PERSPECTIVE

Cataracts Across the Tree of Life: A Roadmap for Prevention and Biomedical Innovation

B. NATTERSON-HOROWITZ, BRET A. MOORE, AMELIA REYNOLDS, LUISA ESPERICUETA, JENNIFER M. HEAD, DANG LAM, RYAN TURNER, DANA M. WILLIAMS, AND DANIEL T. BLUMSTEIN

• PURPOSE: Spontaneous cataracts have been identified in the lenses of animals across a phylogenetically wide range of species. This can be a source of insights and innovation for human health professionals, but many persons may lack awareness of it. By providing a phylogenetic survey and analysis of species with cataract vulnerability, this paper demonstrates how a broad comparative perspective can provide critical information about environmental hazards to human visual health and can spark potential innovations in the prevention and treatment of cataracts in humans.

• DESIGN: Perspectives.

• METHODS: Review and synthesis of selected literature with interpretation and perspective.

• RESULTS: We found 273 recorded cases of spontaneously occurring cataracts in 113 species of birds, 83 species of mammals, 30 species of actinopterygii fish, 10 species of amphibians, 6 species of reptiles, and 1 species of cephalopod.

• CONCLUSION: A phylogenetically wide range of species, including many living in and around human environments, are vulnerable to cataracts. These animals may serve as sentinels for human visual health. Variation in cataract vulnerability across species may also facilitate the identification of resistance-conferring physiologies, leading to accelerated innovation in the prevention and treatment of cataracts in humans. (Am J Ophthalmol 2023;249: 167–173. © 2023 Elsevier Inc. All rights reserved.)

AJO.com Supplemental Material available at AJO.com.
Accepted for publication January 9, 2023.

From the Division of Cardiology (B.N.-H., A.R.), David Geffen School of Medicine at UCLA, Los Angeles, California, USA; Department of Human Evolutionary Biology (B.N.-H.), Harvard University, Boston, Massachusetts, USA; Department of Small Animal Clinical Sciences (B.A.M.), College of Veterinary Medicine, University of Florida, Gainesville, Florida, USA; Department of Ecology and Evolutionary Biology (L.E., D.L., D.M.W., D.T.B.), UCLA, Los Angeles, California, USA; Synergy Scientifics (J.M.H.), Port Orford, Oregon, USA; Department of Organismic and Evolutionary Biology (R.T.), Harvard University, Cambridge, Massachusetts, USA

Inquiries to B. Natterson-Horowitz, Harvard University, Cambridge, Massachusetts, USA; e-mail: natterson-horowitz@fas.harvard.edu

Modern lifestyles, environments, and lengthened lifespans have been implicated in rising rates of human cataracts. However, the pathology itself is not uniquely human. Ocular cataracts have been identified in a phylogenetically wide range of animals, from chordates[1] to cephalopod[2] species. (Figure 1) Since the ancient lens evolved 550 million years ago, evolutionary processes have shaped multitudes of varied lens phenotypes. Among living species, these phenotypic variations provide a window into the evolutionary history that shaped the modern human lens. Beyond this, the varied lens phenotypes observed across the metazoan lineage can be a source of critical information supporting cataract prevention efforts and a guide for innovation in human visual health.

Biomedical research has traditionally focused on a handful of model organisms, including rats, mice, chickens, dogs, and primates,[3] to gain insight into the development of cataracts in humans. However, the phylogenetically widespread occurrence of cataract vulnerability may provide additional insights for human visual health. Physicians may lack awareness of the wide range of species in which cataracts have been identified, perhaps because acquired cataracts are so closely linked to human lifespans and man-made environments.[4] This is unfortunate because expanded awareness of cataract vulnerability across species can lead to the following: (1) earlier identification of environmental hazards threatening human visual health, (2) strengthened cataract prevention efforts centered around environmental threats, and (3) accelerated biomedical innovation for the prevention and treatment of cataracts by studying the biology underlying relative cataract resistance in some species.

Because cataracts can develop in a wide range of animals living in and around human communities, these species can serve as sentinels for human visual health. Like modern-day canaries in the coalmine, some urban squirrels, raccoons, dogs, cats, and birds develop cataracts, an occurrence that could indicate environmental hazards to human visual health. Although vulnerability to cataracts may be widespread across species, not all animals are equally vulnerable. In fact, the degree to which a specific animal taxon may be at risk varies. For many pathologies, small animals are effective sentinels because they develop dis-

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2023.01.007

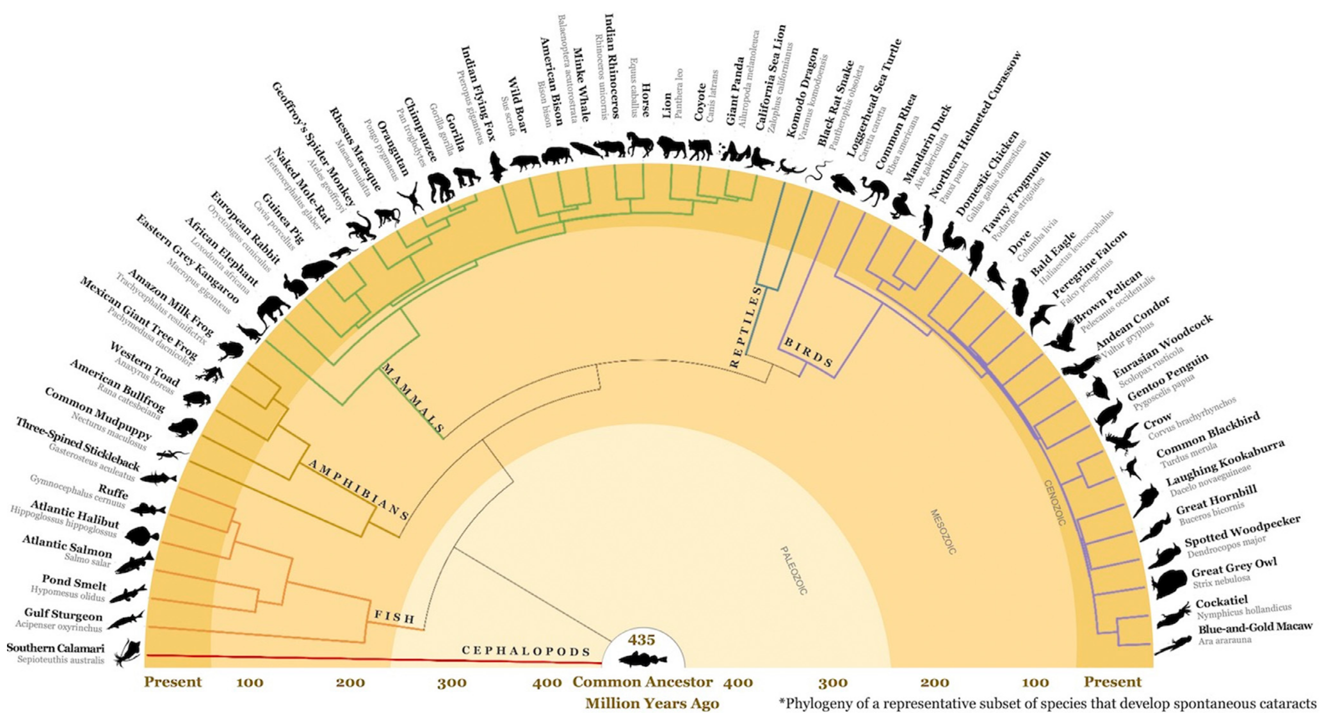

FIGURE 1. Cataracts develop across a phylogenetically wide range of species. Species included in this image were selected from the larger taxonomy of identified species to demonstrate the widespread nature of this vulnerability (the full species list can be found in the Supplemental Material).

ease following a lower level of toxic exposure and often present far earlier than humans.[5-11] Whether this is the case with cataracts is not known. However, an animal's age affects its vulnerability to cataracts, and some evidence suggests that shorter-lived species might be more effective sentinels.[12]

Like all traits, vulnerability to pathology emerges as a consequence of unique selective pressures faced by a taxon over its evolutionary history. Recognition that vulnerability varies across species raises the exciting possibility that species can be identified in which resistance to cataracts is much higher than what is observed in humans. The physiology underlying resistance in these species could serve as a blueprint for innovations in cataract prevention and treatment. Despite this potential, there has been no systematic review to identify the phylogenetic range of cataract vulnerability.

METHODS: SYSTEMATIC REVIEW OF CATARACTS

We conducted a literature search (May 18-25, 2020) for studies of spontaneous cataracts across taxa in PubMed and in Web of Science (Institute for Scientific Information [ISI]). Although search parameters were set to "all databases", the majority of records were retrieved from the Web of Science Core Collection, BIOSIS Citation Index, BIOSIS Previews, and Zoological Record. We used the search terms "mammal*", "bird*", "fish*", "reptile*", "amphibian*", "arthropod*", "animal*", "animalia*", "vertebrate*", and "cataract*". Our final search string successfully resulted in 9914 studies from PubMed and 57,458 studies from Web of Science. Using CADIMA (https://www.cadima.info/), the titles and abstracts of the retrieved studies were first screened for duplicates, followed by screening based on an inclusion criteria. The criteria were as follows: (1) the study addressed spontaneously occurring cataracts, (2) the study focus was non-human animals, and (3) the study was in English and accessible through a University of California—Los Angeles (UCLA) subscription.

Additional reported instances of spontaneous cataracts and clinical cases were also available on the Veterinary Information Network (VIN), and cataract presence or absence within a species was extracted. From PubMed, Google Scholar, and private sources (such as the UC Davis Library), an additional 222 papers were extracted, the full texts of which were filtered through the following inclusion criteria: (1) the paper addressed cataracts in nonhuman animals, (2) the paper described spontaneously occurring cataracts (ie, not experimentally induced, congenitally occurring, or directly secondary to a specific medical condition), and (3) the paper was published in English and accessible either through a UCLA subscription. Of these studies, 72 were included. Of 55,022 studies identified, 338 were ultimately included. A number of limitations were encountered while performing the systematic review (see Limitations section).

In total, there were 190 unique species or subspecies identified in records of spontaneous cataract occurrence. The taxa of the affected species, their common name, and Latin binomial were extracted from each final study.

To illustrate the phylogenetic range of affected species, we created a phylogeny using the Interactive Tree of Life (iTOL, https://itol.embl.de/). From the 190 species, we selected 56 to exhibit the broad family-level diversity of recorded cataract occurrence (the full list of 190 species and subspecies from which the 56 were selected can be found in the Supplemental Material). This phylogeny does not represent a comprehensive list of species; rather, it illustrates the phylogenetic range of cataract vulnerability.

DISCUSSION

• **SENTINELS OF ENVIRONMENTAL HAZARDS TO ENVIRONMENTAL HEALTH:** Humans have long recognized that the health of animals living with and around them can be a source of critical information about the safety of their environments. The natural history of many human pathologies is accelerated when these disorders and diseases occur in other species, especially those with smaller body sizes and shortened lifespans.

Recognizing the emergence of "human" pathology in species living in and around human communities can provide early warning of environmental threats. These animal sentinels can serve an increasingly important role in identifying threats to human health, especially as anthropogenic environmental changes blur boundaries that once demarcated human and animal environments. For example, between 1983 and 1999, unexpectedly high rates of mammary, ovarian, and other adenocarcinomas were found in necropsies of wild beluga whales.[7] This led to the identification of commercial facilities contaminating the waterways, putting humans at risk as well. In 1952, in Minamata, Japan, the emergence of bizarre choreiform movement disorders in cats led to the identification of dangerous levels of methylmercury in local fish. This helped clarify the cause of neuropsychiatric disease in some humans known as "Minamata Disease" and helped prevent further individuals from being affected.[9] Because domestic animals live in close association with humans and are thus similarly exposed, dogs and cats may provide early warning of disease-inducing environmental threats, especially because similar levels of exposure are likely to first affect animals smaller than humans. For example, in 2007, cats and dogs that experienced kidney failure due to melamine in food/infant formula proved to be sentinels for kidney failure in children.[13] Ongoing studies are showing that cats may be secondary to ozone or asthmagens, and nonhuman animals living in our home may be sentinels of human respiratory health.[9] Despite the potential for animals to serve as sentinels of environmental dangers, this approach has not, to the authors' knowledge, been applied to human visual health.

• **SENTINELS OF ENVIRONMENTAL HAZARDS TO VISUAL HEALTH:** Growing evidence suggests that environmental factors may promote or accelerate the formation of cataracts. As such, the surveillance of the lens health of other species living in similar environments may provide early information about hazards to human visual health. Knowledge of the occurrence of cataracts across the tree of life exposes an opportunity for detecting hazardous environmental factors that might otherwise not be detected or might be identified after they have adversely affected human visual health. For example, ultraviolet (UV) light promotes cataractogenesis in humans, especially for people living in regions with higher levels of UV-B radiation.[14] Notably, other species, including mice,[15] frogs (*Hyla regilla* and *Rana aurora*),[16] and rabbits,[17] develop cataracts when experimentally exposed to UV radiation. Animals living in regions with higher levels of UV-B could serve as sentinels for human vulnerability to cataracts. High ambient temperature has also been linked to cataracts, particularly in tropical regions.[18] The occurrence of natural heat-induced cataracts in species such as Atlantic salmon (*Salmo salar*)[19] and the sensitivity of the lens to experimentally induced high temperature in rabbits[20] suggest that these and other species could serve as sentinels for the ocular effects of high temperatures. Although variation exists in the thermal stability of the lens across species,[21] when vulnerable animals are exposed to environmental hazards, they often develop pathology long before it emerges in humans. As such, these animal models can serve as sentinels of cataract-promoting environmental effects.[22,23]

• **EVOLVED ADAPTATIONS:** An additional benefit of a broadly comparative approach to cataract formation is that animals with a level of resistance may be identified. Such species could provide a blueprint for innovative prevention strategies for cataractogenesis in humans. Over the past decade, the identification of animals with reduced vulnerability to some cancers, cardiovascular diseases, infectious diseases, reproductive aging, and even senescence itself is providing new approaches to a number of high-impact human diseases. In the field of oncology, for example, a number of animals with cancer resistance, as well as the mechanisms underlying this resistance, have been identified.[24] An African elephant (*Loxodonta Africana*), for example, has more than 20 copies of *TP53*, the crucial tumor suppressor gene seen mutated in most human cancers. In Abegglen et al's genomic analysis, elephant lymphocytes demonstrated significantly higher P-53—mediated apoptotic responses after DNA damage in comparison to humans, indicating potentially higher cancer resistance.[25]

In other species, cancer resistance arising from different mechanisms has been identified in whales, gray squirrels, cows, and horses. For example, cell contact inhibition, as well as the uniquely long half-life of *TP53* and high rates of nuclear localization in response to DNA damage, appear to confer a degree of cancer resistance in the naked mole rat.[25-27] In bats, mitochondria have evolved to counteract oxidative stress, an effect underlying both pathogen control and tumor resistance.[24] Numerous groups are studying methods for leveraging this biology of cancer resistance in other species to human health. Finally, in dogs, significant breed-based differences in vulnerability to cancers, including osteosarcoma, melanoma, and glioblastoma,[28] have led to advances in human medicine, including limb-sparing therapies[29] and vaccine development.[30]

Recently, the modern giraffe (*Giraffa camelopardalis*), a species with the highest blood pressure, has been proposed as a natural animal model of resistance to adverse effects of hypertension.[31,32] Editing some uniquely mutated giraffe genes into mice appears to confer resistance to angiotensin II and elevated blood pressure, a finding with potential relevance to human heart failure and other pathologies.[31,32] Species have also been identified with both high and very low levels of vulnerability to COVID-19, and this knowledge is providing novel approaches for strengthening human immune responses.[33] Some bat species, for example, have evolved a dampened inflammatory response that protects them from many of the virus's adverse effects.[34]

The relative resistance of some species to both reproductive senescence and aging itself is a growing area of interest. Numerous species with significantly greater longevity than our own have been identified as having the mechanisms that appear to confer this apparent relative resistance to aging. This has sparked much investigation into telomere repair, resistance to oxidative stress, and other mechanisms that could be used to potentially expand longevity in humans.[35]

To date, this approach has not been applied to all aging-related diseases such as cataracts, pulmonary diseases, dementia, etc. More in-depth research on these age-related signaling pathways in "non-model" organisms can be grounded-breaking models for a vast number of age-related diseases.

One species that some researchers have suggested carries a level of resistance to cataractogenesis is the bowhead whale (*Balaena mysticetus*). Bowhead whales live more than 200 years.[36] Given the association between aging and cataracts in humans, it is reasonable to consider whether a long-lived species such as the bowhead whale has evolved adaptations conferring protection from vision-compromising (and therefore fitness-compromising) pathologies. A similar logic directs focus toward species in environments with a high UV and other cataractogenic exposure burden. Such species might have faced especially significant selective pressure to evolve resistance to cataract formation. Whether the bowhead whale (or other species) is actually relatively resistant will require more investigation.

If, in fact, the bowhead whale does have a level of cataract resistance, characterizing the physiologic mechanisms could provide novel pathways for investigation.[37] Looking broadly across taxa could expose species with enhanced vulnerability. For example, the subterranean naked mole rat (*Heterocephalus glaber*) possesses a degenerate visual system and develops cataracts at a young age, even in the absence of UV. This early degeneration makes it a possible natural animal model of enhanced vulnerability.[37,38]

Intraspecies differences in vulnerability to cataracts also offer insights. In dogs age is a significant predictor of risk. Small breeds appear to be at elevated risk as are Retrievers, Standard Schnauzers, Standard Poodles. What factors drive this breed-specific vulnerability is still an active area of research.[39] In cats, age is also a predictor, although feline lens opacities have been reported to develop later in life (at approximately 17 years of age) as compared to approximately 13.5 years of age in dogs.[40] Lifespan may also be a factor driving differences in cataract development among cat breeds. Siamese cats, which tend to live into their late teens, develop cataracts slightly later in life than Domestic Short-hair cats, which have a similar lifespan but are cross-breeds, and Persian cats, which typically live only 10 to 12 years.[40] Horses also possess breed-specific variation in vulnerability to cataract formation, although this has been less studied. Older Appaloosas were found to be more vulnerable to cataracts than other breeds.[41] Morgan horse and Rocky Mountain horse breeds are known to have congenital cataracts, and several other breeds, including Arabian, Belgian, Quarter horse, and Thoroughbred are considered to be predisposed to them.[42]

• **LIMITATIONS:** This paper serves as an invitation to human health professionals to consider the visual health of extant animals as a source of relevant information for human health. Although surveillance of animal populations for infectious diseases has been strengthened in recent years, the systematic surveillance of animal populations for non-communicable diseases, including visual pathology, is limited. Systematic coordinated efforts to obtain, review, and publish the results of wild animal necropsies—including information relevant to visual health— are in their early stages. Cataracts may be identified on examinations in domestic, agricultural, laboratory, and zoological species with significant human contact. However, recent estimates put the number of vertebrate species at 74,140 and the number of vertebrate animal individuals exceeding 1018.[43–45] This means that the vast majority live outside human scientific scrutiny, as it has been estimated that approximately 86% of estimated terrestrial animal species and 91% of marine species on Earth have yet to be identified.[46] Therefore the absence of evidence of cataracts in most species is not evidence of the absence of vulnerability to cataracts, a reality and limitation of the current methodology to comprehensively identify species with vulnerability and resistance to cataracts. For similar reasons, it is currently not possible to arrive at an estimate for the incidence or prevalence of cataracts in many species.

An additional limitation of this approach emerges from some of the issues noted above and the search strategy itself. The focus of this paper is to identify species with "spontaneous cataracts" that is, cataracts emerging during the life course—as opposed to congenital cataracts or those induced in laboratory settings. However, inconsistencies in the methods of diagnosis and terminology used to identify and to describe cataracts regularly appear in the peer-reviewed literature. In many cases, cataracts were identified through gross inspection without histologic confirmation. In addition, in some papers, especially those describing cataracts in very young animals, differentiation between spontaneous or congenital lesions could not be confirmed with certainty.

Identifying animals with relative resistance to cataract formation is only an initial step in discovering the adaptations of resistance with potential translational benefits for humans. The next critical steps will require rigorous, controlled experimentation to both confirm or refute the presence of resistance or vulnerability to cataracts, and to characterize the underlying biological mechanisms. Although species with relative resistance might never be found without some species-spanning surveillance, uncovering the biological mechanisms underlying these characteristics is beyond the scope of the proposed approach.

CONCLUSION

As accelerated environmental change increasingly exposes humans and animals to the same cataractogenic factors, the visual health of other species has taken on new salience for human health. Animal sentinels can act as canaries in a global coal mine for lens health. The phylogeny constructed here reveals the ancient origins of this vulnerability, and represents an invitation to consider how speciation and biodiversity have influenced the vulnerability to pathology in our species. Identifying and decoding biological pathways of resistance that have evolved over hundreds of millions of years may also provide novel approaches to addressing these pathologies.

Ophthalmology is positioned to join oncology, neurology, psychiatry, and other fields that use expanded comparative and phylogenetically informed approaches to gain insights into human health.[47-50] For this to happen, however, human health professionals must gain awareness of the phylogenetically widespread vulnerability to cataracts and the variation of this vulnerability across the tree of life. Moving the field of ophthalmology beyond anthropocentric traditions to more species-spanning and evolutionarily informed perspectives can strengthen our understanding of cataract vulnerability, and can guide efforts to innovate more effective therapeutic and preventive approaches.

Funding/Support: The authors did not receive grant funding to support this work.
Financial Disclosures: The authors report no financial disclosures or conflicts of interest. All authors attest that they meet the current ICMJE criteria for authorship.
Acknowledgments: The authors would like to thank Yaochi Li for her help with constructing the figure. The authors also would like to thank several anonymous reviewers, editors, and Ralph Levinson for their helpful comments on previous versions of the manuscript.

REFERENCES

1. Sivak JG, West JA, Campbell MC. Growth and optical development of the ocular lens of the squid (*Sepioteuthis lessoniana*). *Vis Res*. 1994;34(17):2177–2187. doi:10.1016/0042-6989(94)90100-7.
2. Cerreta AJ, Jr McMullen, Scott RJ, et al. Bilateral phacoemulsification in an African elephant (*Loxodonta africana*). *Case Rep Vet Med*. 2019:1–9. doi:10.1155/2019/2506263.
3. West-Mays J, Bowman S. Animal models of cataracts. *Anim Models Ophthalmic Dis*. 2015:11–29. doi:10.1007/978-3-319-19434-9_2.
4. Liu Y-C, Wilkins M, Kim T, Malyugin B, Cataracts Mehta JS. *Lancet*. 2017;390(10094):600–612. doi:10.1016/s0140-6736(17)30544-5.
5. Rabinowitz PMG, Pappaioanou M, Bardosh KL, Conti L. A planetary vision for One Health. *BMJ Global Health*. 2018;3(5). doi:10.1136/bmjgh-2018-001137.
6. Harada M. Minamata disease: methylmercury poisoning in Japan caused by environmental pollution. *Crit Rev Toxicol*. 1995;25(1):1–24. doi:10.3109/10408449509089885.
7. Martineau D, Lemberger K, Dallaire A, et al. Cancer in wildlife, a case study: beluga from the St. Lawrence estuary, Québec, Canada. *Environ Health Persp*. 2002;110(3):285–292. doi:10.1289/ehp.02110285.
8. Reif J, Schaefer A, Bossart G. Atlantic bottlenose dolphins (*Tursiops truncatus*) as a sentinel for exposure to mercury in humans: closing the loop. *Veterinary Sci.*. 2015;2(4):407–422. doi:10.3390/vetsci2040407.
9. Rabinowitz PM, Scotch ML, Conti LA. Animals as sentinels: using comparative medicine to move beyond the laboratory. *ILAR J*. 2010;51(3):262–267. doi:10.1093/ilar.51.3.262.

10. Miller LA, Royer CM, Pinkerton KE, Schelegle ES. Nonhuman primate models of respiratory disease: past, present, and future. *ILAR J*. 2017;58(2):269–280. doi:10.1093/ilar/ilx030.
11. Fenger JM, London CA, Kisseberth WC. Canine osteosarcoma: a naturally occurring disease to inform pediatric oncology. *ILAR J*. 2014;55(1):69–85. doi:10.1093/ilar/ilu009.
12. Warmack RA, Mansilla E, Goya RG, Clarke SG. Racemized and isomerized proteins in aging rat teeth and eye lens. *Rejuvenat Res*. 2016;19(4):309–317. doi:10.1089/rej.2015.1778.
13. Lewin-Smith MR, Kalasinsky VF, Mullick FG, Thompson ME. Melamine-containing crystals in the urinary tracts of domestic animals: sentinel event? *Arch Pathol Lab Med*. 2009;133(3):341–342. doi:10.5858/133.3.341.
14. Löfgren S. Solar ultraviolet radiation cataract. *Exp Eye Res*. 2017;156:112–116. doi:10.1016/j.exer.2016.05.026.
15. Jose JG. Posterior cataract induction by UV-B radiation in albino mice. *Exp Eye Res*. 1986;42(1):11–20. doi:10.1016/0014-4835(86)90013-8.
16. Novales Flamarique I, Ovaska K, Davis TM. UV-B induced damage to the skin and ocular system of amphibians. *Biol Bull*. 2000;199(2):187–188. doi:10.2307/1542889.
17. Pitts DG, Cullen AP, Hacker P. Ocular effects of near ultraviolet radiation. *Optom Vision Sci*. 1977;54(8):542–559. doi:10.1097/00006324-197708000-00010.
18. Sasaki H, Jonasson F, Shui YB, et al. High prevalence of nuclear cataract in the population of tropical and subtropical areas. *Prog Lens Cataract Res*. 2002:60–69. doi:10.1159/000060806.
19. Bjerkas E, Bjornestad E, Breck O, Waagbo R. Water temperature regimes affect cataract development in smolting Atlantic salmon, *Salmo salar L*. *J Fish Dis*. 2001;24(5):281–291. doi:10.1046/j.1365-2761.2001.00299.x.
20. Al-Ghadyan AA, Cotlier E. Rise in lens temperature on exposure to sunlight or high ambient temperature. *Br J Ophthalmol*. 1986;70(6):421–426. doi:10.1136/bjo.70.6.421.
21. McFall-Ngai MJ, Horwitz J. A comparative study of the thermal stability of the vertebrate eye lens: Antarctic ice fish to the desert Iguana. *Exp Eye Res*. 1990;50(6):703–709. doi:10.1016/0014-4835(90)90117-d.
22. Rabinowitz PMG, Odofin L, Dein FJ. From “us vs. them” to “shared risk”: can animals help link environmental factors to human health? *EcoHealth*. 2008;5(2):224–229. doi:10.1007/s10393-008-0170-4.
23. Neo JP, Tan BH. The use of animals as a surveillance tool for monitoring environmental health hazards, human health hazards and bioterrorism. *Vet Microbiol*. 2017;203:40–48. doi:10.1016/j.vetmic.2017.02.007.
24. Seluanov A, Gladyshev VN, Vijg J, Gorbunova V. Mechanisms of cancer resistance in long-lived mammals. *Nat Rev Cancer*. 2018;18(7):433–441. doi:10.1038/s41568-018-0004-9.
25. Abegglen LM, Caulin AF, Chan A, et al. Potential mechanisms for cancer resistance in elephants and comparative cellular response to DNA damage in humans. *JAMA*. 2015;314(17):1850. doi:10.1001/jama.2015.13134.
26. Deuker MM, Lewis KN, Ingaramo M, Kimmel J, Buffenstein R, Settleman J. Unprovoked stabilization and nuclear accumulation of the naked mole-rat p53 protein. *Sci Rep*. 2020;10(1). doi:10.1038/s41598-020-64009-0.
27. Sedivy JM. How to learn new and interesting things from model systems based on “exotic” biological species. *Proc Natl Acad Sci*. 2009;106(46):19207–19208. doi:10.1073/pnas.0911232106.
28. LeBlanc AK, Mazcko CN. Improving human cancer therapy through the evaluation of pet dogs. *Nat Rev Cancer*. 2020;20(12):727–742. doi:10.1038/s41568-020-0297-3.
29. Withrow SJ, Wilkins RM. Cross talk from pets to people: translational osteosarcoma treatments. *ILAR J*. 2010;51(3):208–213. doi:10.1093/ilar.51.3.208.
30. Schiffman JD, Breen M. Comparative oncology: what dogs and other species can teach us about humans with cancer. *Phil Trans R Soc B Biol Sci*. 2015;370(1673):20140231. doi:10.1098/rstb.2014.0231.
31. Liu C, Gao J, Cui X, et al. A towering genome: experimentally validated adaptations to high blood pressure and extreme stature in the giraffe. *Sci Adv*. 2021;7(12). doi:10.1126/sciadv.abe9459.
32. Natterson-Horowitz B, Baccouche BM, Head JM, et al. Did giraffe cardiovascular evolution solve the problem of heart failure with preserved ejection fraction? *Evol Med Public Health*. 2021;9(1):248–255. doi:10.1093/emph/eoab016.
33. Damas J, Hughes GM, Keough KC, et al. Broad host range of SARS-COV-2 predicted by comparative and structural analysis of ACE2 in vertebrates. *Proc Natl Acad Sci*. 2020;117(36):22311–22322. doi:10.1073/pnas.2010146117.
34. Christie MJ, Irving AT, Forster SC, et al. Of bats and men: immunomodulatory treatment options for COVID-19 guided by the immunopathology of SARS-COV-2 infection. *Sci Immunol*. 2021;6(63). doi:10.1126/sciimmunol.abd0205.
35. Holtze S, Gorshkova E, Braude S, et al. Alternative animal models of aging research. *Front Mol Biosci*. 2021(8). doi:10.3389/fmolb.2021.660959.
36. Borchman D, Stimmelmayr R, George JC. Whales, lifespan, phospholipids, and cataracts. *J Lipid Res*. 2017;58(12):2289–2298. doi:10.1194/jlr.m079368.
37. Schulze-Makuch D. The naked mole-rat: an unusual organism with an unexpected latent potential for increased intelligence? *Life*. 2019;9(3):76. doi:10.3390/life9030076.
38. Edrey YH, Hanes M, Pinto M, Mele J, Buffenstein R. Successful aging and sustained good health in the naked mole rat: a long-lived mammalian model for biogerontology and biomedical research. *ILAR J*. 2011;52(1):41–53. doi:10.1093/ilar.52.1.41.
39. Gelatt KN, MacKay EO. Prevalence of primary breed-related cataracts in the dog in North America. *Vet Ophthalmol*. 2005;8(2):101–111. doi:10.1111/j.1463-5224.2005.00352.x.
40. Williams DL, Fred Heath M. Prevalence of feline cataract: results of a cross-sectional study of 2000 normal animals, 50 cats with diabetes and one hundred cats following dehydrational crises. *Vet Ophthalmol*. 2006;9(5):341–349. doi:10.1111/j.1463-5224.2006.00497.x.
41. Malalana F, McGowan TW, Ireland JL, et al. Prevalence of owner-reported ocular problems and veterinary ocular findings in a population of horses aged ≥15 years. *Equine Vet J*. 2018;51(2):212–217. doi:10.1111/evj.13005.
42. Fife TM, Gemensky-Metzler AJ, Wilkie DA, Colitz CM, Bras ID, Klages DC. Clinical features and outcomes of phacoemulsification in 39 horses: a retrospective study (1993-2003). *Vet Ophthalmol*. 2006;9(5):361–368. doi:10.1111/j.1463-5224.2006.00494.x.

43. *IUCN*. IUCN red list of threatened species. 2022. Accessed Nov 4, 2022. https://www.iucn.org/resources/conservation-tool/iucn-red-list-threatened-species
44. Bar-On Yinon, Phillips Rob, Milo Ron. The biomass distribution on Earth. *Proceedings of the National Academy of Sciences*. 2018;115:201711842. doi:10.1073/pnas.1711842115.
45. Tomasik Brian. How many wild animals are there? *Essays on Reducing Suffering*. 2009-2019. https://reducing-suffering.org/how-many-wild-animals-are-there/.
46. Mora C, Tittensor DP, Adl S, Simpson AG, Worm B. How many species are there on earth and in the ocean? *PLoS Biol*. 2011;9(8). doi:10.1371/journal.pbio.1001127.
47. Tollis M, Schiffman JD, Boddy AM. Evolution of cancer suppression as revealed by mammalian comparative genomics. *Curr Opin Genet Dev*. 2017;42:40–47. doi:10.1016/j.gde.2016.12.004.
48. Parker HG, Meurs KM, Ostrander EA. Finding cardiovascular disease genes in the dog. *J Vet Cardiol*. 2006;8(2):115–127. doi:10.1016/j.jvc.2006.04.002.
49. Briggs JA, Wolvetang EJ, Mattick JS, Rinn JL, Barry G. Mechanisms of long non-coding RNAS in mammalian nervous system development, plasticity, disease, and evolution. *Neuron*. 2015;88(5):861–877. doi:10.1016/j.neuron.2015.09.045.
50. Konopka G, Roberts TF. Animal models of speech and vocal communication deficits associated with psychiatric disorders. *Biol Psychiatry*. 2016;79(1):53–61. doi:10.1016/j.biopsych.2015.07.001.