The 8th American College of Veterinary Pathologists (ACVP) symposium, held at the 2012 Experimental Biology meeting in San Diego, California (http://experimentalbiology.org/content/AboutEP.aspx), was organized by the ACVP Intersociety Experimental Pathology Committee in conjunction with the American Society for Investigative Pathology (ASIP; http://www.asip.org/). The symposium facilitates interactions and cross-disciplinary collaborations between veterinary and physician pathologists, scientists, and basic researchers. The American Society for Nutrition cosponsored this year’s symposium. The symposium topic was evolutionary aspects of animal models. An evolutionary perspective is increasingly being embraced as essential for a comprehensive understanding of disease.12 The symposium highlighted the importance of an evolutionary perspective in the development and use of animal models of human disease. Speakers emphasized how evolution has differentially molded cardiovascular physiology, response to infectious agents, and aging in both man and animals. In addition, the evolutionary trade-offs between phenotypic selection and disease, which has provided many spontaneous animal models of human diseases, were discussed.

Dr Robert Hamlin, The Ohio State University, opened with the challenges for studying cardiovascular disease in a talk entitled: “Animals as models of human cardiovascular disease: the search to overcome outdated evolutionary homeostatic mechanisms.” He addressed the fact that animals used to model human diseases often have very different cardiovascular physiology from humans and how these differences affect the predictive value of safety studies. As an example, cardiovascular drug safety testing was expanded significantly upon discovering that the antihistamine terfenadine is cardiotoxic when not completely metabolized. Its toxic effect is induced by the inhibition of the cytochrome P450 3A4 (CYP 3A4) isoform, a circumstance that caused death in a small percentage of people due to an unexpected interaction with other medications.1,15 CYP 3A4 is inhibited by a variety of commonly prescribed drugs as well as grapefruit.1 In its toxic form, terfenadine induces a prolonged QT interval and thus can trigger a fatal arrhythmia; however, this effect could not be modeled in rats and mice since they do not have the hERG ion channel that caused the human arrhythmia.

Dr Hamlin further emphasized the importance of matching characteristics of the experimental animal with those of the human phenotype. In listing several animals that should not be used to model specific human diseases, he included guinea pigs and dogs as poor subjects for studies of coronary collateralization as their coronary arteries have a much more extensive collateral circulation than is present in human beings. An interesting theme was how many cardiovascular diseases arise or worsen due to outmoded “protective” homeostatic mechanisms. For example, volume depletion was the primary mode of death for prehistoric man; however, in the developed world, the mechanisms that evolved to assist survival in conditions of volume depletion (thirst, decreased urine production, and vasoconstriction) now complicate more modern maladies such as diabetes, congestive heart failure, and pulmonary disease. Such examples emphasize the need for careful consideration of the evolutionary similarities and differences between man and the animals used in research. To summarize, Dr Hamlin questioned how we can expect to model a heterogeneous population with a homogeneous animal model when disease characteristics may be determined by population heterogeneity. He concluded that selecting surrogates to study human pathophysiology should
encompass appreciation of both fundamental phylogenetic relationships and differences in the rate of evolution among anatomical, physiological, and homeostatic phenotypes.

The second talk, presented by Dr Stefan Niewiesk, The Ohio State University, “Of Mice and Men: Evolutionarily, What Are the Best Rodent Models of the Human Immune System for Infectious Disease Research?” highlighted the need for animal models to be both susceptible to the infectious agent under investigation and to have homologous immune responses. He presented perspective on the impact of molding hypotheses in biomedical research to fit recurring use of a single mouse strain, C57BL/6. To demonstrate that this strain is not representative of all mice, he presented information about strain-specific responses. Dr Niewiesk focused his presentation on divergent immunity that results in failure of mouse models to accurately recapitulate human pathophysiology. Evolutionary pressure by infectious agents has resulted in the selection and maintenance of innate immune responses that permit species survival. These responses are not necessarily the same as those in humans. To highlight ongoing selective pressures and their effects on resistance to infectious diseases in animal and human populations, he described population differences in genes that affect resistance to malaria, species-specific mutations allowing IgA-mediated responses to *Staphylococcus aureus*, and the progressive transformation of pathogens from zoonotic to hominoid. Differences in species immune systems reinforce the need for more specific models of the human immune system. Several important nonmurine models of human diseases described included cotton rats (*Sigmodon hispidus*), an immunocompetent model for immune responses to human respiratory pathogens. Similarities between the cotton rat and human immune and respiratory systems include the mutual use of CD150 as measles virus receptor, presence of a receptor for influenza virus and interferon-induced protein induction patterns, distribution of Toll-like receptor 9 and heat shock proteins, production levels of nitric oxide during immune responses, and similar age-induced changes.

The evolutionary focus moved to aging with Dr Steven N. Austad’s (The Barshop Institute for Longevity and Aging Studies, University of Texas Health Science Center, San Antonio, Texas) presentation on the “Evolutionary Aspects of Animal Models of Aging.” He began by defining aging and pointing out that although longevity has independently evolved in several different animals, including humans, the 3 main models used to study human aging—the worm (*Caenorhabditis elegans*), the mouse (*Mus musculus*), and the fruit fly (*Drosophila melanogaster*)—are all very short lived. In addition to raising awareness of phylogeny, the evolutionary perspective emphasizes how laboratory evolution affects the applicability of research to human aging. Laboratory evolution results from the techniques used to rapidly propagate research animals that are well adapted to laboratory conditions. Laboratory fruit flies and mice grow, mature, and reproduce quickly. Studies comparing laboratory strains with their wild-caught counterparts have found significant differences in growth, maturity, litter size, reproductivity, and life expectancy. Additional important consequences of laboratory adaptation in mice include an increase in telomere length and changes in pineal expression of melatonin. Dr Austad underscored that an evolutionary perspective enhances biomedical research by making researchers more attuned to the significant impacts of both the environment in which the studies are performed and the importance of gene interactions on aging phenotypes. He illustrated mouse studies showing that dietary restriction extends life and retards aging; however, genetics significantly influences this effect.

Dr Elizabeth Uhl, The University of Georgia, completed the symposium with “Modeling Disease Phenotypes: How an Evolutionary Perspective Enhances the Questions.” She presented a paradox that evolution has been invoked both as the scientific basis for using animal models of human disease as well as the scientific reason why many animal models do not predict human disease. Scientific support for using animal models includes the remarkable similarities between human and animal genomes, as well as the genetic and phenotypic similarities of many human and animal diseases. Intense breeding selection for specific traits in domestic animals has frequently resulted in disease as an inadvertent consequence. Some of these unexpected diseases, especially in dogs, have provided insight into the genetic basis for human diseases. Paradoxically, concern has been expressed about the inability of animal models to predict human disease outcomes and drug responses. Dr Uhl argued that insufficient attention to incorporating an evolutionary perspective into animal models compounds the predictability. For example, many of the cytochrome P450 enzymes (CYP) evolved to metabolize plant toxins, making diet a factor in which drug-metabolizing enzymes are present. Dietary differences between species and within human populations alter selection pressures on enzymes, resulting in variation in drug responses and adverse reactions. Characterizing variations in CYP genes to predict drug responses is critical to pharmacogenomics. An explosion of molecular and genetic characterization has revealed that many diseases defined by their symptoms and tissue lesions are actually caused by heterogeneous genetic mechanisms. Thus, as animal models based on single genetic/molecular mechanism become increasingly used, they may actually be less predictive for human diseases. Unlike other types of phenotypic variation, evolution has not been considered in either the classification or the definition of disease. Dr Uhl concluded that an evolutionary perspective incorporating animal as well as human diseases would greatly facilitate the context needed for understanding complex pathways and furthermore enhance the usefulness of animal models.

Collectively, these presentations focused attention on the importance of the evolutionary background of both man and the animal models being used to model human diseases. Attendees commented that the evolutionary perspective provided was very informative, particularly as diseases are increasingly being characterized by their gene expression profiles, and such perspective has not previously been highlighted in their research areas.
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The 2013 ACVP symposium, to be held in Boston, Massachusetts, April 20 to 24, will be entitled “Inside-Out: Extracellular Roles for Heat Shock Proteins.” Classically, heat shock proteins are cellular chaperones with fundamentally intracellular roles supporting protein metabolism. They mediate protein folding, trafficking, and assembly, helping cellular homeostasis and protection/recovery from protein denaturing insult. The 2013 symposium will explore advances in our understanding of extracellular heat shock proteins, particularly the 70-kDa isoform (hsp70), and how they regulate inflammatory and immune responses and induce the formation of the protein aggregates characterizing many degenerative disorders. Speakers include Stuart Calderwood, Beth Israel Deaconess Medical Center and the Harvard Medical School; Monika Fleshner, University of Colorado; Michael Oglesbee, The Ohio State University; and Pamela McLean, Mayo Clinic, Florida. The meeting abstract deadline is November 8, 2012.

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