

Animals as Sentinels: Using Comparative Medicine To Move Beyond the Laboratory

Peter M. Rabinowitz, Matthew L. Scotch, and Lisa A. Conti

Abstract

The comparative medicine approach, as applied to the study of laboratory animals for the betterment of human health, has resulted in important medical and scientific progress. Much of what is known about the human health risks of many toxic and infectious hazards present in the environment derives from experimental studies in animals and observational (epidemiological) studies of exposed human populations. Yet there is a third source of “in vivo” knowledge about host-environment interactions that may be underused and -explored: the study of diseases in naturally occurring animal populations that may signal potential human health threats. Just as canaries warned coal miners of the risk of toxic gases, other nonhuman animals, due to their greater susceptibility, environmental exposure, or shorter life span, may serve as “sentinels” for human environmental health hazards. Traditionally, communication between human and animal health professionals about cross-species sentinel events has been limited, but progress in comparative genomics, animal epidemiology, and bioinformatics can now provide an enhanced forum for such communication. The “One Health” concept involves moving toward a comparative clinical approach that considers “shared risks” between humans and animals and promotes greater cooperation and collaboration between human and animal health professionals to identify and reduce such risks. In doing so, it also creates new opportunities for the field of comparative medicine that can supplement traditional laboratory animal research.

Key Words: animal sentinels; comparative medicine; environmental health; One Health; toxicants; zoonosis

Peter M. Rabinowitz, MD, is Associate Professor of Medicine and Director of Clinical Services in the Occupational and Environmental Medicine Program at the Yale School of Medicine, and Matthew L. Scotch, PhD, MPH, is a research scientist in the Yale Center for Medical Informatics, both in New Haven, Connecticut. Lisa A. Conti, DVM, MPH, is Director of Environmental Health for the State of Florida Department of Health in Tallahassee.

Address correspondence and reprint requests to Dr. Peter M. Rabinowitz, Director of Clinical Services, Occupational and Environmental Medicine Program, Yale School of Medicine, 135 College Street – Suite 398, New Haven, CT 06510 or email peter.rabinowitz@yale.edu.

Introduction

Animals as Sentinels for Human Health

In the early part of the 20th century, miners in Great Britain and the United States took caged canaries into coal mines to provide warning of the presence of toxic gases such as carbon monoxide and methane. This use of a canary in the coal mine to provide “sentinel” warning about a human health hazard rested on three facts. First, laboratory exposure experiments had shown that canaries were more susceptible than both humans and other animals (e.g., mice) to the toxic effects of carbon monoxide (Burrell and Seibert 1914). Second, the birds shared the same air space exposures as the humans. Third, the occurrence of carbon monoxide poisoning in a bird (as opposed to a rodent) was readily recognizable to the miners—sick birds fell off their perches and appeared visibly ill—so the miners had time to put on emergency equipment and take other steps to avoid being overcome by the mine gases.

In the early 1960s, Rachel Carson’s publication of *Silent Spring* helped launch the modern environmental movement (Carson 1962). The implication of the book was that, like the canaries in the coal mine, dying birds above ground were acting as sentinels: through their deaths resulting from higher susceptibility, increased exposure, and/or recognizable signs of adverse (nonfatal) health events, they were warning humans of the health risks of widespread use of chemical pesticides such as DDT and other organochlorine compounds.

Just as with toxicants, zoonotic infectious disease agents may be better detected and prevented through the use of animal sentinels. Many zoonotic agents cause symptomatic disease in a number of host animal species or are detectable by serology, polymerase chain reaction, or other diagnostic methods, all of which facilitate their detection, which can in turn provide sentinel warning to humans. For example, the appearance of West Nile virus in the Western hemisphere was discovered by a veterinary pathologist investigating suspicious mortality events in crows and other birds in the vicinity of the Bronx zoo (Lanciotti et al. 1999).

There are at least three reasons why animals can be useful sentinels for zoonotic disease threats to humans. First, animals may be more susceptible than humans to a particular zoonotic agent. Anthrax, for example, is not only a disease of livestock but also a potent human pathogen and potential bioterrorism agent. In 1979, when an unintentional release of anthrax from a Russian biological weapons facility resulted

in human cases of pulmonary anthrax in the local area downwind from the plant, cattle and sheep died as many as 50 kilometers further downwind from the human cases (Meselson et al. 1994). The animals, with their increased sensitivity to the pathogen, thus served as sentinels for a much wider geographic area than where human disease was reported. Second, animals may have a shorter incubation period for an infection compared to humans. And third, animals could be at greater exposure risk than humans due to factors such as diet and more time outdoors.

Animals as Sentinels for Animal Health

The concept of sentinel surveillance and sentinel health events to protect animal health is already familiar to laboratory animal veterinarians who monitor the health of “sentinel colonies” of rodents or other species to determine whether pathogens or toxicants could affect the captive animal population. Beyond the laboratory, “sentinel herds” of domestic livestock are routinely tested for brucellosis and other communicable diseases.

Humans as Sentinels for Animal Health

Comparative medicine works in both directions, and veterinary medicine has adapted therapeutic approaches developed in humans for the treatment of nonhuman animals. In addition, humans may provide sentinel health information about health risks to animals. Because humans are more likely than many animal species to get medical care, including diagnostic services for a particular problem, they may be more likely to be diagnosed with a disease caused by an environmental agent, even if an animal species is more susceptible. Likewise, systems for disease surveillance in a particular area may be more developed for humans than for domestic or wildlife animals, with the result that humans may serve as the “canaries” for animal populations in the area.

For these reasons, greater linkage between human and animal disease surveillance could benefit animal health as well as human health, and help in identifying gaps in animal disease control and reporting systems.

Animal Sentinel Research

One of the great advantages of laboratory animal research is the ability to perform carefully controlled experiments. Yet methods for studying animals outside the laboratory can provide equally useful scientific information.

One method is to place animals in a cage or other enclosure and then expose them to a particular environment (this is the model of the canary in the coal mine). In some areas of the United States, sentinel flocks of poultry are used to monitor and research the environmental risk of West Nile virus or other pathogens (Trevejo and Reeves 2005). Similarly, laboratory rats have been placed under high-voltage power lines to study the effect of electromagnetic field (EMF) exposures

to help determine whether EMF poses a human health threat (Svedenstal et al. 1999). Such research is a form of cohort study, considered in human epidemiology one of the strongest observational study methods.

Another way to closely track an animal population cohort is by capturing, tagging, and recapturing individuals in a naturally occurring animal population, a technique used to study endocrine disruption in fish exposed to effluent from paper mills (Fentress et al. 2006).

Other observational epidemiological techniques include retrospective case control studies of animals. For instance, in a case control study of bladder cancer in Scottish terriers, researchers found an association between herbicide exposure and an increased risk of tumors (Glickman et al. 2004). The well-known historical case example of the “Dancing Cats of Minamata” is described in Box 1.

Comparison of Laboratory Animal Studies and Naturally Occurring Animal Sentinels

There are advantages and disadvantages to studying animals in either the laboratory or the field to learn more about the health effects of toxic and infectious exposures. Table 1 shows some differences between studies using laboratory animals versus natural animal sentinels.

It is costly to maintain laboratory animals in long-term studies of chronic low-level exposures, even though that is how chemical exposures tend to occur in the real world, but animal populations outside the laboratory may naturally experience such exposures. Similarly, reproducing exposures to complex chemical mixtures may be a challenge in the laboratory but is the way exposures normally occur in nature. Furthermore, in contrast to naturally occurring animal populations, emerging environmental hazards are unlikely to be identified in a laboratory experiment and the diversity of animal species that can be studied to look for environmentally induced health effects is restricted in the laboratory setting.

At the same time, there are disadvantages and challenges to studying natural animal populations, including the inability to study controlled exposures in an experimental fashion, the difficulty of tracking individual animals, and the difficulty of controlling other variables.

The Need for Comparative Medicine to Move Beyond the Laboratory

Major breakthroughs in medical research have resulted from comparative medicine and its use in research involving laboratory animals. Yet clinical human medicine as currently practiced remains quite noncomparative, with little clinical interaction between human health clinicians and their veterinary counterparts to compare clinical experience regarding shared health risks.

The clinical management of asthma in humans is an example of this disconnect. Most human clinicians who treat asthma are unaware that some cats naturally develop an airway

Box 1 Case example of shared health risk between animals and humans: The Dancing Cats of Minamata

The scientific literature reveals many examples in which animals and humans share risk of exposure to toxins or infectious agents. These accounts highlight the value of animals as sentinels for human health and the need to systematically compare animal and human health surveillance data, as illustrated in this case example.

In the early years after World War II, the Nippon Chisso plant in Minamata, Japan, became the major producer of vinyl chloride in that country, with a process that involved the use of mercury. Waste from the plant was dumped into the nearby bay, and die-offs of fish were soon observed. In 1952, cats in the town began developing neurological symptoms that included an abnormal, prancing gait and bizarre behavior such as throwing themselves against stonewalls or into the bay where many drowned. The “dancing cat disease” resulted in the death of many local cats.

It was not until several years later that local physicians began to recognize human cases of central nervous system disease, characterized by stumbling gait, confusion, and progression to stupor, coma, and death. Preliminary epidemiological surveys revealed that all of the patients had in common a diet high in fish from the bay.

Despite suspicion that pollution in the harbor was responsible for the outbreak of human illness, the company and local politicians refused to accept that the company’s actions could be responsible for the “Minamata disease.” Then in 1959, 3 years after reporting the first human cases, the chief physician for the city hospital, Dr. Hajime Hosokawa, conducted an experiment that consisted of giving a cat food sprinkled with waste from the Chisso factory. The cat developed cramps, salivation, tremor, abnormal movements, and other neurological problems. When the study was criticized as being the reaction of only one cat, Dr. Hosokawa repeated the experiment with 10 cats. The results were originally suppressed but eventually provided some of the key evidence that Minamata disease was methylmercury poisoning from consumption of fish contaminated with mercury.

It has been estimated that as many as 10,000 persons were affected in this tragic incident. If the outbreak of neurological disease in the cats had been adequately investigated at the time it occurred, many of the human cases could have been prevented (Aronson 2005; Eto et al. 2001).

syndrome that closely resembles human asthma (compared to many laboratory animal models). It is likely that environmental exposures play a role in the pathophysiology of cat asthma, so cats could be sentinels for environmental asthmagens that also affect humans. But there is little significant communication between the animal and human health communities about this possible connection (Reinero et al. 2009).

Barriers to Implementation of the Animal Sentinel Concept

Factors preventing the better integration of human and animal disease information and the vigorous use of human and animal sentinel surveillance to identify shared health risks fall into three interrelated categories: professional segregation, data separation, and evidence gaps.

Table 1 Comparison of health hazard studies using laboratory animals vs. natural animal populations (animal sentinel data)

Characteristic	Studies of laboratory animals	Studies of natural animal populations
Suitability for testing long-term, low-dose exposures	Difficult and expensive	Good
Suitability for testing chemical mixtures	Difficult	Good
Ability to detect emerging novel pathogens or chemical hazards in the environment	No	Yes
Species diversity	Limited	Not limited
Generalizability to “real world exposures”	Often limited	Good
Tracking of individuals	Easy	Difficult
Control of exposure and other variables	Easy	Difficult
Study methodology	Experimental	Experimental, observational

Professional Segregation

Despite the interrelatedness of many human and animal health issues, in most parts of the world human health and veterinary professionals develop in isolation from each other, from graduate school throughout professional training, and thereafter there are no significant channels of communication between the two types of health care providers. One manifestation of this professional segregation is that while many academic medical centers employ veterinarians in their departments of comparative medicine, these animal health professionals frequently have very little contact with human health clinicians in the same institution. They may also be isolated from their colleagues at schools of veterinary medicine.

One result of professional segregation is the tendency, among human health professionals, to adopt an “us vs. them” approach to animal health issues, considering animals only in terms of the risks they may pose to human health. Thus a deer mouse can pose a human health risk as a reservoir of a disease pathogen deadly to humans (hantavirus). From this it logically follows that management strategies to reduce the risk of zoonotic disease due to deer mouse exposure include avoidance of animal contact and elimination of rodent populations near human habitations where possible. In the same way, human health professionals may express concern that a household pet is a source of zoonotic disease exposure. While such concern is important for the health of the humans, it neglects the fact that both animals and humans may serve as sentinels for the “shared risk” of exposure to pathogens in the environment (Rabinowitz and Conti 2009).

Data Separation

In the United States, clinical data are not shared between human and animal health providers, and disease surveillance for human and animal disease is also performed separately. Human cases of reportable disease are reported to local and state health departments, and farmers, veterinarians, and regional veterinary diagnostic laboratories report animal disease data to the state department of agriculture. Other agencies, such as state departments of environmental protection and of fish and wildlife, participate in wildlife disease surveillance. But although environmental protection agencies are responsible for monitoring forest and wildlife resources and may be aware of wildlife die-offs or other disease events, contact between such agencies and veterinary or public health authorities is frequently limited. Furthermore, in contrast to public health reporting requirements, there are few mandates for disease reporting in wildlife populations.

On an international level there has been limited sharing of surveillance data between human health agencies such as the World Health Organization and animal health organizations such as the World Organisation for Animal Health (OIE) and the United Nations Food and Agriculture Organization. This situation appears to be changing, however, as in 2006 these three organizations launched a Global Early

Warning System for Major Animal Diseases Including Zoonoses (GLEWS; www.glews.net).

Evidence Gaps

The third major barrier to use of a “One Health” approach is the persistence of important gaps in scientific information and understanding about linkages between human and animal disease outcomes in response to environmental health threats (Rabinowitz et al. 2008). As a result, when an outbreak of disease occurs in an animal population, there may be a delay in recognizing the human health relevance. For example, the etiology of recent outbreaks of limb deformities in amphibians, colony collapse disorder in honeybees, and white nose syndrome in bats remains unclear, although environmental factors are believed to be responsible. And even if an etiology were established, so little is known about the susceptibility of these species to a particular hazard compared to humans that extrapolating to human health may be difficult or impossible. Yet even identifying the causative agent in the animals could help generate hypotheses about human health risks.

Part of the reason little is known about susceptibility differences between humans and many animal species is that the research has not been done. As mentioned above, surveillance data are rarely compared between animal and human populations, and there remains a paucity of evidence about the actual use of animal sentinels to effectively predict and mitigate human health risk for many infectious and toxic hazards in the environment.

At a time when human health professions have embraced the concept of evidence-based medicine, more effort is necessary to systematically assemble the evidence to support routine (and expanded) use of animals as sentinels for human health.

Strategies to Overcome Barriers to Use of Animal Sentinels

Support from Professional Groups

The One Health resolutions adopted in recent years by the American Veterinary Medical Association (www.avma.org/onehealth) and the American Medical Association (Nolen 2007) represent unprecedented attempts to overcome professional segregation and enhance the flow of information between human and animal health professionals. Comparative medicine specialists are trained and more experienced than many of their professional colleagues in the use of animal sentinel information, so they would seem to be natural leaders in this effort.

Adaptations in Professional Training

Thinking comparatively about human and animal health in the clinical realm leads naturally to the “shared risk” paradigm. Training clinicians in this paradigm could help identify

key environmental health risks that affect—or, as in the recent wildlife examples cited above, may turn out to affect—both humans and animals, and also help discover ways to jointly address such risks.

Creation of Registries and Databases

Promising developments in the field of comparative oncology—dogs, for example, have been recognized as the only nonhuman species that develops a lethal prostate cancer (Waters and Wildasin 2006; also see Gordon and Khanna 2010 for a discussion of comparative oncology, Withrow and Wilkins 2010 for dog models of osteosarcoma)—have led to the creation of animal tumor registries to track cancer occurrence, and these may eventually be linked with human tumor registries to better identify environmental causes of cancer.

In infectious diseases, there is also a greater willingness to link epidemiological and molecular information about pathogens that occur in humans and nonhuman animals. In addition to GLEWS there is the Global Initiative on Sharing Avian Influenza Data (<http://platform.gisaid.org>) for the international sharing of influenza virus sequences from both human and animal isolates.

To make use of animal sentinels as a source of *in vivo* data, there is a need to apply principles of evidence-based medicine to observational research on animal populations and environmental hazards. To that end, the Canary Database (<http://canarydatabase.org>) is a web-based effort to characterize the current state of scientific evidence on animals as sentinels for human health hazards. The database includes information about comparative susceptibility and exposure between humans and nonhuman animals, and will feature systematic reviews highlighting key issues for research as well as successful models of sentinels. This work can provide a framework for future evidence-based approaches to linking human and animal health.

These initiatives may facilitate the linkage of human and animal disease information in the future as well as the development of the interspecies sentinel disease concept.

Areas of Research to Reduce Gaps in Evidence

Linking animal and human health in clinically informative ways using species found outside laboratories will require an extension of existing comparative medicine techniques. In particular, the following types of research could contribute to progress in this area:

- Greater characterization of the genomes of multiple species will enable molecular approaches for examining shared genetic susceptibilities to toxic and infectious environmental hazards.
- Epigenetic research is needed to understand the impact of environmental factors on the expression of genes in multiple species.

- Molecular techniques such as strain fingerprinting and genetic sequence analysis can improve understanding of the evolution of pathogens that cross between animal and human populations and the factors that drive pathogen adaptation.

Conclusion

It appears that there is scientific value in expanding the application of the comparative medicine approach outside the tightly controlled laboratory environment. Greater interaction between comparative medicine specialists and their colleagues in both human and animal medicine could result in improved disease surveillance and wider application of animal models. Scientists in other disciplines are discovering ways to encourage collaboration among diverse groups of professionals working toward a common goal, as demonstrated by the Large Hadron Collider at the European Organization for Nuclear Research, a project involving over 7,000 scientists from 85 countries (Holly 2009). Applying this collaborative model to the challenges of comparative medicine could result in a productive One Health effort leading to the enhanced identification and prevention of health risks that affect both humans and other species.

Acknowledgments

This material is based on work supported in part by National Library of Medicine (NLM) Communication Systems Grant 5G08LM007881.

References

- Aronson SM. 2005. The dancing cats of Minamata Bay. *Med Health R I* 88:209.
- Burrell G, Seibert F. 1914. Experiments with small animals and carbon monoxide. *J Indust Eng Chem* 6:241-244.
- Carson R. 1962. *Silent Spring*. Boston: Houghton Mifflin.
- Eto K, Yasutake A, Nakano A, Akagi H, Tokunaga H, Kojima T. 2001. Re-appraisal of the historic 1959 cat experiment in Minamata by the Chisso factory. *Tohoku J Exp Med* 194:197-203.
- Fentress JA, Steele SL, Bart HL Jr, Cheek AO. 2006. Reproductive disruption in wild longear sunfish (*Lepomis megalotis*) exposed to Kraft Mill effluent. *Environ Health Perspect* 114:40-45.
- Glickman LT, Raghavan M, Knapp DW, Bonney PL, Dawson MH. 2004. Herbicide exposure and the risk of transitional cell carcinoma of the urinary bladder in Scottish terriers. *JAVMA* 224:1290-1297.
- Gordon IK, Khanna C. 2010. Modeling opportunities in comparative oncology for drug development. *ILAR J* 51:214-220.
- Holly K. 2009. Viewpoint: What business leaders can learn from CERN's collaborative management model. In *Bloomberg Business Week*. Posted May 20, 2009. Available online (www.businessweek.com/innovate/content/may2009/id20090520_115971_page_2.htm); accessed May 15, 2010.
- Lanciotti RS, Roehrig JT, Deubel V, Smith J, Parker M, Steele K, Crise B, Volpe KE, Crabtree MB, Scherret JH, Hall RA, MacKenzie JS, Cropp CB, Panigrahy B, Ostlund E, Schmitt B, Malkinson M, Banet C, Weissman J, Komar N, Savage HM, Stone W, McNamara T, Gubler DJ. 1999. Origin of the West Nile virus responsible for an outbreak

- of encephalitis in the northeastern United States. *Science* 286: 2333-2337.
- Meselson M, Guillemin J, Hugh-Jones M, Langmuir A, Popova I, Shelokov A, Yampolskaya O. 1994. The Sverdlovsk anthrax outbreak of 1979. *Science* 266:1202-1208.
- Nolen RS. 2007. AMA adopts one-health policy. *JAVMA News*, August 1. Available online (www.avma.org), accessed April 26, 2010.
- Rabinowitz PM, Conti LA. 2009. *Human-Animal Medicine: Clinical Approaches to Zoonoses, Toxicants, and Other Shared Health Risks*. St. Louis: Elsevier/Mosby and Saunders.
- Rabinowitz PM, Odojin L, Dein FJ. 2008. From “Us vs. Them” to “Shared risk”: Can animals help link environmental factors to human health? *Ecohealth* 5:224-229.
- Reinero CR, DeClue AE, Rabinowitz P. 2009. Asthma in humans and cats: Is there a common sensitivity to aeroallergens in shared environments? *Environ Res* 109:634-640.
- Svedenstal BM, Johanson KJ, Mattsson MO, Paulsson LE. 1999. DNA damage, cell kinetics and ODC activities studied in CBA mice exposed to electromagnetic fields generated by transmission lines. *In Vivo* 13:507-513.
- Trejejo RT, Reeves WC. 2005. Antibody response to *Culex tarsalis* salivary gland antigens among sentinel chickens in California. *Am J Trop Med Hyg* 72:481-487.
- Waters DJ, Wildasin K. 2006. Cancer clues from pet dogs. *Sci Am* 295:94-101.
- Withrow SJ, Wilkins RM. 2010. Cross talk from pets to people: Translational osteosarcoma treatments. *ILAR J* 51:208-213.