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Review

Beyond the Laboratory: Emerging Landscape of Animal Studies – the Influence of National Academies of Sciences Activities and Publications

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Research involving the study of animals in laboratory settings over the past century has transformed our understanding of human and animal health.[1] In recent decades, the study of animal life has shifted with expansion into disciplines and domains beyond traditional laboratory-based approaches.[2] From studies of behavioral changes in wildlife species to clinical studies on pet dogs and cats, studies of animal life are increasingly integral to a widening range of research domains.[3–6] Novel and critical insights are emerging from this broadened research landscape, but at the center of all studies on animal life are the basic biological insights that laboratory animal research exposes.[1,2]

For over 60 years the Institute for Laboratory Animal Research (ILAR), a program unit within the Division of Earth and Life Sciences of the National Academies of Sciences, Engineering and Medicine, has provided support, guidance, and leadership in laboratory animal research.[1] Throughout the 20th and 21st centuries, ILAR has focused on developing research activities to expand and advance animal laboratory research, publicizing laboratory animal guidelines, joining medical organization committees (The United Nations Educational, Scientific, and Cultural Organization; International Union of Biological Sciences; Council for International Organizations of Medical Sciences), and creating global standards for laboratory animal studies.[7] Over time, ILAR publications have emphasized both traditional animal models and other species in providing crucial information about human health.[8–10] Today, ILAR activities such as workshops and roundtables are calling attention to the importance of animals outside the laboratory—from discussions on animal welfare challenges and the accurate taxonomy of wildlife to predicting zoonotic spillover and pandemic threats.[11–13]

As the range of disciplines studying animals expands, it is both fitting and timely to reflect on the key role ILAR has played in fostering and shaping this emerging research landscape. This paper highlights the centrality of NAS and ILAR's transdisciplinary contributions to One Health, Planetary Health, and related emerging research domains. The importance of continuing NAS and ILAR's promotion of transdisciplinary knowledge exchange is heightened given the environmental challenges to human and animal health anticipated in the coming decades.

CENTRALITY OF LAB ANIMAL RESEARCH

The intensification of climate change and ecological degradation have heightened awareness of how environments impact the health of humans and other animals.[14–19] Shared vulnerability to environmentally-induced disease is an evolutionary legacy of conserved biology.[18] Biological insights emerging from laboratory animal research have provided insights ranging from the identification of pathological pathways induced by carcinogens and toxicants across vertebrates to the development of predictive modeling of the spread of zoonoses.[20–27] This body of scientific knowledge is relevant to many emerging research domains. ILAR publications have featured insights from lab animal research as the connective tissue linking new life science disciplines.

Linking Pathogens and Environmental Contaminants to Human Health

Environmental hazards are rapidly emerging as a leading threat to human health. Animals living in and around human

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communities share vulnerability to the same pathologies impacting our species. As such, these animals can serve as sentinels that alert experts to human health hazards.[18] Sentinels are likely to play a more central role in protecting human health in the decades to come given the anticipated health effects of climate change and air-, water-, and land-based contamination. Now more than ever, it is important to note that alerting human communities to environmental hazards depends on the ability of relevant state and federal wildlife agencies to communicate quickly and effectively with one another. NAS and ILAR activities have consistently featured the value of sentinels for detecting pathogenic threats to human health.

Aguirre et al, Eisen et al, McNamara, and many other authors have provided critical insights into the molecular mechanisms underlying transmission, pathogenesis, and the immunological responses to many zoonoses.[14,15,23,28–30] For instance, ILAR publications have featured studies of SARS-CoV-2 in African Green monkeys and ferrets and have used the woodchuck as an animal model for hepatitis B infection in humans, revealing a broader understanding of immune responses, potential therapeutics, and vaccine approaches.[28,31–33]

Tracey McNamara from the ILAR Journal reflects on the West Nile Virus as "an excellent example of how animal studies contribute to human health."[23] In the summer of 1999, Dr. McNamara became concerned about the large number of crows dying at the Bronx zoo. Steele et al's examinations of these birds showed varying degrees of meningoencephalitis and severe myocarditis.[34] Although there were delays, ultimately it was the work of the National Veterinary Services Laboratories, US Department of Agriculture, that examined genomic sequences from infected birds, which were then compared with those of infected humans. Public health officials were then able to warn the public about the first appearance of West Nile Virus in the western heliosphere.[23]

As climate change and other forms of ecological degradation have intensified, environmental factors have been increasingly linked to adverse health effects in humans and animals. One example is air pollution–a leading environmental health threat responsible for 7 million deaths annually.[35,36] The adverse health effects of air pollution in humans and animals has been featured in a plethora of studies within the ILAR Journal. For example, in 2017, Miller et al featured the effects of microbes and pollutants on lung disease pathogenesis but also as a key catalyst in the development of pulmonary vaccines.[33] In Rabinowitz et al in ILAR Journal, researchers fostered recognition that pulmonary disease in domestic cats may be secondary to ozone or asthmagen and that these animals living in our homes may be sentinels of human respiratory health; however, more transdisciplinary research is required.[18,33]

According to Doll and Peto, environmental exposures including chemical carcinogens account for up to 80% of all human cancers.[37] ILAR publications have been key to understanding the impact on climate change conditions and carcinogen exposures. Walter et al in ILAR Journal has featured decades of (over 70 years of laboratory) research on *Xiphophorus* (swordtails) and *Xenopus* (clawed frogs), which have revealed basic biologic mechanisms underlying environmental links to skin cancer, including dangerous levels of UV exposure, potential DNA repair mechanisms, and viral etiologies of melanoma.[38] Law et al's study on carcinogenicity testing provided mechanistic evidence for how zebrafish and the Japanese medaka react to varying levels of carcinogenic exposure.[22] ILAR Journal publications such as Sweet et al have helped identify UV-induced melanomas in wild fish populations that are now serving as sentinels for hazardous environments increasing human skin cancer risk.[39] Insights such as these are proving critical to human health as ozone depletion and increased UV radiation are increasing human skin cancer risk.[40]

Altieri et al in PNAS has pointed to the 400 coastal ocean dead zones as a sobering indicator of the threat contamination poses to life itself.[41] ILAR Journal has published many other studies linking aquatic contaminants to health issues such as cancer, in both animal and human populations.[20,22,23,39] Notably, beyond ILAR, the National Academies have sponsored workshops and other activities featuring the alarming environmental changes now recognized as posing leading threats to human health. For instance, the 2020 Annual NAS Ocean Plastic presentation featured the devastating effects of over 15 trillion pieces of microplastic and 180 million tons of toxic waste throughout the marine trophic cascade.[42,43]

Land-based contaminants are also increasingly linked to human deaths; three-quarters of global agricultural land may soon become unproductive due to toxic pesticide pollution in soil, surface water, and/or groundwater.[44] Again, numerous ILAR Journal publications have provided critical evidence linking at least 1000 toxicants, including pesticides, organic solvents, and metals to human neurotoxicity.[19] In Winn et al from ILAR Journal, the authors demonstrate the importance of transgenic fish as models in environmental toxicology from groundwater, streams, and rivers close to human communities.[45]

Knowledge of this kind empowers scientists and policymakers, giving them evidence to advocate and effect necessary change to protect the health of human and animal life.

ONE HEALTH, PLANETARY HEALTH, AND NEW ANIMAL RESEARCH DOMAINS

ILAR has played a significant role in fostering the growth and strength of these important transdisciplinary initiatives.[46] In the past 18 years, ILAR Journal and NASEM workshops have focused on a range of One Health related concerns.[46–49] For example, Fenger et al explored how dog models can be used for translational approaches to osteosarcoma in humans.[50]

Planetary Health focuses on the connection between the Earth's natural systems and the health of humans and other forms of life on Earth. National Academies programs and the ILAR Journal have advanced the integration of environmental and human domains through new findings on the critical impacts of climate change, environmental degradation, ocean acidification, ozone depletion, and more on both human and animal health.[14,51–53]

While recognizing the interdependence of human, animal, environmental, and planetary health is critically important, it is only half of the battle. Understanding the precise biological nature of these threats is the life-saving other half. Laboratory animal research provides this knowledge. To maximally leverage research across these new domains, scientific communities would be wise to follow in ILAR's tradition of transdisciplinary knowledge exchange and the promotion of critical insights from the animal laboratory and beyond.

FACING 21ST-CENTURY CHALLENGES

"In nature," observed pioneering environmentalist Rachel Carson, "nothing exists alone."[54] What Carson observed to be true of the natural world is equally true of the disciplines that study its complexity and seek to protect it. The era of siloed fields of life science research is now fading from view. Emerging in its place is a new ecosystem of transdisciplinary and collaborative animal studies research. The promise of this emerging research landscape is great. As humans, animals, and our planet face an uncertain and challenging future, so too is the need for this broadened research landscape. Decades of ILAR and ILAR Journal successes in promoting transdisciplinary knowledge exchange and fostering interdisciplinary research collaborations stand as a powerful guide for future efforts continuing this important work.

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