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Opinion

Evolution: The Founding Principle of Animal Models of Human Disease

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In 1999, the Kansas Board of Education eliminated evolution from its statewide science-teaching standards. Although the teaching of evolution was reinstated as a science standard two years later, it remains that approximately 25% of the biology teachers in Kansas believe not in man's evolution, but rather in the Biblical account of creation, which holds that God designed the Earth and all that is in it (1). The controversy over the standing of biological evolution is not peculiar to Kansas, and carries over into several other states in the North and South (2). Indeed, about 35% of American adults think the Bible is literally true, including the creation and age of the Earth (3). Yet, since Darwin published his *Origin of Species* in 1859 (4), the principle of evolution has become one of the cornerstones of biological science. Within the medical sciences, there can be no better example of how evolution underscores man's relationship to other animals than in the area of animal models of human disease. The study of animals in health and disease as a means to better understand the human condition is predicated on the common linkage of living animals. As a scientific principle, biological evolution should provide a sound explanation for the validity of animal modeling. As a sustaining principle, it should also provide insight for new research paradigms. With all this controversy in the public arena, it may be useful to assess the role that evolution has played in animal modeling and how it may influence the future of medical research.

To begin, the principle of biological evolution can be stated as living beings on Earth have been changing and the ones that exist today are descendants from those who were here earlier (5). This definition, as simple as it is, has two important elements that reflect on animal models of human disease. The first is ancestral relatedness of animals. The phylogenetic history of *Homo sapiens* can be told over the course of the past almost four billion years since life first began on Earth. During that geologic time, humans have evolved from single-cell organisms, developing their own genome of an estimated 30,000 to 40,000 genes. Along the way, humans have inherited certain essential genes and the proteins encoded by these genes, which even today, are shared by rather primitive animals. For example, the amino acid sequence for the actin molecule has diverged in humans and other eukaryotes by only 10% in the past billion years (6). Indeed, the frequently cited 98.7% homology of DNA sequences between chimpanzees and humans speaks to this ancestral relatedness (7, 8). The phylogenetic relatedness of humans with other animals holds that a shared genetic background allows for shared vulnerabilities to disease and explains why some animal models of human disease can serve as true homologues (genotypically and phenotypically) to the human condition.

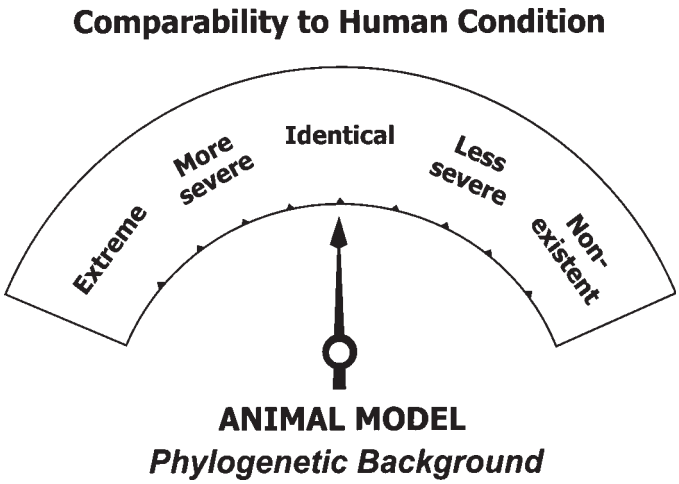

Figure 1. Animal model meter. Comparability of animal models with the human condition can span the spectrum from extreme to nonexistent.

However, the other essential element to biological evolution is that animal species have been and continue to change. Darwin's greatest contribution was not the original concept of evolution, but his explanation for the mechanism of this change. Operatively, natural selective forces act on different populations of animals over long periods and usually with geographic separation. Each resulting species represents an end-product of a unique set of natural selective pressures acting on a random set of genetic mutations, so that by definition, two species are different. The phylogenetic relationship of humans to other animals is not a linear one, as suggested by the *scala naturae* or the Great Chain of Being (9), but rather a small branch of a larger tree composed of hundreds or thousands of cladistic intersections. This genetic diversity among animals must translate into various patterns of disease vulnerability. For this reason, animal models of human disease often, perhaps usually fail to match identically with the human condition (10, 11). If one thinks of an "animal model meter" (Fig. 1) as a way to compare a condition in animals with that in humans, some animal models may register as identical or similar, others as more severe,

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and still others as less severe or even non-existent (the so-called "negative models"). Each model reflecting the full spectrum, from being more severe than the human condition to non-existent, has potential value depending on the scientific question. The bottomline is that, because of the differences between animal species, animal models are usually imperfect.

Recognizing that evolution explains the strengths and the weaknesses of animal models of human disease, can the principle of biological evolution provide further insight into the study of disease? The knowledge gained from animal models concerning specific diseases has been so tremendous that animal model development most certainly will continue. However, as the 21st century ushers in a genomic approach to health and disease, the concept of Darwinian medicine becomes apparent (12-14). As we begin to understand the complexity of organismal genomes, we can begin to ask certain questions not possible before. Instead of focusing on individual diseases and how they affect individuals, the Darwinian medical approach asks questions for a species. The question may no longer be why do certain individuals succumb to a particular disease, but rather, what is it about the species that makes it vulnerable to the disease at all? Appreciating that each animal species has a genomic background that has been molded by different sets of genetic mutations and selective forces, the Darwinian medical approach, while daunting in its scope and complexity, promises an even deeper understanding of disease in humans and animals.

The promise and the practice of animal modeling of human diseases are inextricably linked to the principle of evolution. It is the very principle of Darwinian evolution that validates the use of animals as models of human disease. Evolution is the principle by which animal species that are phylogenetically close to humans as well as distant can succeed or fail in serving as a model. Genetic mutability and natural selection over evolutionary time have yielded a set of extant animal species whose diversity certainly provides the likelihood that most human conditions can be found spontaneously or induced experimentally. However, recognizing the diversity of disease vulnerabilities between animals and the outbred nature of humans, we should not insist on perfection in our animal models. From a Darwinian medical perspective, their "blemishes" are insightful! Yet, although biological evolution clearly serves as the founding principle of animal modeling, scientists must recognize that evolution amazingly still generates much continuing controversy within the general public. Indeed, soon after Darwin published his book on natural selection, an aristocratic Victorian woman was quoted as saying (15): "Let us hope that what Mr. Darwin says is not true; but, if it is true, let us hope that it will not become generally known."

With the beginning of the 21st century, and just the initial glimpse of how understanding of the the human genome may impact medicine, the investigation of animal models of human diseases and their evolutionary perspectives holds a promise of an even greater understanding of the human condition.

References

1. **Washington Post.** 2001. Kansas board revives teaching of evolution. February 15, p. A10.
2. **Doyle, R.** 2002. Down with evolution—creationists are changing state educational standards. Scientific American **March:**30.
3. **Holden, C.** 1999. Breakdown of the year: creationists win in Kansas. Science **286:**2242.
4. **Darwin, C.** 1859. On the origin of species by means of natural selection. Murray, London.
5. **Kent, G. C. and R. K. Carr.** 2001. Comparative anatomy of the vertebrates, 9th ed, p. 22. McGraw-Hill, Boston.
6. **Doolittle, R. F.** 1995. The origins and evolution of eukaryotic proteins. Philosophical Transactions of the Royal Society of London - Series B Biological Sciences **349:**235-240.
7. **King, M.-C. and A. C. Wilson.** 1975. Evolution at two levels in humans and chimpanzees. Science **188:**107-116.
8. **Enard, W., P. Khaitovich, J. Klose, S. Zollner, F. Heissig, P. Giavalisco, K. Nieselt-Struwe, E. Muchmore, A. Varki, R. Ravid, G.M. Doxiadis, R.E. Bontrop, S. Paabo.** 2002. Intra- and interspecific variation in primate gene expression patterns. Science **296:** 340-343.
9. **Mayr, E.** 2001. What evolution is, p. 5-7. Basic Books, New York.
10. **Pollard, T. D.** 2002. The future of biomedical research—from the inventory of genes to understanding physiology and the molecular basis of disease. J.A.M.A. **287:**1725-1727.
11. **Elsea, S. H. and R. E. Lucas.** 2002. The mousetrap: what we can learn when the mouse model does not mimic the human disease. I.L.A.R. **43:**66-79.
12. **Williams, G. C. and R. M. Nesse.** 1991. The dawn of Darwinian medicine. Q. Rev. Biol. **66:**1-22.
13. **Nesse, R. M. and G. C.Williams.** 1999. Research designs that address evolutionary questions about medical disorders, p. 16-23. *In* S. C. Stearns (ed.), Evolution in health and disease. Oxford University Press, Oxford.
14. **Nesse, R. M. and G. C. Williams.** 1996. Why we get sick: the new science of Darwinian medicine. Vintage Books, New York.
15. **Gould, S. J.** 1999. Darwin's more stately mansion. Science **284:**2087.