

Chapter Eighteen

Evolution of Disease Monitoring in Laboratory Rodents

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In general usage, the term “disease monitoring” in animals is defined as the evaluation of a percentage of animals in a given population at regular intervals for evidence of disease. This concept is simple and does not change with time. However, what does change continually is our knowledge of disease pathogenesis, systems for maintaining animals free of disease, methods for testing for disease, etc. These changes have resulted in gradual evolution of monitoring practices.

This discussion will be about the evolution of disease monitoring practices as they pertain to laboratory rodents. Because infections have played a major role in causing disease in rodents, considerable emphasis will be given to microbiologic monitoring. “Disease” will be considered in the broad sense to include both clinical and subclinical forms. Much of the discussion will be centered around some of the historical occurrences that have served as forces to bring about the evolution. The occurrences that have been chosen for discussion are as follows:

- Establishment of common interest groups
- Development of protective caging systems
- NIH funding of training
- Evolution of testing methods
- Developments in NIH animal programs

Establishment of Common Interest Groups

When rodents were first being used in biomedicine (from about 1910 to 1950) (1,2), there were many confusing disease problems and little organized effort to solve them. Many of the rodent facilities were ill-suited for holding animals; facility managers were inexperienced in disease prevention and little was known

about naturally-occurring diseases of rodents; multiple simultaneous infections in animal colonies were common and resulted in misleading disease descriptions; sources of known disease-free animals were essentially non-existent; and laboratories were exchanging animals and specimens with other laboratories, even between continents, without regard for spread of infections. Most of the people who published on rodent diseases did so because the diseases interfered with their use of rodents in studies of human diseases. Some outstanding articles were published even before 1920, e.g. by Theobald Smith (3) and Ernest Tyzzer (4), but the findings were communicated slowly to the relatively few people at that time who had interest in the control of laboratory animal diseases. Because of this situation, we owe a debt of gratitude to the group of “Chicago five” who organized the Animal Care Panel in 1950 (5). The primary purpose of the Animal Care Panel, which was renamed the American Association for Laboratory Animal Science (AALAS) in 1967, was to disseminate information to members of a new emerging field which was to become “laboratory animal medicine”. The members of the Chicago five were Bennett J. Cohen of Northwestern University, Nathan R. Brewer of the University of Chicago, Robert J. Flynn of the Argonne National Laboratory, Elihu Bond of the University of Illinois, and William F. Schroeder of the Hektoen Institute of Medical Research. These individuals, many of whom went on to make major additional contributions, are often credited with the founding of laboratory animal medicine as a field. Many of the findings reported in the Proceedings of the Animal Care Panel became the basis for establishing the early disease monitoring programs. In subsequent years, a number of organizations with similar goals joined in the overall effort to disseminate information:

- 1950 Animal Care Panel (now AALAS)
- 1952 Institute of Laboratory Animal Resources (now Institute for Laboratory Animal Research) (ILAR)
- 1956 International Council for Laboratory Animal Science (ICLAS)
- 1957 American College of Laboratory Animal Medicine (ACLAM)
- 1966 American Society of Laboratory Animal Practitioners (ASLAP)
- 1979 American Committee on Laboratory Animal Disease (ACLAD)

Development of Caging Systems

Another series of happenings that influenced disease monitoring involved the development of caging systems that offered protection against infections. This began in the mid-1940s with the first publications of methods for successful “germ free” rearing of rodents in animal isolation units by Reyniers and Trexler et. al. (6) in this country, and Gustafsson in Sweden (7). This marked the beginning of a major change in approaches to the commercial production of rodents free of infectious diseases. In the 10 years following the onset of germ free (axenic) animal production, the idea crystallized in the minds of a number of people that large scale production of “clean” animals could be accomplished by using germ free techniques to caesarian-derived rodents into a highly protected “barrier” type facility with filtered air and sterilized food and water. Initial publications on these procedures were by Reyniers, who first suggested the term “gnotobiotite” for an animal that “...can be accurately described with respect to contamination” (8), and by Foster (9). By the early 1970s, this system was becoming widely established. Also, by the late ‘70s a second part of the equation was coming into play, i.e., the development of caging



FIG. 1. Dr. Lisbeth M. Kraft

sity first demonstrated the use of “filter cages” to control the spread of a highly contagious virus, epidemic diarrhea of infant mice (EDIM) (10). In the process, she established the principle of using individual cages to isolate rodents from contagious infections. Dr. Kraft also showed that the success of filter cages was dependent upon the use of a filtered-air hood for all animal manipulations, including cage changing and supply of food and water. Although Kraft proved the efficacy of this system, the cages were little more than cylinders of wire mesh covered with fiberglass filter material, which were too cumbersome to handle for large scale animal production. This approach was improved somewhat by the development of “filter caps” made of wire mesh and fiberglass to fit over mouse cages (11). The next major step was the development in the mid to late 1970s by Bob Sedlacek (Figure 2) of a raised snug-fitting filter cap with edges that overlapped the sides of standard shoebox cages and was fitted with Remyay® filter medium protected by a perforated aluminum plate (12). In Sedlacek’s words, it holds animals in a filter-topped enclosure “...analogous to a large petri dish”. In 1980, he asked Lab Products, Inc. to produce this cage system which we know today as the microisolation cage. This type of cage and a modified version for use with forced air ventilation has become the primary means to protect rodents in an environment potentially contaminated by undesirable infectious agents.

These developments have affected disease monitoring in several ways. The ability of vendors to produce large numbers of animals free of common infections and the ability to maintain them in that state in the laboratory setting has greatly increased the interest in monitoring the animals. It has become sort of axiomatic that “the cleaner the animals, the greater the interest in testing them to prove their continuing infection-free state”. The microisolation cage, however, presents a problem for monitoring. Properly managed, it is so effective in preventing contagion that an introduced infection in a single cage would likely be limited to that cage. This is good, unless one is attempting to find the contaminated cage. The usual practice of testing animals in a small percentage of cages selected at random would have very low probability of finding the affected cage. To be assured that microisolation cages have not been compromised, some monitoring programs have resorted to exposing separately caged sentinel animals to soiled bedding from the microisolation cages. This has the

systems to keep commercially-produced clean animals clean when they were received into dirty laboratories. We have to go back to the late 1950s, however, to witness the birth of a new idea that would eventually make this possible. That was when Dr. Lisbeth Kraft (Figure 1) at Yale Univer-

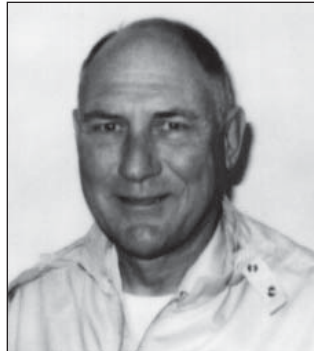


FIG. 2. Mr. Robert S. Sedlacek

obvious drawback that some of the rodent infections such as mycoplasma and cilia-associated respiratory (CAR) bacillus are difficult to transmit in bedding. Regardless of the monitoring problem, it is hard to fault this caging system because of its effectiveness in preventing contagion.

NIH Funding of Training

The evolution of disease monitoring was influenced greatly by the development of funding programs at the National Institutes of Health (NIH) to support training in laboratory animal medicine. The early history of these programs, beginning with the funding of a few training programs in 1959 by the Physiology Training Committee of the Institute of General Medical Sciences, has been chronicled by Clarkson (13). These programs were later transferred to the Animal Resources Branch (ARB) which was established in 1962 by Dr. Willard H. Eyestone (Figure 3) in the newly established Division of Facilities and Resources. The ARB, was reorganized and named the Comparative Medicine Program (CMP) in 1990 (see Chapter 11 for more information on ARB). Over 500 graduate veterinarians have received formal training in laboratory animal science under institutional training grants sponsored by CMP (renamed Comparative Medicine Area in 1996)(14).



FIG. 3. Dr. Willard H. Eyestone

Those individuals were trained in outstanding programs in top academic institutions in the United States. Their training and research experience in clinical medicine, microbiology, comparative pathology, genetics and molecular biology has resulted in the rapid characterization of many important laboratory animal diseases, which in turn has stimulated the continued development of methods for disease detection and monitoring.

The Evolution of Testing Methods

Monitoring practices were especially influenced by the evolution of testing methods for infectious diseases. A major surge in the use of serologic procedures began in the late 1950s when virus-defined rodents were needed for cancer studies. The surge was led by the efforts of Dr. Wallace Rowe and his coworkers, especially Dr. Janet Hartley, of the National Institute of Allergy and Infectious Diseases at NIH (Figure 4). The essence of what Dr. Rowe wanted to do and actually accomplished was stated by him at an ICLAS symposium in Czechoslovakia in 1961:

“The approach which we have followed has been to attempt to define the viral flora of mice, to classify the agents, to elucidate their natural history, and to devise reliable laboratory procedures for the recognition of active infection with the agents (virus detection) and for the recognition of previous infection (serologic procedures). In particular, development of serologic procedures has received the greatest emphasis, since these have the great advantage of cheapness, rapidity, and applicability to large scale work” (15).

Dr. Rowe also went on to describe how the mouse antibody production test, or “MAP test”, which he invented, could be used in lieu of the more cumbersome viral isolation procedures for demonstration of active viral infections (15). Dr. Rowe published numerous descriptions of rodent viruses and was the first to survey multiple mouse colonies for incidences of



FIG. 4. Drs. Wallace P. Rowe and Janet Hartley

selected viruses (15, 16, 17, 18). Clearly, his efforts were a major factor in changing the way we monitor laboratory animals for viral infections. The poster that he drew to depict the relationship of mice and their viruses is well known among the workers of that era (Figure 5). During interviews of people who knew Dr. Rowe, statements were made such as “He was the granddaddy of lab animal virology” (Michael Collins) and “There were many who encountered lab animal viruses and published their findings, but Wally Rowe was the first to study the viruses systematically” (Pravin Bhatt). The American Committee on Laboratory Animal Disease sponsors the Wallace P. Rowe Lecture in his honor and memory every year at the national AALAS meeting.

Another important step in the evolution of test methods was

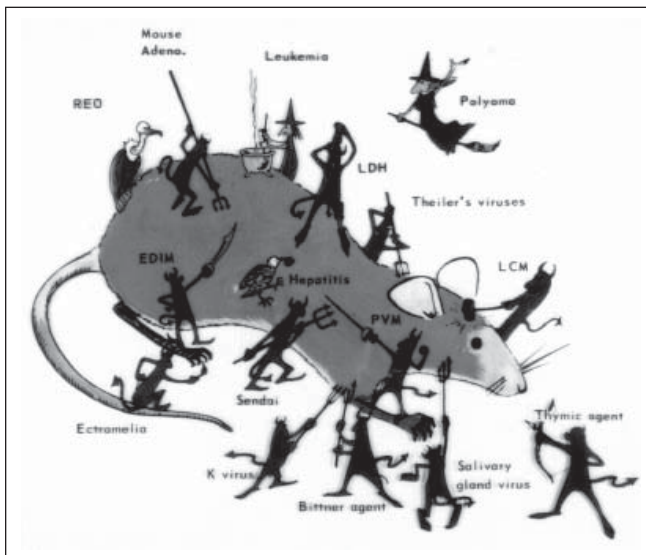


FIG. 5. Poster drawn in the early '60s by Dr. Wallace Rowe.

the development of “micro-procedures” for serologic testing. These procedures, which were first described by Takatsy in Hungary in 1955 (19) and modified for routine use by Sever at NIH in 1962 (20), used very small quantities of serum for testing, thereby making it possible to test a single mouse serum for multiple viruses.

Still another major step in the evolution of testing was the holding of a “Symposium on Viruses of Laboratory Rodents” at the Center for Disease Control (CDC) in Atlanta in 1965. This symposium, which was sponsored by the National Cancer Institute (NCI) and CDC, introduced 220 scientists of varied backgrounds to the value of virus-defined laboratory rodents,

as well as the need for monitoring to continually demonstrate the level of definition. The symposium was published as an NCI Monograph, Number 20, in 1966, with Bob Holdenreid as editor. The program committee was composed of people very active in the field, including Wallace Rowe and Jack Parker (21). Perhaps equally important was the holding of a workshop following the symposium to provide instructions on reagent preparation and micro-procedures for testing by complement fixation and hemagglutination methods (Figure 6). The workshop was attended by about 30 people and was directed by Elizabeth VonKaenel and Lizabeth Odum of Microbiological Associates, Inc. (renamed BioReliance Corporation in 1997). The NCI/CDC symposium and the workshop are considered by many to have stimulated the beginning of large scale commercial testing of laboratory rodents.

In more recent times, advances in methodology that have improved monitoring capabilities include:

- 1975–1998 Molecular approaches including the use of monoclonal antibodies (1975), recombinant or selective antigen components (1980), and polymerase chain reaction (1985) (22)
- 1976 Introduction of the microplate ELISA for detection of serum antibody to infectious agents (23)
- 1977–1978 Introduction of Teflon® coated multiwell slides for use in performing immunoassays (24)
- 1989 Development of antibody reference reagents for infectious agents of mice and rats (25)

Other important meetings that updated information on disease monitoring and methodologies include a symposium in Hungary in 1962 on *The Problems of Laboratory Animal Disease* (26), the 7th ICLAS symposium in Utrecht in 1979 on *Animal Quality and Models in Biomedical Research* (27), a CIIT conference in Raleigh, N.C. in 1983 on *Complications of Viral and Mycoplasma Infections in Rodents to Toxicology Research and Testing* (28), and a conference at NIH in 1984 on *Viral and Mycoplasma Infections of Laboratory Rodents. Effects on Biomedical Research* (29). In addition, the *Manual of Microbiologic Monitoring of Laboratory Animals* was produced in 1986 with a second edition in 1994, by the Laboratory Animal Science Project, within the framework of the U.S.-Japan Agreement on Cooperation in Research and Development in Science and Technology (30, 31), and the text on *Infectious Diseases of Laboratory Mice and Rats* was published in 1991 by the National Research Council (32). In the 1970s and 80s, the well known ACLAM series of texts on the biology and diseases of laboratory animals provided basic information vital to the design of monitoring approaches.

Developments in NIH Programs

The history of the NIH animal colonies dates back to the early years of NIH. The roles played by Samuel Poiley and George Jay in directing the development of the colonies was documented in detail in *Laboratory Animal Science* in 1980 by McPherson (33). Through the years, a number of decisions were made that changed the management of the colonies. A few of the decisions that gave new direction to disease monitoring practices in this country will be discussed.

Prior to 1970, the health status of the NIH colonies was assessed mainly by examination of animals that were sick or found dead. In other words, overtly ill animals were examined in a diagnostic program. True monitoring, or evaluation of predetermined numbers of randomly selected rodents at



FIG. 6. Attendees of the workshop held during the NCI/CDC Symposium on Viruses of Laboratory Rodents, in Atlanta in 1965: First Row, Left to Right: R.A. Elliot (Eli Lilly Co.); Nicola M. Tauraso (NIH); Herbert D. Soule (Detroit Inst. Cancer Research); Donald Martin (Oak Ridge Nat'l Laboratory) Second Row, Left to Right: Ernestine Teeter (Oak Ridge Nat'l Laboratory); Lizabeth Odum (Microbiological Associates, Inc.); Elizabeth VonKaenel (Microbiological Associates, Inc.); Joan E. Margison (Charles Pfizer Co.); Janis McMillen (Univ. of Kansas Med Center); Susan Tiffany (Baylor Univ. College of Medicine) Third Row, Left to Right: Leman Black (Charles River Breeding Laboratories); William M. Evans (N. Y. State Dept. of Health); Gladys Sather (Univ. of Pittsburgh); Jeannie Hubbard (Baltimore Biological Labs); Helen L. Casey (CDC); Nancy Rogers (Nat'l. Inst. Neurol. Diseases and Blindness); Lloyd D. Jones (Fitzsimmons General Hospital) Fourth Row, Left to Right: Charles P.Lattuada (A.R. Schmidt Co.); Raymond D. Ediger (Fort Detrick, MD); James Davis (Flo Laboratories); Howard W. Clapp (Upjohn Co.); Paul H. Smith (Plum Island Animal Disease Laboratory); James R. Ganaway (Comp. Path Sect., NIH); Kenneth Quist (CDC); Robert S. Stone (Univ. of New Mexico).

regular intervals for evidence of disease (clinical or subclinical) began abruptly in 1971 when the NIH animal colonies were hysterectomy-derived into a newly constructed "barrier" facility. The adage that "the cleaner the animals the greater the interest in proving they are clean" quickly took effect. An elaborate program to monitor for a long list of viral, bacterial, and parasitic infections was established. This program was designed and set in motion by two outstanding microbiologists, Dr. James R. Ganaway and Dr. Thomas D. Moore of the Comparative Pathology Section (CPS). Shortly thereafter, NIH came under severe pressure to reduce job slots. Dr. Joe Held was Director of the Laboratory Aids Branch at that time, which included the research animal programs. In 1972, he made a difficult decision, which turned out to be correct, to contract out the production of a large number of the rodents to be used in NIH research. This was done with the stipulation that the contractors must use breeders from the NIH nucleus colonies and that the contractors' animals must meet certain health specifications when delivered to NIH researchers. This was extremely important, because it likely provided major impetus for animal vendors to establish microbiologic monitoring programs and to begin reporting the health status of their animals to the animal users. Additional impetus came from the establishment of the NCI's rodent colonies (1974) and associated diagnostic laboratory (1975) in the Frederick Cancer Research and Development Center at Frederick MD (34), as well as the stringent requirements for defined animals developed over time by the National Toxicology Programs of the National Institutes of Environmental Health Sciences.

These happenings occurred at a time when knowledge of laboratory animal disease pathogenesis and methods for testing were evolving rapidly and users were beginning to test animals from various sources, including vendors. With the availability of commercial testing, interest in defining the health status of

colonies gained momentum. At NIH, additional pressure to monitor was brought about by the designation of the NIH nucleus and foundation colonies of rodents as a collaborating "Center for Defined Animals" by the World Health Organization in the late 1970s (35). In 1980, following the 1979-1980 outbreak of mousepox at multiple sites in the U.S. (36), the Importation Quarantine Service was started at NIH. This program, initially designed by Dr. J. David Small and modified over time during operation by CPS, mainly protected NIH against the introduction of ectromelia, lymphocytic choriomeningitis, and hantaviruses. Also in 1980, at the National AALAS meeting in Indianapolis, Dr. Albert E. New (National Cancer Institute) and Dr. Steven H. Weisbroth (Anmed/Biosafe, Inc.) moderated a roundtable discussion on "Microbiological and Chemical Monitoring of Rodent Colonies" (37). The discussion encompassed many aspects of monitoring, and included heated debate about the importance and extent of monitoring that should be performed by animal vendors. By 1985, most of the larger vendors had developed increasingly sophisticated testing programs and were providing the results to users either routinely or upon request, in efforts to market the health status of their colonies. These events and others were clear signs of a rapidly evolving need for microbiological monitoring as an important element of laboratory animal medicine and biomedical research.

Summary

Over a period of about 50 years, we have witnessed change from a situation in which efforts were made to detect poorly characterized diseases of laboratory rodents occurring rampantly in makeshift animal quarters, to today's circumstance in which we are using refined methods to monitor animals that are generally expected to be purchased free of infections and can be expected to remain free in facilities with protective environments. This has been the result of the numerous advances and developments brought about by the foresight, training, and efforts of countless individuals working in the laboratory animal medicine field, many of whom have not been mentioned in this abbreviated history of the evolution of disease monitoring practices.

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