

*Chapter Nineteen*

# Evolution of Disease Patterns in Laboratory Rodents: The Post-Indigenous Condition

Steven H. Weisbroth, DVM

It has been over 100 years since the Norway rat, *Rattus norvegicus*, and the house mouse, *Mus musculus* were first domesticated and albino variants introduced to European, and then American laboratories to be used as basic tools for support of scientific investigation (1,2).

From the beginning, issues of rodent health surfaced as important concerns, not only to the investigator, but also to the service personnel charged with the care of these animals. A rich body of literature extends back to the late 1800s that describes the diseases of laboratory animals. However, over that century, the list of indigenous infectious diseases of each particular rodent species has not remained static, rather, the lists have undergone change in etiologic agents of concern as disease control programs have been successively brought to bear, particularly during the last several decades.

Some sense that things are changing can be seen by taking a look at changes over time in the types of research articles being published on infectious diseases of laboratory rodents. To that end, Table 1 summarizes categories of disease agents in *Laboratory Animal Science* (LAS) article titles for entire years, taken at five-year intervals. The shift in agents of concern as time has gone on over this 30-year period is quite apparent. For example, look at the pattern of articles on murine viruses over the years.

Comprehensive rodent health surveillance programs are oriented to the systematic diagnostic examination of sample groups of animals against a predetermined list of pathogenic agents. Properly conducted, findings in the sample group can be used to infer presence of the detected agents in the larger population they represent. In developing the lists of agents of concern, it

is first necessary to understand that each animal species is host to an etiologic spectrum composed of arthropod ectoparasites, helminth and protozoan endoparasites, bacterial, viral, rickettsial and fungal forms typically associated by common diagnostic experience as indigenous to that species. For testing purposes, the etiologic classes are organized into panels of the more common indigenous agents for the rat and mouse, respectively (see Table 2). They form the basis for a spectrum of agents that high quality research rodents are expected to be found free of and are widely used as procurement specifications. Over the years, the principle effect of disease control, eradication, and exclusion programs has been to systematically reduce both the range of diversity and the frequency of encountering the agents within these etiologic classes. With the rodents, the following stages in this process can be recognized.

## *I. Stage of Domestication: 1880–1950*

As rodents were domesticated, and then brought into the laboratory, they brought with them practically the entire range of infectious agents associated with their wild counterparts. Under conditions of improved sanitation, nutrition, and maintenance of the breeding colonies within stable, indoor environments; a number of infectious conditions became progressively infrequent or simply disappeared from laboratory colonies. Such agents as the rickettsias, numerous helminths, bacterial forms such as *Leptospira*; the rat bite fever agents *Spirillum minus*; and *Streptobacillus moniliformis*, and even the salmonellas serve as examples of agents that disappeared, or which became notable by their infrequency under husbandry conditions that applied during the first half of this century.

## *II. Gnotobiotic Derivation: 1960–1985*

That is not to say that the general health of laboratory rodents or standards for the care of these animals in the 1950s was all that good. Biomedical research expanded greatly in the decades after World War II, and with it a burgeoning of the demand and utilization of laboratory rodents. The ravages of primary mycoplasmal, bacterial, and viral pathogens imposed serious limitations on the successful conduct of biomedical investigation and testing programs reliant on the use of laboratory rodents. Scientists of that generation will recall an era when the curtailment, or even cancellation, of study after study because of intercurrent disease was common, not the rare exception. It was in this environment, and as an outgrowth of concern to improve disease control programs and advance standards for animal care, that the disciplines of laboratory animal science and laboratory animal medicine emerged. Organizationally, the American Association for Laboratory Animal Science (AALAS), the American Association for Accreditation of Laboratory Animal Care (AAALAC); now named the Association for Assessment and Accreditation of Laboratory Animal Care International and the American College of Laboratory Animal Medicine (ACLAM) were formed in that era to promote, channel, and formalize implementation of technologic advances as they came along.

At a certain point in the 1950s and 1960s it became clear that none of the standard veterinary approaches of improved husbandry and sanitation, vaccination, or antibiotic chemotherapeutics could effectively address the relentless effects of intercurrent disease on the research process. If infectious disease was the freight train hurtling through rodent populations, surely *Mycoplasma pulmonis*, the agent of respiratory mycoplasmosis, was the engine that motivated the turn to a

Table 1. Frequency of Rodent Etiologic Agents in LAS Article Titles

Etiologic Agents	1965	1970	1975	1980	1985	1990	1995
Parasites	1	1	4	4	1	0	0
	Syphacia	Syphacia	Eimeria Cysticercosis Hymenolepis Myobia	Syphacia Trixacarus Obeliscoides Encephalitozoon	Dentostomella		
Bacteria/ Fungi	7	3	3	4	1	3	8
	Bordetella Pseudomonas Salmonella Citrobacter Pasteurella S. pneumoniae Trichophyton	B. piliformis Pasteurella	Pasteurella Bordetella Aspergillus	Pasteurella B. piliformis Citrobacter Staphylococcus	C. kutscheri	Streptobacillus CARB Pasteurella	CARB (2) Helicobacter H-A Coryneform C. difficile (2) Pasteurella C. kutscheri
Mycoplasma	0	1	2	1	1	0	1
Viruses*	1	1	0	1	5	11	6
	EDIM	ECT		KV	SDAV/RCV MHV (2) CMV ECT	SDAV/RCV (5) MHV (3) SEN REO MTV	SEN MVM/MPV RVHD LCM HAN

\*Viral acronyms are defined in Table 3.

different approach to control or eradicate these conditions. The different approach was to prevent disease by excluding it.

Henry Foster of Charles River Breeding Labs and C. N. Wentworth Cumming of Carworth Farms were among the first to perceive that the principles of gnotobiology, developed originally to explore the dimensions of germ-free biology, could also be applied to large scale production of laboratory rodents from which the ineradicable diseases of the parents could be excluded by cesarean derivation (3–6). The process, which is carried out under aseptic conditions, is initiated by hysterectomy of the gravid uterus from a donor female. The gravid uterus is passed through by antiseptic immersion into an isolator with sterile interior and life support systems capable of maintaining a germ-free environment. At some point, the germ-free animals are then “associated” by oral inoculation with the four to six microbial forms necessary for normal intestinal morphology and physiology (7). These associated animals, termed gnotobiotics, are usually retained in isolators as nucleus colonies to produce progeny destined for transfer to large barriered production colonies. The offspring from within the barrier are offered for sale or for institutional use, and also generate the breeders to continually repopulate the barrier. In principle, such breeding barriers may be continued indefinitely, unless routine testing or clinical signs indicate a break, or penetration of the barrier, by an unacceptable microbial agent.

The process was remarkably effective as a means of providing rodent stocks free of the common primary bacterial, parasitic, and mycoplasmal diseases. At the time, little was known about the viral status of such animals, but more importantly, since there was little clinical perception of infection, there was correspondingly little concern about their presence in rodent hosts.

As managers of commercial and institutional breeding colonies became adept with the principles and practice of gnotobiotic derivation, the process was adopted as the standard throughout the field and such terms as “pathogen free” and “specific pathogen free (SPF)” came into common parlance to

describe the status of such animals (8,9). It was only in recent years, after the aggregate burden of the primary bacterial, helminth, protozoan, arthropod, and mycoplasmal agents had been substantially reduced, that the more subtle physiologic and morphologic effects of the murine viruses could be appreciated. While on the one hand it is true that the same gnotobiotic process that excludes the other etiologic classes also effectively excludes viruses, on the other, it is also true that the laboratory animal establishment—the rodent breeders, facility directors, and scientific users—in the decades from 1960 through 1980 either knew and tolerated viral enzootics out of uncertainty as to their significance, or were unaware of their presence in production barriers and user facilities. In the absence of clinical signs and lesions, the effects of the murine viruses on their hosts was not appreciated, or in most cases, even recognized. That state of affairs could not last long as a growing swell of research reports and conferences began defining the effects of the murine viruses. This concern ushered in the next stage, the unfinished business of the murine viruses.

### III. Eradication of the Indigenous Murine Viruses: 1980–1996

The murine viruses as a group have only limited potential for serious clinical manifestation. In fact, most of the murine viruses were discovered, or initially encountered, as contaminants of research utilizing some transplantable neoplasm, tissue culture, or biologic derivative from clinically silent, but infected rodent hosts. They are listed in Table 2. In practice, viral panels are chosen that balance the economic efficiency of testing against the desired range of serologic inquiry. Core panels feature reduced numbers of viral agents to test only for the most prevalent. Standard panels have a larger number of agents, and extended or comprehensive panels a maximal number, the latter usually used where it is desired to define the viral status of a given rodent group or source for some benchmark purpose.

Mouse pox (ectromelia) is the practically singular example

Table 2. Pathogen Panels for Rodent Comprehensive Health Surveillance Profiles

1. Arthropod ectoparasites  
Genera include: Myobia, Myocoptes, Radfordia, Polyplax, Psorergates, Notoedres, Demodex, Liponyssus.
2. Helminth endoparasites.  
Genera include: Aspicularis, Syphacia, Hymenolepis, Trichosomoides.
3. Enteric protozoa.  
Genera include: Hexamita (Spirotrunculus), Giardia, Entamoeba, Trichomonads, Eimeria.
4. Bacteria:

Clostridium piliforme	Mycoplasma pulmonis
Bordetella bronchiseptica	Mycoplasma arthritis
Cilia-Associated Respiratory Bacillus	Pasteurella pneumotropica
Citrobacter rodentium	Pseudomonas aeruginosa
Corynebacterium bovis (H-AC)(athymics only)	Salmonella sp.
Corynebacterium kutscheri	Staphylococcus aureus
Klebsiella pneumoniae	Streptobacillus moniliformis
Klebsiella oxytoca	Streptococcus pneumoniae
5. Hemoprotozoans (Rickettsia).  
Hemobartonella Eperythrozoon.
6. Other  
Encephalitozoon cuniculi Pneumocystis carinii
7. Viruses

(a) Mouse Virus Acronyms	Virus Name	(b) Rat Virus Acronyms
PVM	Pneumonia Virus of Mice	PVM
REO-3	Respiratory Enteric Orphan III	REO-3
GD-7	Theiler's Murine Encephalomyelitis Virus	GD-7
SEN	Sendai	SEN
LCM	Lymphocytic Choriomeningitis Virus	LCM
HAN	Hantaan Virus	HAN
	Sialodacryoadenitis Virus/Rat Coronavirus	SDAV/RCV
	Kilham's Rat Virus	KRV
	Rat Parvovirus	RPV
	Toolan's H-1 Virus	TH1
MVM	Minute Virus of Mice	
MPV	Mouse Parvovirus	
MHV	Mouse Hepatitis Virus	
KV	Kilham's Virus	
EDIM	Epizootic Diarrhea of Infant Mice	
MAV	Mouse Adenovirus	
ECTR	Ectromelia	
POLY	Polyoma	
MCMV	Mouse Cytomegalovirus (Salivary Gland Virus)	
MTV	Thymic Virus	
LDHV	Lactic Dehydrogenase Elevating Virus	

of a virus with high potential for morbidity and mortality in mouse stocks. Several of the others, -Lymphocytic Choriomeningitis (LCM), Sialodacryoadenitis Virus (SDAV), Sendai (SEN), Mouse Hepatitis (MHV) and Kilham's Rat Virus (KRV)-serve as examples of agents that are ordinarily asymptomatic, or with only low grade potential for pathogenicity in adult random-bred rodent stocks. Yet these have been indicted as agents of disease, in conventional terms, by some niche of susceptibility conferred by age group, by the genetic status of certain inbred or mutant stocks, and by rodents rendered immunodeficient by some heritable or manipulative process. In this connection, recent years have seen a great expansion in institutional populations of immunodeficient mutant and transgenic stocks that have acted as flash points for clinical episodes in rodents having increased susceptibility to agents that are ordinarily opportunistic or clinically silent in their normative rodent counterparts. Agents that include several of the *Helicobacter* species, the hyperkeratosis-associated coryneform agent *Corynebacterium bovis*, *Pneumocystis carinii* and

several of the viruses (MHV, MVM, and PVM) are all extensively documented as clinically important infectious hazards for this higher risk population (see emerging conditions).

More important, by virtue of their clinical silence in immunocompetent outbred stocks and inbred strains, are the many murine viruses that introduce some variability of biochemical or reflexive cellular response to infection that interferes with certain kinds of research. Most of the murine virus infections act as examples of the phenomenon. Viruses including minute virus of mice (MVM), murine cytomegalovirus (MCMV, RCMV), mouse hepatitis virus (MHV), Sendai (SEN), lactic dehydrogenase elevating virus (LDV), encephalomyelitis virus (GD7 or GD-VII), respiratory enteric orphan-3 (REO3), mouse adenovirus (MAV), and many others have been documented as agents that perturb some aspect of cellular or subcellular function so as to compromise the object of research, while the host animals remain clinically asymptomatic.

By the early 1980s immense pressure from the biomedical

research community, similar to that in the late 1950s, began to develop as a result of too frequent viral complication of research in the areas of molecular biology and biotechnical research and product development (10,11,12). This pressure resulted in two conferences in the U.S. that were vital to changing perceptions about the importance of murine virus infections: Complications of Viral and Mycoplasmal Infections in Rodents to Toxicology Research and Testing, sponsored by the Chemical Industry Institute of Toxicology at the 6th CIIT Conference on Toxicology, 1983 and a conference given at the NIH, 1984, Viral and Mycoplasmal Infections of Laboratory Rodents: Effects on Biomedical Research. Reports of both conferences were published (13,14).

For about the last 10 years, or somewhat longer, an unofficial, but nonetheless consensually accepted international effort, has been made to implement a virus-free standard for laboratory rodents. It is important to understand that virtually every biomedical research institution in the country has had to come to grips with the scientific community's collective resolution to conduct research with virus-free rodent stocks. This effort has involved commercial and institutional rodent suppliers, the animal care unit administrators who procure and maintain rodent stocks, and the scientific users who conduct and report research results. In short, the entire chain that deals with supply, care and use of laboratory rodents.

In the late 1960s John Parker had begun commercially offering serologic tests for several of these agents to determine the antibody status, and by inference, the viral exposure status of sera from rodent colonies (15). Later, the viruses of concern were expanded and organized into panels characteristic of, or indigenous to, particular rodent hosts. Later still, reagents to enable testing and detection were made widely available to enable large scale surveillance programs. This strategy, the use of antibody detection in sera from colony residents or sentinels, has been widely adopted as standard practice to evaluate murine viral contaminant status of rodent colonies. The effort has been quite successful, when viewed from a larger perspective. Over the last 10–15 years both the diversity of murine viruses and the frequency with which such infections are encountered, have declined markedly. Although certain sectors of rodent usage may have lagged the general trend (16), in large sectors of rodent use, we appear to be in the terminal, mopping-up stages of this international effort.

It is also true; however, that progress in viral eradication has not occurred without periodic shut downs at user facilities and individually wrenching dislocations in research programs. Every animal care program director has had to learn the techniques for prevention, control, and eradication of murine virus infections, and how to deal constructively with the political balancing act required to achieve the support and compliance of institutional investigators. Most well managed animal care programs operate, at present, for long periods of time without serologic evidence of viral exposure, and without detection of other indigenous agents by routine surveillance. Laboratory animal specialists can take deserved pride in having guided the research animal effort in this country to the present level of quality. So, is the war over? Have the good guys won? Are we to become like the Maytag repair man waiting for the phone to ring? Not really.

#### IV. Post-Indigenous Disease

Perversely, the diseases keep coming. What makes them different is that they don't appear in Table 2 amongst the agents defined by history and experience as indigenous to the par-

ticular rodent hosts. For that reason, I am suggesting the term "post-indigenous" as a descriptor for an unfolding cluster of seemingly new conditions diagnostically taking shape as time goes on. Table 3 is a somewhat subjective (and not exhaustive) listing of disease candidates as post-indigenous. These conditions have several common threads that suggest themselves from the author's perspective at a diagnostic laboratory:

1. Most of these conditions have only been recognized in the last several years. There is no basis of prior experience for understanding the provenance of these conditions. It is not clear if they are truly emergent, or rather, that they now may be more readily recognized in the absence of indigenous agents, or more likely, whether both situations are at play.
2. Given the recent arrival, or at least, recent recognition of these conditions, there is only a scanty base of literature to draw on for understanding the biology of these infections and the strategies for their management and eradication. These are currently very active areas of investigation.
3. On the whole, these conditions are clinically mild or inapparent. Many have not been associated with morphologic lesions, or physiologic changes, and several may only be recognized by serologic reaction without other concomitants or means of corroborating infection.
4. It is by no means clear for any of them that the infectious reservoirs are other rodents and lagomorphs, or rather, whether these conditions are communicated by contact with the humans associated with their care and use. That is to say, the reservoirs for Sendai, MHV, mites, pasteurellas, pinworms, etc., are well established as residing in other rodents and lagomorphs. This relationship is not clearly established with the cluster of emergent conditions being discussed here, and indeed, a good deal of anecdotal evidence suggests otherwise. If not from other rodents, where might such infections originate? This is an open question at present.

In the author's opinion, the relatively open and unrestricted exposure of barrier-produced laboratory rodents to their human contacts (animal care personnel and investigators) after arrival at the user institution poses one of the last unexamined and essentially unregulated aspects of the research animal environment. Surely it is an area we are going to have to look at more closely. The rationale for so doing can be illustrated as follows:

Even under the best of circumstances to limit exposures, animals readily become colonized with microbial forms by virtue of human contact. For example, consider a large commercial breeding barrier with capability for sterilizing all incoming animal diets and equipment, HEPA-filtration of incoming air, treatment of drinking water, and strict standards for personnel entry (disrobing of street clothes, showering, donning of sterile outerwear inclusive of gloves, headcover, jumpsuit, footwear and surgical masks—or even headcovers with forced HEPA-filtered ventilation). When gnotobiotics are introduced from the isolator into such environments, it is commonly observed that in a matter of only four to eight weeks these animals become colonized by a range of microbial forms that should be interdicted and prevented from entry by the barrier procedures. Such organisms are not necessarily pathogenic, and are known to include enteric forms like *E. coli*, *Aerobacter*, *Pseudomonas* and *Klebsiella*, and skin forms like *Staphylococcus epidermidis* and *S. aureus*. Where are such bacterial forms coming from? Given the rigor of barrier standards, what are the realistic possibilities? Under the circumstances described, the potential for a rodent

Table 3. Emerging Disease  
Conditions of Laboratory Rodents and Lagomorphs

1. *Helicobacter* infections of mice, rats, and hamsters (17–20)
2. Beta-hemolytic *Streptococcus* infections of mice (21)
3. *Staphylococcus aureus* infections of athymic mice (22, 23)
4. Hyperkeratosis-Associated coryneform infections of athymic mice (24–26)
5. Rabbit Cilia-Associated Respiratory Bacillus (CARB) infection (27)
6. Atypical (newly recognized) parvovirus infections of rats and mice (28–30)
7. *Pneumocystis carinii* infections of immunodeficient rodents (31)
8. Atypical reovirus and parainfluenza virus infections of guinea pigs (32)

source seems quite remote. Isn't it reasonable to conclude that in spite of the rigorous use of personnel outerwear, these agents are being disseminated from animal care personnel, perhaps by microbe laden leakage of air from around the cuffs and masks? Isn't it logical that, if non-pathogens like *E. coli* can colonize rodents, that pathogens like parvoviruses could be vectored by human contacts as well?

At user institutions, with some exceptions, there are practically no limitations to direct contact of animals with humans or their microbe-bearing exhalations, saliva, dander and other detritus, emanations and excretions. One hoary exception that does limit or regulate human contact would be the current pre-employment test requirement that tuberculin positive results will disqualify prospective animal care technicians for contact with nonhuman primates. In few other cases are there formal rules that limit or regulate access to animals or return to work (for animal care technicians) following illness or remission of clinical signs (e.g. sneezing, coughing, fever). It is time for us to begin thinking seriously about the human contacts that animals are exposed to as representing potentially realistic reservoirs for the agents now being encountered as undesirable microbial contaminants of laboratory rodents, and potentially, as vectors for agents associated with post-indigenous diseases.

It seems that at any given point in time, specialists are trained to recognize, for each animal species, a certain spectrum of indigenous pathogens which are accepted as objectively pertaining in terms of common experience. This spectrum in turn, sets the approximate boundaries of the differential diagnostic possibilities for causes of infectious disease. What the history of the laboratory rodents seems to demonstrate, is that this spectrum as a concept is not a list frozen for all time, but rather, more closely represents a moving boundary in which old pathogens are eradicated, creating invasive opportunities for new, and periodic reconstitution of the list. In practice, the process is recognized as moving gradually and the cast of characters for each host species adjusted as circumstances seem to warrant. As examples, parvovirus was added to the list of canine viruses after the author left veterinary school, but glanders (an eradicated disease of horses)—had been deleted from the equine list even before he got there.

There appears little doubt that at present laboratory animal science is witnessing a major restructuring of the list of indigenous pathogens of the laboratory rodents, a process accelerated by the highly structured and microbially limited environments permitted by good laboratory animal practice. Circumstances seem to suggest that the reservoirs for many

of these newer conditions may be the humans with which the more microbially limited rodent hosts come in contact. If so, scientists may need to consider how to standardize and regulate such contacts more rigorously than is done at present.

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