

Chapter Ten

The History of National Institutes of Health Intramural Programs in Laboratory Animal Science

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Introduction

For the past 50 years the National Institutes of Health (NIH) has been a rapidly growing federal institution with primary responsibility for the biomedical research of the U.S. Public Health Service (USPHS). This research is carried out in its own facilities — the intramural program — and through grants and contracts in other institutions — the extramural program. Virtually all of the NIH research has depended upon the use of laboratory animals. Until 1962, the intramural program was larger than the extramural program, and much of the scientific staff concerned with developing and managing NIH's research had used research animals and were interested in caring for them properly.

For nearly all of this century the NIH has been managed by leaders with firsthand familiarity with research animal problems. All directors of NIH and its predecessor laboratory from 1904 to 1970 were involved in laboratory research and used animals. Nearly all leadership staff came from the NIH intramural programs and most had used animals.

Pre-NIH, The Hygienic Laboratory, Washington, DC 1904–1937

In 1904 the federal Hygienic Laboratory in Washington, DC, moved to a new building on a five-acre tract at 25th and E Streets, NW (now the site of the Kennedy Center). This laboratory was established at the Marine Hospital, Staten Island, NY, in 1887, for work on cholera and other infectious diseases. It moved to Washington in 1891. Federal activity on infectious diseases expanded in 1904, including work on Rocky Mountain Spotted Fever. Significantly, the laboratory's parent organiza-

tion was renamed the Public Health Service a few years later, in 1912, with greatly expanded responsibilities.

In authorizing the 1904 move and expansion of the Hygienic Laboratory, Congress noted that the location would “provide room for stables and outdoor runs for the animals.” The move away from Capitol Hill to the U.S. Navy property at 25th and E Streets in Washington may also have been motivated by pressure from recent efforts to outlaw vivisection in the District of Columbia. Three bills to that effect had been introduced in Congress between 1896 and 1900. (1)

When researchers arrived at the new laboratory, they received a memorandum of instructions from the director, Dr. Milton Rosenau. It included the words: “Be kind to animals; teasing or molesting or in any way annoying animals will not be tolerated under any circumstances. Animals are to be used in the proper work of the laboratory, but anything which inflicts pain upon them will not under any circumstances be allowed.” (2)

A 1920 organizational chart of the Hygienic Laboratory shows that E.K. Foltz was inspector for humane treatment of animals. Around 1934 a separate facility for raising animals was built on the grounds. Sam Poiley, a long-time member of AALAS, was the first director of this facility. (3)

By the mid 1930s the NIH was looking for a larger site. Several suburban Washington areas had been examined when the Luke Ingalls Wilson family of Bethesda offered to donate land to provide NIH a place for its laboratories and animals.

NIH to Bethesda 1937

Bethesda residents, including the Chamber of Commerce, were not in favor of NIH in their midst. But Wilson was very persuasive, and eventually the community agreed. The NIH gratefully accepted the transfer, which was accomplished in a series of land donations from 1936 to 1940. The NIH moved to Bethesda in 1937; Building One was dedicated by President Franklin D. Roosevelt in 1939. (4) Buildings on the Bethesda campus are numbered according to the sequence in which Congress authorized funds for their planning.

Poiley reported in 1937 that the animal-breeding program occupied the basement, first, and third floors of Building Three. (3) The second floor was occupied by a group called “Public Health Methods.” This hardly ideal arrangement ended when Building Nine was built for the rodent production colony in 1943. Building Nine was used until the Building 14 series was occupied in 1954. It was a plain facility with nine-foot ceilings, and was used to its maximum internal height. Those who remember that mice were kept in 11-inch diameter glass museum jars at that time can easily imagine some of the problems encountered in this facility.

Evolution in Bethesda and Environs

At the close of World War II, both the Administration and the Congress were interested in expanding the federal contribution to medical research based on the recent discovery of antibiotics, the ability to control parasites chemically, and advances in diagnostic and surgical capabilities. This expansion was to take place at the NIH, so the campus would be enlarged to more than 300 acres by acquisition of the Town and Country golf course to the south, part of the Sisters of Visitation property to the west, and the Peters property on Wisconsin Avenue, known now as “Stone House.”

The cornerstone of this expansion would be a clinical center of nearly 3 million square feet, which would put NIH for the first time into clinical investigation. It was decided that this

new NIH should include an expansion of all laboratories. This would include a very modern laboratory animal facility of more than 150,000 square feet at the south edge of the campus to provide central animal production, animal quarantine and holding, animal surgery, and diagnostic pathology.

The Formation of the Central Animal Facility

Dr. James H. Steele, the first veterinarian in the Commissioned Corps of the Public Health Service, recalls that he had been given the opportunity to work on some special infectious disease studies at NIH in 1946. While there he became well acquainted with Dr. Harold Stuart, a distinguished pathologist in the National Cancer Institute. Dr. Stuart told Dr. Steele that “what we need is a good veterinary pathologist.”



FIG. 1. Dr. William T.S. Thorp, veterinary pathologist who came to NIH in 1947 and began the Laboratory Aids Branch (renamed Veterinary Resources Program in 1980) as the largest central laboratory animal program in the nation.

Dr. Steele recruited Dr. W.T.S. Thorp, who started a comparative pathology section. (5) Beginning in 1947 Dr. Thorp and his staff designed and supervised the development of what was to become a model animal facility. This facility was to be managed and operated by a Laboratory Aids Branch, which Dr. Thorp formed in 1949. This was judged to be one of the most advanced laboratory animal facilities of its time and attracted visitors from all over the world. It is interesting that such a modern facility with modern housing and husbandry practices could have been developed to such an elegant level without the benefit of animal welfare regulations, American

Association for Accreditation of Laboratory Animal Care (AAALAC) oversight, or an NIH Guide. Dr. Thorp didn't even have an Animal Care and Use Committee.

By this time diseases of laboratory animals were becoming known as a special problem to researchers. The pathology section set up by Dr. Thorp became an essential NIH entity, and later was headed by Dr. Willard H. (Hal) Eystone. The Laboratory Aids Branch achieved AAALAC accreditation in 1966. It was renamed the Veterinary Resources Branch in 1972, and eventually called the Veterinary Resources Program (VRP). The central service animal facility provided specified central services such as procurement, quarantine, surgery, long-term holding, and health examinations. Animals could be utilized in research in this facility, or they could be issued to the user research laboratory. The program did not include all animal facilities at that time and does not today. However, it is the “central animal facilities of the NIH.” There have been, and continue to be animal facilities in the clinical center and at least 12 other buildings on the NIH campus. The categorical institutes support work in these buildings, but space is assigned and controlled by NIH headquarters.

The animal portion of the Laboratory Aids Branch, the “Central Services Animal Program” of the 1950s and 1960s was divided into the animal production section, which produced nearly all of the rodents used in the NIH intramural programs — up to 1,000,000 rodents per year — and the animal hospital section, which provided quarantine, holding, and surgical services for the large laboratory animals. This section also was



FIG. 2. Supervisor Gus Harmon (left) and veterinarian Charles McPherson catch monkeys in NIH Primate Quarantine Unit in the 1950s. Contrast the lack of personal protective devices with what is used today.

responsible for developing and managing a farm animal facility. In the 1960s it managed the “NIH Farm”—three acres located in south Gaithersburg and provided to NIH for \$1 per year by Eugene Casey, who was a holder of large parcels of real estate in the county. This site is still recognizable as the Gaithersburg



FIG. 3. The NIH farm in Gaithersburg, MD, in 1953. The barn (upper right) is now Gaithersburg Community Center on route 355 south.

Community Center located in a large barn. The farm held dogs, sheep, horses and other hoofed stock as needed. This operation was moved to Poolesville, Md. in 1960 and is now known as the NIH Animal Center. In 1962 new buildings were built for farm animal holding, dog and cat holding, and quarantine. Eventually a primate facility was also built.

In the 1950s the NIH “Central Animal Facility” was of special interest internationally because of its size and the modern methods of animal raising and holding. It was particularly interesting to animal protectionists because it kept the dogs and cats in large runways and had the appearance of a typical veterinary clinical animal hospital. At that time the animal protection community and the research community frequently communicated in friendly and constructive terms. Protectionists often visited NIH animal facilities.



FIG. 4. Aerial view of the NIH Animal Center in Poolesville, Maryland 1980.

Dogs could be donated to research, and some communities did this. The District of Columbia, which had a history of coming under antivivisectionist legislation, had arranged in the 1950s to donate dogs to local research facilities in the Washington area. NIH received its share of dogs from the DC Pound. It also had a member on the DC Animal Allocation Board, which established standards for care and housing in institutions receiving dogs. In 1961 the DC Pound allocated 801 dogs as follows: Howard University 533; Georgetown University, 13; George Washington University, 60; National Institutes of Health, 195. That year the pound also destroyed 1900 dogs. NIH received about 3,000 dogs from all sources that year. As part of that total the NIH also received 136 dogs from the Talbot County Humane Society, and about 300 from the Roanoke dog warden.

From 1954 until about 1970, the Animal Production Section was the largest part of the Laboratory Aids program. It produced nearly all the laboratory rodents used at the NIH and occupied the majority of the Building 14 complex, nearly 100,000 square feet. The NIH Animal Genetic Resource was central to this program and provided numerous strains of inbred rodents required by various NIH researchers.

In the early 1970s the NIH began to purchase most laboratory animals rather than raise them. This happened primarily



FIG. 5. Dr. Sara Jane Moore and Dr. William Gay demonstrating restraint for administration of intravenous anesthesia in 1960. Dr. Moore was the first woman veterinarian commissioned in any of the uniformed services of the United States.

because the National Cancer Institute (NCI) decided to contract rodent production for their large drug-testing program. Continuing government efforts to reduce employment levels further lowered the number of animal production workers. Nonetheless, the program still had the responsibility to provide the intramural investigators with the animals essential to their research programs. It also was essential to carefully monitor purchased animals for their microbiologic and genetic conformity to the “in house” standards that had already been established. The Veterinary Resources Program (VRP) had the primary responsibility for this monitoring.

Research

An important contribution of the Veterinary Resources Program was the role played by its Comparative Pathology Section, directed for many years by Dr. Anton (Tony) M. Allen. Other early major contributors to defining a number of diseases of laboratory animals were Dr. Robert Haberman and Fletcher (Pete) Williams. Research conducted by Dr. Allen and his collaborators, such as Dr. James Ganaway, provided knowledge on various diseases and etiologic agents—such as simian hemorrhagic fever, respiratory mycoplasmosis of rats, Tyzzer’s disease, and cilia associated respiratory (CAR) bacillus. The centralized program also led to research on other aspects of laboratory animal care and management, such as nutrition work by Dr. Joe Knapka, and genetics work by Dr. Carl Hansen. Their findings led to improvement of research within the entire NIH community of investigators and those receiving extramural support. Dr. Joe Knapka’s open formula rations saved the government literally millions of dollars in lab animal feed costs while improving feed quality and helped to raise the standards of animal feeds in the entire laboratory animal community.

VRP staffers’ collaboration with a variety of intramural scientists in the various categorical institutes were mutually advantageous. Much of the work done in the infectious disease field is a good example.

The following are highlights of some of the accomplishments of the VRP staff:

- Development of techniques for gnotobiotic production. This work assisted in the production of animal models for microbiological and infectious disease studies in which exact knowledge of which microorganisms were present was vitally important.
- Development of improved formulations for laboratory animal diets, which improved feed quality and helped raise the standard of animal feeds in the entire laboratory animal community.
- Development of genetic monitoring systems for rodents, which lead to better animal models for research on inherited diseases and opened the way for development of transgenic animals.
- Identification of a variety of infectious agents, especially in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID). This work was very important to infectious disease research, since it enabled investigators to separate their work on agents being studied from agents which were animal diseases.
- A central animal surgery with skilled professional and technical staff to serve all of NIH and assure adequate anesthesia, analgesia, trained surgical skills, and post-operative care. This program was particularly important to early cardiovascular surgery and subsequent organ transplantation.



FIG. 6. NIH Laboratory Aids Branch mouse breeding room using museum jars to cage mice. Damara Bolte is the facility supervisor checking colony records in 1957.

- Development of a foxhound breeding colony with universal blood donors, and the use of plasmapheresis for ungulate blood collection.
- Development of new techniques for the socialization and psychologic well being of various animal species essential in biomedical research. As animals became more important to research on chronic and degenerative diseases, and thus lived in the laboratory longer, this effort was very important to their well being and to meeting the requirement of federal laws regarding their welfare.
- Assured high quality, humane care for all animals in the NIH research programs. This work greatly aided researchers in complying with the proliferation of federal laws passed in the interest of animal welfare.
- Served as a focal point for the development of U.S. Government interagency activities in relation to animal use and care. These activities were extremely helpful in developing guidelines/regulations for implementing federal animal welfare legislation in a practical and workable manner.

NIH Individual Institutes Develop Programs

In several institutes veterinarians, were important members of the research staff. For example, Dr. Willard Wright became one of the leaders in parasitology research in NIAID beginning in the 1930s. It was natural for other members of the institute staffs to look to these veterinarians for guidance and assistance for solving their laboratory animal problems. There are several such individuals who served in this capacity over the years. We have chosen not to mention them by name here since the emphasis of this review pertains to the centralized NIH Laboratory Animal Science activities.

Several institutes formed their own laboratory animal programs in the 1970s. Today there are 15 such programs, each headed by a veterinarian. The animal care programs of the categorical institutes in the intramural program manage about as many animals as the Veterinary Resources Program. Their veterinary directors meet monthly under the chairmanship of Dr. Gene Bingham to advise Dr. James Taylor and the NIH office of Animal Care and Use on laboratory animal activities. The entire intramural NIH Animal Care and Use Program was AAALAC accredited in 1993.

Even though it was not a formal Laboratory Animal Training Program, many of today's active leaders in the field served in this program at early stages in their careers.

Policy Making at the NIH

The Veterinary Resources Program (VRP) was one of the earliest centralized animal care programs, and has been an effective and important factor in improving laboratory animal care and use in this country. When polio vaccines were developed, VRP supplied nonhuman primates for polio virus vaccine testing by what was then called the Division of Biological Standards.

In 1974, the Government of India placed an embargo on the export of rhesus monkeys used for these tests. At that time the Drs. Joe Held, William Gay, and Robert Whitney were given the responsibility to deal with this problem. They began by establishing an Interagency Primate Steering Committee (IPSC), which included representatives from all of the Public Health Service agencies that needed nonhuman primates for some aspect of their research or testing programs. Because of the importance of these animals to programs in other parts of the government, in time the committee's membership was broadened to include additional agencies from the Department of Defense, Veterans Administration, National Science Foundation, and Environmental Protection Agency. The committee developed a National Primate Plan, and we began to learn a lesson regarding the power of the press and public opinion (6).

The IPSC worked to develop a good plan to produce, coordinate use, and conserve primates. It soon became evident that this committee could be an ideal vehicle to consider and make recommendations regarding the use of all species of animals in many activities of concern to the federal government. In 1983, the Assistant Secretary for Health reorganized the IPSC as the Interagency Research Animal Committee (IRAC) with wider membership and broader responsibilities including conservation, use, care, and welfare of research animals. NIH remained the lead agency, with the Division of Research Services (DRS) providing administrative support. In 1985 a statement of "U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training" was prepared by the IRAC at the request of the Office of Science and Technology Policy. This statement was published in the *Federal Register* on May 20, 1985, expressing acceptance of the principles by the federal agencies participating in the IRAC.

During the revision of what was to become the 1985 *Guide for the Care and Use of Laboratory Animals*, IRAC advised the Committee revising the *Guide* on the development of new policies concerning the use of laboratory animals in government programs.



FIG. 7. Dr. Walter Newton, manager NIH germ free resources 1960. Shown with Reyniers type stainless steel isolators.

During that period some groups were urging that individual investigators be licensed, as they had been in the United Kingdom, if they were to use laboratory animals. The IRAC committee was convinced that the proper care and use of laboratory animals is really a broad institutional responsibility, and that the best way to ensure compliance with the NIH requirements was to place that responsibility on the institution. IRAC strongly urged that the mechanism of institutional responsibility be used.

There was debate about whether or not accreditation by the American Association for Accreditation of Laboratory Animal Care (AAALAC) (now named the Association for Assessment and Accreditation of Laboratory Animal Care International) should be required. It was decided that although not mandatory, such accreditation would be *prima facie* evidence of compliance with the *Guide*. It was also decided to develop policies that were consistent with new principles and policies being developed by the Council of Europe, in the hope that the world would not end up with a patchwork of differing standards and requirements, which could lead to poorer laboratory animal care and hinder their use in research, testing, and teaching.

The NIH—from the time of its move to Bethesda to the present has had one of the largest research animal programs in the U.S. This came about to meet a fundamental need of the various institutes in their research programs for high quality research animals. A decision was made early in the evolution of the program to be involved in attempts to contribute to advances in laboratory animal research, care, nutrition, and facility development. Many of the individuals who participated in these activities eventually became involved in NIH extramural programs aimed at the support of similar resources required in a wide range of institutions carrying out research supported by NIH's extramural programs.

The NIH intramural laboratory animal science program

provided an excellent resource for laboratory animal science development. It was only natural that eventually it would also encompass policy and guideline development. Involvement of the leaders of the laboratory animal community in all its programs was encouraged, and all these activities have been open to public review. The NIH culture encouraged participation in professional associations which benefited employees working in this field. They had the privilege of exchanging information with and receiving guidance from the leaders in the field of laboratory animal science in the United States and other parts of the world. AALAS has been a key element in this regard.

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