

PREPRINT VERSION OF

Patients are not rodents writ large

GREEK, R. Patients are not rodents writ large. *Am J Med Sci*. 2011 Oct;342(4):345.

For journal version go to <http://journals.lww.com/amjmedsci/pages/default.aspx>

In this issue, Dario Ringach presents his views of the controversy surrounding the use of animals in biomedical research. His position on the scientific merits of animal use focuses on claims he ascribes to me. I thank the editors of the *American Journal of the Medical Sciences* for allowing me this response.

Essentially every claim Ringach assigns to me is a gross misrepresentation, a straw man argument, red herring, *ad hominem* attack, or other fallacy. Further, much of the philosophy of science he presents is inconsistent with facts and definitions easily obtained from standard texts. Given that countering his claims one-by-one would require more space than is available, I will simply present my actual position howbeit in abbreviated form.

Greek, Shanks, and Greek have stated the following in a number of different ways in a number of different publications.¹⁻⁵ Humans and animals are examples of complex systems that have diverged into different species as a result of the operation of evolutionary mechanisms over long periods of time. Species, and even strains, manifest different responses to the same stimuli due to differences with respect to: 1. genes present; 2. mutations in the same gene (where one species has an ortholog of a gene found in another); 3. proteins, protein activity, and protein-protein interactions; 4. gene regulation and or expression; 5. genetic networks; 6. organismal organization (humans and rats may be intact complex systems, but are differently complex); 7. environmental exposures; and 8. evolutionary histories. These reasons explain the immense empirical evidence revealing that members of one species, strain or breed, or even patients in the same family often respond differently to drugs and experience different diseases.

We have readily acknowledged that society has been the beneficiary of the results of careful scientific studies of animals. There is value in basic research and in using animals in basic research. Studies of animals have prompted important hypotheses about basic biological principles and have contributed greatly to our scientific understanding of life. Such studies will continue to illuminate these matters. Moreover, basic research using animals continues to play a valuable heuristic role by prompting new ways of thinking about human biological problems of interest.

Basic research however, is a separate issue from whether animal models are predictive (demonstrate a high positive predictive value and negative predictive value) of human outcomes vis-à-vis drug development and the study of the causes and cures of human

diseases. Perturbations of seemingly identical complex systems, for example monozygotic twins,⁶ can result in dramatically different outcomes. Therefore, we have reason to doubt that one species can predict for another, the outcome of processes that occur at levels of organization not amenable to study by reductionism.⁷⁻¹⁰ This position is supported by other scientists¹¹⁻¹⁶ and by medical science's current emphasis on personalized medicine.^{17, 18}

References

1. **Greek R and Greek J.** Is the Use of Sentient Animals in Basic Research Justifiable? *Philos Ethics Humanit Med* 2010;5:14.
2. **Shanks N and Greek R.** *Animal Models in Light of Evolution.* Boca Raton: Brown Walker, 2009.
3. **Shanks N, Greek R and Greek J.** Are Animal Models Predictive for Humans? *Philos Ethics Humanit Med* 2009;4:2.
4. **Shanks N, Greek R, Nobis N and Greek J.** Animals and Medicine: Do Animal Experiments Predict Human Response? *Skeptic* 2007;13:44-51.
5. **Greek R.** Letter. *Dogs, Genes and Drugs.* *American Scientist* 2008;96:4.
6. **Javierre BM, Fernandez AF, Richter J, Al-Shahrour F, Martin-Subero JI, Rodriguez-Ubrea J, Berdasco M, Fraga MF, O'Hanlon TP, Rider LG, Jacinto FV, Lopez-Longo FJ, Dopazo J, Forn M, Peinado MA, Carreno L, Sawalha AH, Harley JB, Siebert R, Esteller M, Miller FW and Ballestar E.** Changes in the Pattern of DNA Methylation Associate with Twin Discordance in Systemic Lupus Erythematosus. *Genome Res* 2010;20:170-179.
7. **Regenmortel MHVV.** Biological Complexity Emerges from the Ashes of Genetic Reductionism. *Journal of Molecular Recognition* 2004;17:145-148.
8. **Van Regenmortel MH.** Reductionism and Complexity in Molecular Biology. Scientists Now Have the Tools to Unravel Biological and Overcome the Limitations of Reductionism. *EMBO Rep* 2004;5:1016-1020.
9. **Jura J, Wegrzyn P and Koj A.** Regulatory Mechanisms of Gene Expression: Complexity with Elements of Deterministic Chaos. *Acta Biochim Pol* 2006;53:1-10.
10. **Editorial.** End of the Interlude? *Nat Biotechnol* 2004;22:1191.
11. **Giri S and Bader A.** Foundation Review: Improved Preclinical Safety Assessment Using Micro-Bal Devices: The Potential Impact on Human Discovery and Drug Attrition. *Drug Discovery Today* 2011;16:382-397.
12. **Geerts H.** Of Mice and Men: Bridging the Translational Disconnect in Cns Drug Discovery. *CNS Drugs* 2009;23:915-926.
13. **Horrobin DF.** Modern Biomedical Research: An Internally Self-Consistent Universe with Little Contact with Medical Reality? *Nat Rev Drug Discov* 2003;2:151-154.
14. **van der Worp HB, Howells DW, Sena ES, Porritt MJ, Rewell S, O'Collins V and Macleod MR.** Can Animal Models of Disease Reliably Inform Human Studies? *PLoS Med* 2010;7:e1000245.
15. **Gura T.** Cancer Models: Systems for Identifying New Drugs Are Often Faulty. *Science* 1997;278:1041-1042.
16. **Wall RJ and Shani M.** Are Animal Models as Good as We Think? *Theriogenology* 2008;69:2-9.

17. **Spielman RS, Bastone LA, Burdick JT, Morley M, Ewens WJ and Cheung VG.** Common Genetic Variants Account for Differences in Gene Expression among Ethnic Groups. *Nat Genet* 2007;39:226-231.
18. **Wang L, McLeod HL and Weinshilboum RM.** Genomics and Drug Response. *N Engl J Med* 2011;364:1144-1153.