PRE-PRINT VERSION OF

Complex systems, evolution, and animal models

PUBLISHED IN *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences*. 2011;42(4):542-4
doi:10.1016/j.shpsc.2011.07.001

ARTICLE AVAILABLE AT
http://www.elsevier.com/wps/find/journaldescription.cws_home/600658/description

Complex systems, evolution, and animal models

Ray Greek, Niall Shanks

Abstract. In this paper, we respond to arguments made concerning our position regarding animal models (Shelley, 2010) by briefly examining the fact that animals (human and nonhuman) are complex systems that have different evolutionary trajectories. This historical fact has implications for using animals as predictive models for human response to drugs and disease.

Keywords: animal models, complex systems, evolution, prediction, medicine

In Shelley's "Why test on animals to treat humans?" (Shelley, 2010), he discusses positions and concepts set forth by various people including ourselves. We appreciate Shelley taking note of our respective works. However, we feel the need to point out that the work we have done together over the last decade (the references to our works that Shelley cited were, on average, over a decade old), largely as a result of knowledge stemming directly or indirectly from the Human Genome Project, adds support as well as another dimension to our position. These insights are not covered in our older works. In this paper, we wish to highlight our more recent work and what it implies for some of Shelley's conclusions.

We have explained our position in detail in (Shanks & Greek, 2009) and more briefly in (Shanks, Greek, & Greek, 2009). We have very clearly acknowledged that animal use in science and research has value, the lack of predictability for human response to drugs and disease notwithstanding. Our position can be summarized as follows (from Shanks & Greek, 2009, pp358-359). Living complex systems belonging to different species, largely as a result of the operation of evolutionary mechanisms over long periods of time, manifest different responses to the same stimuli due to: (1) differences with respect to genes present; (2) differences with respect to mutations in the same gene (where one species has an ortholog of a gene found in another); (3) differences with respect to proteins and protein activity; (4) differences with respect to gene regulation; (5) differences in gene expression; (6) differences in protein-protein

interactions; (7) differences in genetic networks; (8) differences with respect to organismal organization (humans and rats may be intact systems, but may be differently intact); (9) differences in environmental exposures; and last but not least; (10) differences with respect to evolutionary histories. These are some of the important reasons why members of one species often respond differently to drugs and toxins, and experience different diseases. Immense empirical evidence supports this position.

There are several characteristics about complex systems that are relevant to our position (Van Regenmortel, 2004). One is that the causes and effects of the events that a complex system experiences are not proportional to each other. Another is that the parts of a complex system are linked to and affect one another in a synergistic manner. In other words, there is positive and negative feedback. Complex systems are also robust, meaning they are resistant to change because of redundancies in the system. Probably the most important aspects of complex system as they pertain to the use animal models to predict human response to drugs and disease are that: 1. complex systems are very dependent upon initial conditions; 2. perturbations to the system have effects that are nonlinear (large perturbations may result in no change while small perturbations may wreak disaster); and 3. the whole is greater than the sum of the parts. To put all this in the context of using animals in research, very small differences in the genetic makeup of two otherwise very similar species can result in very different responses to drugs and disease.

One question that arises when any authors, ourselves included, use examples to highlight a concept is whether the examples are representative of the whole. We place the empirical evidence of animal models giving very different results from humans in the areas of toxicity, drug metabolism, research in HIV/AIDS, neuroscience and so forth in the context of what is know about complex systems (Mayr, 1998, p18) (Miska, 2003) (Editorial, 2004) (Ottino, 2004) (Van Regenmortel, 2004) and evolutionary biology. The knowledge from these two fields allows us to develop a theory that explains the empirical evidence and that allows development of future hypotheses and testing of those hypotheses.

For example, a common claim is that by genetically modifying organism A with a gene from organism B, the outcome from perturbations of system B will resemble those from A. In response to this claim, we would point out that both organisms are complex system networks and thus response to perturbations, even in the presence of the same genes, will in all likelihood vary (Jansen, 2003) (Thein, 2005) (Agarwal & Moorchung, 2005) (Boone, Bussey, & Andrews, 2007) (Dowell, et al., 2010). Evolution has arrived at exactly that situation in animals. Gene function depends on background conditions and modifier genes. They are not independent and isolated parts, like pistons. (A piston works the same way regardless of which compatible engine it is put in). Further, much empirical evidence has revealed that genetically altering an animal does not, in fact, reproduce the condition that existed in humans (Nijhout, 2003) or even in different strains of the same species (Pearson, 2002) (Dixit & Boelsterli, 2007) (Regenberg, et al., 2009). Nowhere is this more noteworthy than in the field that is currently referred to as personalized medicine or gene-based medicine (Miklos, 2005) (Weiss, et al., 2008) (Herscu, Hoover, & Randolph, 2009) (Kasowski, et al., 2010). Men and women respond differently to

drugs and disease (Simon, 2005) as do different ethnic groups (Gregor & Joffe, 1978) (Cheung, Warman, & Mulliken, 1997) (Haiman, et al., 2006). Even monozygotic twins do not always react the same to drugs or disease (Wong, Gottesman, & Petronis, 2005) (Fraga, et al., 2005) (Bruder, et al., 2008) (von Herrath & Nepom, 2009) (Javierre, et al., 2010). This puts the disanalogy argument (LaFollette & Shanks, 1996) in new light.

This leads us directly to the prediction issue that Shelley discusses. While it is true that not every species and every experiment has been tested for predictive value, the fact remains that many such tests have been performed directly or indirectly (Litchfield, 1962) (Smith & Caldwell, 1977, pp. 331-356) (Fletcher, 1978) (Ennever, Noonan, & Rosenkranz, 1987) (Sietsema, 1989) (Lumley, 1990) (Igarashi, 1994) (Igarashi, Nakane, & Kitagawa, 1995; Igarashi, Yabe, & Noda, 1996) (Johnson, et al., 2001) (Weaver, et al., 2003) (Shanks & Greek, 2009; Shanks, et al., 2009), and the empirical evidence strongly supports the theory, based on evolutionary biology and complexity, that says that two complex systems, despite the similarities, will never be similar enough to predict response to drugs and disease. The fact that *intra*species differences per above negate a predictive value high enough to satisfy the demands of medicine clearly indicates that *inter*species differences will not allow prediction either.

As we have stated (Shanks & Greek, 2009), the exact value for prediction, in the form of positive predictive value (PPV) and negative predictive value (NPV) does not need to be known. In medical science, a PPV and NPV in the 0.9 neighborhood are needed and animal models fail to even approach these values. Thus animal models are not predictive for human response to drugs and disease, regardless of the so-called alternatives.

Finally, in light of the above, we conclude that the burden of proof is on those who claim that animal models *are* predictive for drug and disease response. There exists both empirical evidence and strong supporting theoretical considerations that they should not be and in fact are not.

We thank Shelley for including our research in his article and hope these comments add to the discussion regarding animals as predictive models for human response to drugs and disease.

Conflicts of Interest
None

References
Agarwal, S., & Moorchung, N. (2005). Modifier genes and oligogenic disease. *Journal of Nippon Medical School, 72*, 326-334.

Boone, C., Bussey, H., & Andrews, B. J. (2007). Exploring genetic interactions and networks with yeast. *Nature Reviews. Genetics, 8*, 437-449.

Bruder, C. E., Piotrowski, A., Gijsbers, A. A., Andersson, R., Erickson, S., de Stahl, T. D., Menzel, U., Sandgren, J., von Tell, D., Poplawski, A., Crowley, M., Crasto, C., Partridge, E. C., Tiwari, H., Allison, D. B., Komorowski, J., van Ommen, G.

J., Boomsma, D. I., Pedersen, N. L., den Dunnen, J. T., Wirdefeldt, K., & Dumanski, J. P. (2008). Phenotypically concordant and discordant monozygotic twins display different DNA copy-number-variation profiles. *American Journal of Human Genetics, 82*, 763-771.

Cheung, D. S., Warman, M. L., & Mulliken, J. B. (1997). Hemangioma in twins. *Annals of Plastic Surgery, 38*, 269-274.

Dixit, R., & Boelsterli, U. (2007). Healthy animals and animal models of human disease(s) in safety assessment of human pharmaceuticals, including therapeutic antibodies. *Drug Discovery Today, 12*, 336-342.

Dowell, R. D., Ryan, O., Jansen, A., Cheung, D., Agarwala, S., Danford, T., Bernstein, D. A., Rolfe, P. A., Heisler, L. E., Chin, B., Nislow, C., Giaever, G., Phillips, P. C., Fink, G. R., Gifford, D. K., & Boone, C. (2010). Genotype to Phenotype: A Complex Problem. *Science, 328*, 469.

Editorial. (2004). End of the interlude? *Nature Biotechnology, 22*, 1191.
Ennever, F. K., Noonan, T. J., & Rosenkranz, H. S. (1987). The predictivity of animal bioassays and short-term genotoxicity tests for carcinogenicity and noncarcinogenicity to humans. *Mutagenesis, 2*, 73-78.

Fletcher, A. P. (1978). Drug safety tests and subsequent clinical experience. *Journal of the Royal Society of Medicine, 71*, 693-696.

Fraga, M. F., Ballestar, E., Paz, M. F., Ropero, S., Setien, F., Ballestar, M. L., Heine-Suner, D., Cigudosa, J. C., Urioste, M., Benitez, J., Boix-Chornet, M., Sanchez-Aguilera, A., Ling, C., Carlsson, E., Poulsen, P., Vaag, A., Stephan, Z., Spector, T. D., Wu, Y. Z., Plass, C., & Esteller, M. (2005). Epigenetic differences arise during the lifetime of monozygotic twins. *Proceedings of the National Academy of Sciences of the United States of America, 102*, 10604-10609.

Gregor, Z., & Joffe, L. (1978). Senile macular changes in the black African. *The British Journal of Ophthalmology, 62*, 547-550.

Haiman, C. A., Stram, D. O., Wilkens, L. R., Pike, M. C., Kolonel, L. N., Henderson, B. E., & Le Marchand, L. (2006). Ethnic and racial differences in the smokingrelated risk of lung cancer. *The New England Journal of Medicine, 354*, 333-342.

Herscu, P., Hoover, T. A., & Randolph, A. G. (2009). Clinical prediction rules: new opportunities for pharma. *Drug Discovery Today, 14*, 1143-1149.

Igarashi, T. (1994). The duration of toxicity studies required to support repeated dosing in clinical investigation—A toxicologists opinion. In N. M. C Parkinson, C Lumley, SR Walker (Ed.), *CMR Workshop: The Timing of Toxicological Studies to Support Clinical Trials* (pp. 67-74). Boston: Kluwer.

Igarashi, T., Nakane, S., & Kitagawa, T. (1995). Predictability of clinical adverse reactions of drugs by general pharmacology studies. *The Journal of Toxicological Sciences, 20*, 77-92.

Igarashi, T., Yabe, T., & Noda, K. (1996). Study design and statistical analysis of toxicokinetics: a report of JPMA investigation of case studies. *The Journal of Toxicological Sciences, 21*, 497-504.

Jansen, R. C. (2003). Studying complex biological systems using multifactorial perturbation. *Nature Reviews. Genetetics, 4*, 145-151.

Javierre, B. M., Fernandez, A. F., Richter, J., Al-Shahrour, F., Martin-Subero, J. I., Rodriguez-Ubreva, J., Berdasco, M., Fraga, M. F., O'Hanlon, T. P., Rider, L. G., Jacinto, F. V., Lopez-Longo, F. J., Dopazo, J., Forn, M., Peinado, M. A., Carreño, L., Sawalha, A. H., Harley, J. B., Siebert, R., Esteller, M., Miller, F. W., & Ballestar, E. (2010). Changes in the pattern of DNA methylation associate with twin discordance in systemic lupus erythematosus. *Genome Research, 20*, 170-179.

Johnson, J. I., Decker, S., Zaharevitz, D., Rubinstein, L. V., Venditti, J. M., Schepartz, S., Kalyandrug, S., Christian, M., Arbuck, S., Hollingshead, M., & Sausville, E. A. (2001). Relationships between drug activity in NCI preclinical in vitro and in vivo models and early clinical trials. *British Journal of Cancer, 84*, 1424-1431.

Kasowski, M., Grubert, F., Heffelfinger, C., Hariharan, M., Asabere, A., Waszak, S. M., Habegger, L., Rozowsky, J., Shi, M., Urban, A. E., Hong, M. Y., Karczewski, K. J., Huber, W., Weissman, S. M., Gerstein, M. B., Korbel, J. O., & Snyder, M. (2010). Variation in Transcription Factor Binding Among Humans. *Science, 328*, 232-235.

LaFollette, H., & Shanks, N. (1996). *Brute Science: Dilemmas of animal experimentation*. London and New York: Routledge.

Litchfield, J. T., Jr. (1962). Symposium on clinical drug evaluation and human pharmacology. XVI. Evaluation of the safety of new drugs by means of tests in animals. *Clinical Pharmacology and Therapeutics, 3*, 665-672.

Lumley, C. (1990). Clinical toxicity: could it have been predicted? Premarketing experience. In C. Lumley & S. Walker (Eds.), *Animal Toxicity Studies: Their Relevance for Man* (pp. 49-56). Lancaster: Quay.

Mayr, E. (1998). *This Is Biology: The Science of the Living World*. Cambridge, MA: Belknap Press.

Miklos, G. L. Gabor. (2005). The human cancer genome project--one more misstep in the

war on cancer. *Nature Biotechnology, 23*, 535-537.

Miska, D. (2003). Biotech's twentieth birthday blues. *Nature Reviews. Drug Discovery, 2*, 231-233.

Nijhout, H. F. (2003). The Importance of Context in Genetics. *American Scientist, 91*, 416-423.

Ottino, J. M. (2004). Engineering complex systems. *Nature, 427*, 399.

Pearson, H. (2002). Surviving a knockout blow. *Nature, 415*, 8-9.

Regenberg, A., Mathews, D. J., Blass, D. M., Bok, H., Coyle, J. T., Duggan, P., Faden, R., Finkel, J., Gearhart, J. D., Hillis, A., Hoke, A., Johnson, R., Johnston, M., Kahn, J., Kerr, D., King, P., Kurtzberg, J., Liao, S. M., McDonald, J. W., McKhann, G., Nelson, K. B., Rao, M., Siegel, A. W., Smith, K., Solter, D., Song, H., Sugarman, J., Vescovi, A., Young, W., Greely, H. T., & Traystman, R. J. (2009). The role of animal models in evaluating reasonable safety and efficacy for human trials of cell-based interventions for neurologic conditions. *Journal of Cerebral Blood Flow and Metabolism, 29*, 1-9.

Shanks, N., & Greek, R. (2009). *Animal Models in Light of Evolution*. Boca Raton: Brown Walker.

Shanks, N., Greek, R., & Greek, J. (2009). Are animal models predictive for humans? *Philosophy, Ethics, and Humanities in Medicine, 4*, 2.

Shelley, C. (2010). Why test animals to treat humans? On the validity of animal models. *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences, 41*, 292-299.

Sietsema, W. K. (1989). The absolute oral bioavailability of selected drugs. *International Journal of Clinical Pharmacology, Therapy, and Toxicology, 27*, 179-211.

Simon, V. (2005). Wanted: women in clinical trials. *Science, 308*, 1517.

Smith, R. L., & Caldwell, J. (1977). Drug metabolism in non-human primates. In D. V. Parke & R. L. Smith (Eds.), *Drug metabolism - from microbe to man* (pp. 331-356). London: Taylor & Francis.

Thein, S. L. (2005). Genetic modifiers of beta-thalassemia. *Haematologica, 90*, 649-660.

Van Regenmortel, M. H. (2004). Reductionism and complexity in molecular biology. Scientists now have the tools to unravel biological and overcome the limitations of reductionism. *EMBO Reports, 5*, 1016-1020.

von Herrath, M., & Nepom, G. T. (2009). Remodeling rodent models to mimic human type 1 diabetes. *European Journal of Immunology, 39*, 2049-2054.

Weaver, J. L., Staten, D., Swann, J., Armstrong, G., Bates, M., & Hastings, K. L. (2003). Detection of systemic hypersensitivity to drugs using standard guinea pig assays. *Toxicology, 193*, 203-217.

Weiss, S. T., McLeod, H. L., Flockhart, D. A., Dolan, M. E., Benowitz, N. L., Johnson, J. A., Ratain, M. J., & Giacomini, K. M. (2008). Creating and evaluating genetic tests predictive of drug response. *Nature Reviews. Drug Discovery, 7*, 568-574.

Wong, A. H., Gottesman, II, & Petronis, A. (2005). Phenotypic differences in genetically identical organisms: the epigenetic perspective. *Human Molecular Genetics, 14 Spec No 1*, R11-18.