The many and diverse activities are summarized as follows:

- Studies to help ensure the availability of high quality, disease-free stocks of laboratory animals for biomedical research;
- Studies to develop and characterize a variety of natural and induced research animal models, including both mam-

malian and non-mammalian species;
- National shared resources of scarce and unique laboratory animals which are needed by researchers, but are not available from other sources;
- Basic and applied research problems related to various types of laboratory animals;
- National and regional repositories for the creation, phenotypic analyses, cryopreservation, and distribution of genetically altered and mutant strains of animals;
- Studies to improve the health and overall well-being of laboratory animals;
- Resources to provide an array of biological materials (e.g., marine invertebrate animals, yeasts, fungi, viruses, and cell lines) for use in biomedical research;
- Professional training in laboratory animal science and comparative pathology, as well as research career development of graduate veterinarians; and
- Information resources (e.g., registries, reference centers, and newsletters) to collect, classify, and distribute valuable information related to research animals.

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