Animal Models in Light of Evolution

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For my dogs Brutus, Gnasher, and Lummocks
N.S.

♦

In memory of my mother
R.G.

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TABLE OF CONTENTS

TABLE OF FIGURES

PART I

♦

HISTORY AND BACKGROUND

CHAPTER 1

♦

INTRODUCTION

There is a principle which is a bar against all information,
which is proof against all arguments and which cannot
fail to keep a man in everlasting ignorance—
that principle is contempt prior to investigation.

—Herbert Spencer

Why this book?

The drug phenylephrine is used in pregnant women and is similar to epinephrine in that both drugs known can be used to increase blood pressure. When women are in labor or when they are having a cesarean section, their blood pressure may decrease because of blood loss or the administration of an epidural to decrease or eliminate pain. In these instances a drug may be administered in order to keep blood pressure within normal limits.

When one of us (RG) was completing his residency in anesthesiology, phenylephrine was contraindicated for use in pregnant women. Phenylephrine was never used in women who were pregnant. Administering phenylephrine to a woman in labor or undergoing a C-section would probably have resulted in the resident changing careers or at least specialties. Phenylephrine was thought to decrease blood supply to the baby thus risking numerous complications. This view of phenylephrine was taught to anesthesiologists and obstetricians as being incontrovertibly true since the late 1960s/early 1970s. The drug given to women who needed blood pressure support was ephedrine instead of phenylephrine.

All that changed in the late 1990s/early 2000s. It was at that time that someone noticed that phenylephrine did not really harm the fetus as had been taught for decades to tens of thousands of physicians. The reason for this contradiction was that all the studies that showed phenylephrine was harmful had been done in animals, mainly sheep (Cooper et al. 2002; Lee, Ngan Kee, and Gin 2002). Humans are not sheep. People died as a result of the mistaken application of the above results from animals to

humans. These examples, and other instances like them (see [(Greek and Greek 2000; Greek and Greek 2002)]) are the reason for this book.

The issues we have just alluded to have reverberations in, for example, the field of cancer research. Thus Dennis, writing in *Nature* in 2006 reports:

> It was in 1991 that Bob Weinberg first realized he had a problem with mice. He and his postdoc Tyler Jacks were trying to develop a mouse model for retinoblastoma, a childhood cancer of the retina. It results from the loss of a gene called *Rb*, so the team genetically engineered mice to lack the same gene. But the mice didn't get retinoblastoma. Instead, they developed tumours in their pituitary glands. The finding shocked Weinberg. "Up until then, *I had always believed that all mammals were biologically equivalent*," he says: "This planted the seeds of doubt in my mind."
>
> Weinberg, based at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts, is one of the pioneers of the molecular age of cancer research. He was involved in the early work on the first human cancer-causing and cancer-suppressing genes in the early 1980s. But when he saw that mutations in such genes didn't cause the same kind of cancer in mice and humans, he began to ask himself why. He became aware of other examples that challenged researchers' faith in how accurately mice could replicate human tumours, and has since sought to bring this to his colleagues' attention. "There is a laundry list of problems with mouse models of cancer," he says. (Dennis 2006) (Emphasis added.)

Just because two things are similar does make them interchangeable. The chemist Primo Levi in his autobiography *The Periodic Table* warns against using the "almost-the-same" in chemistry:

> I thought of another moral…that one must mistrust the almost-the-same…the practically identical, the approximate, the or-even, all surrogates, and all patchwork. The differences can be small, but they can lead to radically different consequences, like a railroad's switch points; the chemist's trade consists in good part in being aware of these differences, knowing them close up, and foreseeing their effects. And not only the chemist's trade. [(Levi 1984) p60]

There are two words for knowledge in the German language. *Kennen* means *knowledge by acquaintance*. This meaning can also be found in archaic English, as in "Do ye *ken* John Peel. . . ." The other German word for

knowledge is *wissen*. This is not mere knowledge by acquaintance, but is that kind of knowledge that involves *understanding*, and has a conceptual component. The German word for science is *wissenschaft*. Science in this sense means much more than a passing acquaintance with facts. Science has a conceptual component involving the understanding, interpretation and analysis of (among other things) observations, experiments and data in the broad sense. A large part of this book is devoted to the question of the interpretation and understanding of what has been revealed by the biomedical sciences. In particular, we will be concerned to bring out the implications of evolutionary biology for the fruits of these activities.

This book can also be categorized under the heading of *philosophy of science* and as such it is important that we spend a moment to discuss some of the salient features of philosophy of science. Philosophy of science in the analytic tradition has traditionally studied words like *prediction*, *theory*, *law*, *and hypothesis* and has been concerned to elucidate and clarify the meanings of these terms. Philosophers of science have also examined methodologies employed in various branches of science (some of these investigations are comparative, some are critical). Other traditional concerns in the philosophy of science have revolved around the concept of *evidence*. Such issues concern the nature of evidence, the methods used to gain access to it, and its subsequent evaluation. One of the hallmarks associated with the dawn of modern science was the realization that not all evidence was on a par—that evidence had to be examined for quality and for relevance to problems of interest (witch-hunters had plenty of evidence to support their accusations, for example, but most of it was rubbish extracted under conditions of torture). Learning to think clearly about these and related matters involves critical thinking (and this in turn involves the study of reasoning errors that are common enough to be categorized under the heading of *fallacies*).

Given these points of interest, philosophers of science have many of the same concerns as scientists themselves. The motto for the Royal Society for the Advancement of Science (the world's oldest scientific society) is *Nullius in Verba*, which means, roughly speaking, "don't take anyone's word for it." This is as good a starting point for science as it is for philosophy of science. In a way, sound philosophy of science, like good science itself, is a rational, critical extension and elaboration of sound commonsense.

Issues surrounding critical thinking about science have been neglected in the context of science education. Thus Williams has recently pointed out in *The Scientist*:

> As a science educator, I train science graduates to become science teachers. Over the past two years I've surveyed their understanding of key terminology and my findings reveal a serious problem. Graduates, from a range of science disciplines and from a variety of universities in Britain and around the world, have a poor grasp of the meaning of simple terms and are unable to provide appropriate definitions of key scientific terminology. (Williams 2008)

In an editorial accompanying the Williams article, *The Scientist* editor Gallagher stated:

> You might expect that newly minted science graduates—who presumably think of themselves as scientists, and who I'd thought of as scientists—would have a well-developed sense of what science is. So it's pretty shocking to discover that a large proportion of them don't have a clue . . . [Williams] found that a sizeable proportion of science graduates entering teacher training couldn't define what is a scientific fact, law or hypothesis. (Gallagher 2008)

The issue of animal experimentation in biomedical research has traditionally been of interest to experimental biologists, theoretical biologists and historians of science. Insofar as philosophers have had an interest in these matters, it has been primarily from the standpoint of the ethics of animal use in research. In this book, we hope to show that standard uses of animals in biomedical research raise a host of issues in the philosophy and methodology of science that have nothing to do with the ethical confines of traditional philosophical interest. An examination of animal experimentation from the standpoint of ideas rooted in the philosophy of science, will, we hope, illuminate issues about the nature of science itself, especially experimental science (a matter all too often neglected by philosophers of science). If successful, perhaps experimentalists may come to see their activities in a different light. There is, after all, a big difference between *doing* science on the one hand, and *making sense* of what one has actually done—and *why*—on the other.

At this point, we should explain how we will be using some terms. We will use interchangeably the terms and phrases *animal model*, *animal-based research*, and *animal experimentation* to mean the use of any nonhuman animal for scientific research and testing purposes. We will use the word *animal* to mean nonhuman animals even though we do of course realize humans are also members of the Animal Kingdom. We will discuss the meanings of the words *hypothesis* and *prediction* (along with allied concepts)

in more detail in later chapters dealing specifically with the prediction question in biomedical research. We will be concerned thereto ask under what conditions (if any) can results in animal test subjects be extended and extrapolated to human populations of interest. In other words, when do animal experiments predict human outcomes, and how are these predictions to be tested and validated. (We recognize here, and throughout the book, that animals are used in many ways in biomedical research, and the use of animal subjects to predict human outcomes is but one use of animals in biomedical research, albeit a very important one).

In this book, we present a critical analysis of the use of animals in the context of biomedical research aimed at *predicting* human responses with respect to such matters as the study of disease, the safety of pharmaceutical products, and the effects of environmental toxins. We will raise concerns about the clinical relevance of *predictive animal modeling*. We will argue first that there is a large body of empirical evidence undergirding these concerns. Second we will argue that the concerns we raise have a solid theoretical grounding from both the standpoint of evolutionary biology and dynamical systems theory (especially its implications for the study of complexity). Third we will argue that there are serious methodological and evidential concerns raised by the practice of predictive animal modeling. These issues will be presented in ways that are relevant to professional biologists, as well as those interested in the history and philosophy of science. As is the case with any volume that crosses disciplinary lines, some will find some of the material simplified while others will appreciate the foundations explained by that same material. We beg the reader's indulgence and ask her to remember that others who are not specialists in her field will be reading the sections that fall in her domain of expertise. Our goal has been to explain the concepts so a college science major could understand the basic issues.

In September 2003, in a debate with one of the authors of this volume (RG)—a debate that took place at the Labour Party conference in Bournemouth, England—Dr Ian Gibson, MP (a biologist by training) stated in response to a question about the odds of an animal model getting the right answer in the context of drug testing: "Well, I mean Ray would say seventy: thirty [against] or something like that, I would say fifty: fifty." Even those who defend predictive animal modeling appear to be modest about the prospects of scientific fruit from those research practices.

In an August 4, 2004 article in the *New York Times* titled, "In Drug Research, the Guinea Pigs of Choice Are, Well, Human," Andrew Pollack observes of a new trend in the search for new drugs:

> Drug researchers are conducting small, fast, relatively inexpensive tests on people to get a quick gauge of a drug's promise before committing to full-scale clinical trials that may involve hundreds of patients, millions of dollars and many years of study . . . In the past, many of these experiments might have been done only on animals. Often called experimental medicine, the approach is meant to reduce the huge costs of drug development and speed the most promising treatments into the marketplace . . . And scientists and industry executives, while acknowledging the potential for ethical issues, say that experiments on people are more reliable, because animal tests often fail to accurately predict whether a drug will work on people.

In an article published in *The British Medical Journal*, Pound et al. have recently observed:

> Clinicians and the public often consider it axiomatic that animal research has contributed to the treatment of human disease, yet little evidence is available to support this view. Few methods exist for evaluating the clinical relevance or importance of basic animal research, and so its clinical (as distinct from scientific) contribution remains uncertain. Anecdotal evidence or unsupported claims are often used as justification—for example, statements that the need for research is "self-evident" or that "Animal experimentation is a valuable research method which has proved itself over time." Such statements are an inadequate form of evidence for such a controversial area of research. We argue that systematic reviews of existing and future research are needed. (Pound et al. 2004)

In an FDA White Paper issued in March 2004, titled, "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products," the authors observe that a new medical compound entering Phase 1 human trials after up to a decade of preclinical screening (using animal models) has about an 8% chance of reaching the market [(FDA News 2006) p 8]. Concerning the causes of this state of affairs the authors observe:

> A number of authors have raised the concern that the current drug discovery process, based as it is on *in vitro* screening techniques and animal models of (often) poorly understood clinical relevance, is fundamentally unable to identify candidates with a high probability of effectiveness. [(FDA News 2006) p. 9]

Because the use of animals as research subjects has been a source of moral controversy, there has been a growing interest in the scientific and lay communities concerning the roles played by animals in the biomedical sciences. Much of this interest has been prompted by the relatively recent (circa 1980) animal rights movement (and related social movements) in the United States and Western Europe. This is *not* our concern in the present volume where our focus is on matters of science and not morality. This point deserves emphasis. We fully realize this book has potential implications for a whole host of extra-scientific questions about the conduct of biomedical research (though not necessarily the ones you might think). However, those implications, important thought they may be for persons with relevant interests, are debates for another day.

We do not deny that our discussion may be of relevance to some limited aspects of moral debates surrounding the use of animals in biomedical research. Moreover, we do not deny that our volume has relevance to public policy debates concerning the use of increasingly scarce biomedical research funds. These research activities, insofar as they promise great value to human health and well-being, receive widespread public support. Still, there is no escaping the *animal issue*. Large numbers of animals are consumed annually in the name of predictive biomedical research. Estimates vary but even conservative estimates place the number of animals used in these research endeavors in the United States alone to be of the order of millions per year (see Appendix 1).

Certainly lurking behind our central concerns in this book is a social cost-benefit analysis of current research practices. Giles wrote of this issue in *Nature*:

> In the contentious world of animal research, one question surfaces time and again: how useful are animal experiments as a way to prepare for trials of medical treatments in humans? The issue is crucial, as public opinion is behind animal research only if it helps develop better drugs. Consequently, scientists defending animal experiments insist they are essential for safe clinical trials, whereas animal-rights activists vehemently maintain that they are useless. (Giles 2006)

It is, of course, possible to have concerns about the reality of the social benefits promised by animal investigators, their lobbyists and policy advocates, that are quite independent of any interest in animal rights. Increasingly burdened taxpayers, many of whom couldn't care less about animal rights, for example, have a strong interest in the pursuit of such matters. In the spirit of the Royal Society, they are fed up with being told

to take someone else's word for it (one way or the other). We cannot settle these contentious questions and what little we do have to say has been relegated to the appendices accompanying the main body of our arguments.

Interest has also been generated because of new developments in science itself. These developments are derived in no small measure from various genome projects and their implications for the relative positions of humans and other animals in nature. The new biological discipline of genomics reflects the fruits of these inquiries. The biomedical implications here can be seen in such fields as pharmacogenomics and toxicogenomics.

The purpose of this book is to address the ability, or lack thereof, of animals to predict human response and to see what other roles they may have in research and testing. We will argue that claims concerning the great utility of animals as predictive models of human biomedical phenomena are unsupported by evidence and are compromised by both methodological issues and issues arising from basic biological theory.

In this book we will thus discuss the following propositions:

1. *When the animal model community discusses the use of animals in research they give the definite impression that such results have been and will be translated directly to humans.* (The community here includes those who use animals as models for humans, their employers, those in the press who support their activities, and so on.) Some theorists in these debates acknowledge the difference between basic and applied research but even these commentators often encourage belief in the predictive utility of animal models with respect to translational research. Interestingly enough, animal welfare activists often buy into these claims about the predictive utility of animal-based research, hoping (with varying degrees of disingenuity) that animal-based research can be replaced by non-animal methods that work *just as well*. We will argue here that they should be careful what they wish for given the actual predictive track record of animal-based research.
2. *Animal models are not predictive for humans, indeed even different humans respond differently to drugs and disease, for many reasons.* We will discuss some of these reasons and we will examine the meaning of the word *predict*—a matter that calls for attention if only because it has acquired a semantic shiftiness that makes its usage highly susceptible to equivocation in public discussions of these matters.

3. *Animals can be used in science in many endeavors that have little or nothing to do with prediction.* Animals can be used as bioreactors, for the study of other animals of the same species or strain, as an aid in learning and so forth. Clearly, one can obtain much important basic scientific knowledge that may or may not go on to be important in the study of human disease. It is here however that we again criticize the animal model community. There are indeed important connections between basic biological research on animals on the one hand, and human medicine on the other, but these connections are typically much more distant and indirect and suggestive than those engaged in predictive animal modeling tell the public and their policy makers.
    a. Organisms belonging to different species or even different strains of the same species may manifest different responses to the same stimuli due to:
        i. differences with respect to genes present, and also with respect to the versions (*alleles*) of genes present;
        ii. differences with respect to mutations in the same gene (where one species has an ortholog of a gene found in another);
        iii. differences with respect to proteins and protein activity;
        iv. differences with respect to gene regulation;
        v. differences in gene expression;
        vi. differences in protein-protein interactions;
        vii. differences in genetic networks (robustness, pleiotropy etc);
        viii. differences with respect to organismal organization (humans and rats may be intact systems, but may be differently intact);
        ix. differences in environmental exposures; and last but not least
        x. differences with respect to evolutionary histories.

    These are some of the important reasons why there are species differences with respect to the response to drugs and toxins, and why different species (and strains of a given species) experience different disease states.
    b. Even nearly identical organisms (e.g., chimpanzees and humans in some debates, or monozygotic twins in other contexts) may respond differently to drugs and experience differ-