

Comments on criticism from Adrian Morrison in his book *An Odyssey With Animals*

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In 2002, Adrian R. Morrison published in *Perspectives in Biology and Medicine* an article titled "Perverting medical history in the service of "animal rights." (Morrison 2002). In the article he criticized many, including Jean and me, who have questioned the use of animals in research and drug testing. In 2009, Morrison published essentially the same criticism of the book Jean and I wrote, *Sacred Cows and Golden Geese* (Continuum 2000), in his book *An Odyssey With Animals* (Oxford University Press) (Morrison 2009). I will here address his criticisms.

Because much of Morrison's criticism of us revolves around taking things out of context we will quote his section on us in its entirety, going line by line or paragraph by paragraph through the five pages he devoted to us. (Incidentally, according to the index, we received more pages in his book than did any other topic or person.)

Personal story

Because so much of this essay is quotes I will use blue type to designate Morrison's words and black for the words of others including myself.

Morrison begins:

Ray Greek, a physician (an anesthesiologist), and Jean, a veterinarian (a dermatologist), begin their book, *Sacred Cows and Golden Geese*, with a remarkable anecdote. While they were students of medicine and veterinary medicine, their respective course work led them to believe that their patients, human and animal, were too different in their diseases and reactions to medicines to warrant the use of animals to advance human medicine. [p103]

What we actually said (yellow highlight added):

Comparative medicine may not be everyone's idea of a riveting dinner topic, but it is ours. This book grew out of our meal-time conversations during the 1980s. Those were the years of our professional education one of us as a veterinarian, and the other as an anesthesiologist.

When our animal and human patients exhibited the same symptoms, discussion became most heated. This was because diagnoses and treatment plans for animals frequently differed for humans. Pitting the veterinarian's dictates on the one hand against the physician's on the other, we would each get huffy and self-righteous, then whip out our textbooks to prove our accuracy. Many references later, sure enough, according to the books, we were both right. Well, this was puzzling! These discrepancies flew in the face of what we had been taught to revere. Animal experimentation was an inviolable convention--a political sacred cow. Everything we had been taught, from fetal pigs forward, suggested that animals were just like humans, a bit furry and funny looking perhaps, but otherwise just the same.

Like everyone, we had been convinced by many familiar determinants: animal experimentation for human medical research had a time-honored history. Milestones supposedly garnered from animal studies were constantly in the media. As medical students, we were well familiar with the government's requirement for animal assays in drug development and its financial rewards to research institutions. Certainly, grant money for such projects was vital to the incomes of our teachers and universities. Indeed, our medical training pivoted on assumed anatomic, biochemical, and physiological characteristics shared by man and beast.

This sizable and persuasive rationalism averred that animals were ideal test beds for human therapies. So, why then was Ray's human patient with high cholesterol developing coronary heart disease and Jean's dog with high cholesterol experiencing a thyroid disorder? Why do women who have had hysterectomies need to fight osteoporosis while neutered cats live longer, healthier lives? And why are humans not vaccinated for parvo and dogs for rubella? Our dinner conversations suggested that most animal diseases simply do not occur in humans. Conversely, the major killers of humankind are extraordinarily rare among the four-legged set.

Plainly, if there was parity, it was not universal. Sure, the basics are the same. Fundamental cell activity and metabolic processes--the stuff of research decades ago--correspond in animals and humans. Still, we thought, why did scientists use animals back when human autopsy, tissue culture techniques, or human observation could have provided the same information? Some animal experimentation led to developments. But in how many cases were the animals necessary? Animals can be used to grow viruses, but so can petri dishes and human tissue cultures. All mammalian blood--animal and human--has components in common, so why not use human blood for totally accurate results? Moreover, when it came to present-day research--mostly involving microbiology on the most complex levels--why scrutinize species whose physiologic response to disease, disease manifestation, and disease incidence so clearly deviates from

human response? Logic, it seemed to us, even back then when we had but few comparisons, was somehow amiss.

Both of us had performed animal experimentation. We knew from experience how similar the gross anatomy of animals and humans is, and how dissimilar are the details. For example, all mammals have a four-chambered heart that pumps blood, but our own education taught that at the cellular level mammals react very differently to medications. All land mammals have four limbs, but attempts to test surgeries of the aorta on dogs fail because dogs' circulation is different in part due to their walking on four extremities while we walk on two. Animals and humans both secrete gastric juices and other chemicals. However, the gastric fluid in dogs' stomachs is much more acidic than ours. This is why Fido can gobble down uncouth matter without upsetting his stomach, and humans cannot.

Scientists have a name for one-to-one correspondence between all elements in two or more living systems. Isomorphism. Clearly, animals are not isomorphic with humans. With systems as complex as the human body, very small dissimilarities not only negate isomorphism but also have radical implications. Grossly, animals are alike, that is why we are all part of the animal kingdom. We differ on the cellular and molecular level, and, importantly, that is where disease occurs.

We, the tireless medical students, became more inquisitive. We asked the kind of questions everyone asks when confronted with the subject of animal experimentation. No one really wants to torture animals, but look where a history of animal experimentation has led us. Where would we be today without the antibiotics, the scanners, the modern surgical techniques, and the host of medications used daily to treat everything from heart disease to arthritis to cancer? If animal-models are not employed, what or who will be? Few people aspire to be the first patient of an inexperienced surgeon or the first person to take a new drug. Moreover, we rationalized, is it not reassuring to know that new advances have been thoroughly tested on animals, found not only safe, but also effective?

But how safe, how effective are these animal-modeled advances? Investigating further, we learned that though cardiac-bypass surgery was practiced extensively on animals, when first tried on humans, the patients actually died. Penicillin kills guinea pigs and is not effective in rabbits. Were these troubling examples common ones? Or were they exceptions to the rule? Apparently not, we found. Roughly fifteen percent of all hospital admissions are caused by adverse medication reactions. And legal drugs, which made their way to the public via animals, kill approximately 100,000 people per year. That is more than all illegal drugs combined and costs the general public over \$136 billion in health care expenses.¹

We found the actual merit of using animal tissues--in the culture medium, as heart valves or for insulin, or to produce monoclonal antibodies, and so forth--was by no means as advantageous as we had been led to believe. There were heavy risks, sometimes resulting in human illness and even death. And no one was mentioning the less dangerous treatments these therapies delayed. Likewise underestimated was the potential for animal-borne viruses that might mutate into

a more deadly and contagious form in the human body. When we began to collect data, the fatally infectious protein particles called prions, (which could inhabit all animal tissue and which medicine has no way to thwart) had yet to reveal themselves. Now that prions have been front page news, from the incidences of Mad Cow disease, everyone should know that mining animals for treatments is courting disaster. But they do not.

We had been led to believe that the majority of medical advances had come about as the result of research carried out on animals. Now we wondered was this truth or propaganda?

We do not deny that we are both "animal lovers," to some extent motivated by our affection for animals and our concern for their well being. However, more essentially, we are both medical doctors and scientists. For ten years, Ray performed the most demanding branch of anesthesiology in cardiopulmonary and transplantation surgeries. Jean became one of the top veterinary dermatologists in the world. We have both published extensively in the scientific literature. Our lifestyle and careers are grounded in science. Logic, reason, data, causal relationships, verifiability, repeatability, and all other tenets of the scientific paradigm--these provide the hard scientific foundation for our choices, both personal and professional.

We were finding, through scientific research, that extrapolating data from animals to humans is either misleading, unnecessary, dangerous, or all three.

The strongest tenet that arises from science is predictability. To be reliable, a model should have predictive value. That is science. In medicine, strong models assume four factors: the same symptoms, the same postulated origin of disease, the same neurobiological mechanism, and the same treatment response. The truth is that though certain animals may fulfill some of the same criteria as humans in some incidences, no animal consistently fulfills all four. This means that animals are not strong models for human disease.

It also means that all data recovered from animal model experiments must be scaled. Scaling is a scientific term that, generally, refers to "the fudge factor." Since we are all putting our lives and the lives of our loved ones in the hands of supposedly rigorous science, is not a model that requires so much fudging grossly inadequate--especially since humans themselves provide the perfect model?

Given all these peculiarities, we began to ponder just how humans do benefit from animal experimentation. We asked physicians how it had specifically contributed to their field. Surgeons denied knowledge of any specific contributions, but referred us to pediatricians. Pediatricians knew of no significant achievements in pediatrics that relied on animals, but referred us to psychiatrists. Psychiatrists pointed out the drawbacks to studying psychosis in mice and suggested we contact the internists. And it continued. Each specialist, though unaware of true animal-model successes in his own field, was convinced that other specialists were reliant on this protocol. They too had bought what was fast appearing to us as a bill of goods. [(Greek and Greek 2000) p15-18]

Morrison's assertion that we said that humans and animals "were too different in their diseases and reactions to medicines to warrant the use of animals to advance human

medicine” is misleading at best. Many advances have relied on knowledge gained from basic research on animals or research that led to knowledge about very fundamental properties of animal life. Whether this knowledge could have been obtained without animals may be a discussion worth having, but no one can deny history unfolded as it did. As the reader can ascertain from reading our actual words we said animals and humans have things in common but in terms of predicting human response to drugs and disease, no, animals cannot be so used.

It is informative that Morrison uses material only from our first book and not material from more recent publications. We go into much more detail in later works and some of the later works were written for a more scientifically literate audience than the first book. (See *Specious Science* (Continuum 2002), and Shanks, Greek, Nobis, and Greek, *Animals and Medicine: Do Animal Experiments Predict Human Response?* In *Skeptic* 2007;13 (3):44-51. If you have a background in science we recommend Shanks, Greek, and Greek, *Are animal models predictive for humans?* In *Philos Ethics Humanit Med* 2009;4(1):2. And Shanks and Greek, *Animal Models in Light of Evolution* (Brown Walker 2009).)

Comparative medicine

Morrison continues:

Certainly, my experience has been quite different, for the activities and relationships at the veterinary school where I have spent my professional career at the University of Pennsylvania with other professions are based on the concept of comparative medicine-One Medicine; Many Species-as we tout in our brochures. Our view is that we can learn about disease and its cures in all species by working together. In fact, it was a famous Philadelphia physician and signer of the Declaration of Independence, Benjamin Rush, who urged the establishment of a school of veterinary medicine at the University of Pennsylvania.

Morrison’s comment “One Medicine; Many Species” is certainly where we disagree with him. Medicine is not even practiced the same among humans. Different genotypes require different interventions and are susceptible to different diseases (Shanks and Greek 2009). We will return to this point repeatedly.

Morrison:

Several of my contemporaries in our clinics did quite a bit of their residency training at the Hospital of the University of Pennsylvania because they were studying in the early days of developing specialties in veterinary medical practice, around 1960. Our Section of Comparative Medical Genetics studies a number of genetic diseases in animals that model the human conditions quite nicely⁸.

I do not know what “quite nicely” means. If Morrison is equating *nice* with *predictive* then he is wrong. (I will continue to quote Morrison by indenting his words with out other notation.)

Further, Dr. Charles Cornelius: the former dean of the College of Veterinary Medicine in Davis, California, has listed about 350 diseases that humans and animals share wholly or in considerable part, rabies being a perfect example. And the list continues to grow.

Sharing diseases does not mean the way humans and animals respond is the same nor that a treatment that works for one will work for another. All diseases can be said to have commonalities among animals if one uses a broad enough definition. Our point was that animals cannot predict human response for drug and disease response. Humans and nonhuman primates share infection from HIV however the response could not be, practically, more dissimilar.

Morrison's way of communication is obviously aimed for the nonscientific audience. We have no problem with this as many of our books and articles are also so aimed. However, first and foremost what an author states should be correct; regardless of the audience. There is nothing wrong with *dumbing down* as long as the concept in question is truthfully preserved.

The Greeks emphasize in their book that they are not interested in animal rights but only in demonstrating that using animals in research endangers human health. In their words, "the animal model harms people." Nevertheless, they acknowledge help from a variety of organizations associated with the animal rights and liberation movement, such as the American-Antivivisection Society [AAVS], the Medical Research Modernization Committee [MRMC], and the Physicians Committee for Responsible Medicine [PCRM].

Morrison is here attempting to prove us guilty by association. Association alone is insufficient for proving a person guilty of whatever accusation. For example, Morrison and his peers have huge vested interests in the *status quo* as it pertains to using animals in science. They have made their careers out of this endeavour and hence have their egos tied up in the perceived validity of the process. Also, many still have a financial interest in using animals, as that is how they obtain grants from which they derive their salaries and so forth. None of this means that what they say about using animals is wrong. The value of using animals in research must be judged by how well the process *works*; how well the results from animals predict human response, if that is how animals are being used or how well animals function as heuristic devices, if that is how they are being used. Guilt by association does not make Morrison and his peers wrong any more than taking money from animal protection groups makes our positions wrong. All positions must be judged on the merits.

Not surprisingly, the people who want to fund some of our work are animal advocates. That being said we have been very outspoken against many in the animal protection movement, especially on issues of science. Not what one would expect if our integrity was outweighed by our desire for money (See http://www.navs.org/site/News2?page=NewsArticle&id=7867&news_iv_ctrl=1081 and http://www.navs.org/site/News2?page=NewsArticle&id=7861&news_iv_ctrl=1081 and http://www.navs.org/site/News2?page=NewsArticle&id=7823&news_iv_ctrl=1081)

for examples.) To the best of my recollection, the only groups that have ever given money to Americans For Medical Advancement are the National Anti-Vivisection Society of Chicago and the New England Anti-Vivisection Society of Boston. We thanked PCRM, AAVS, and MRMC because they had done research that we took advantage of and used in our book. We stand behind what we said and any mistakes are ours alone. But others had pointed us in the direction of references and so forth that we then checked for ourselves before using. Such practice is common in science writings. We also found material in the writing of groups that disagree with our position. We did not thank them, as that would have been gauche.

But as Michael Festing has stated, "The Siren song of Ray and Jean Greek is highly seductive to those who campaign against the use of animals in research. If all models are scientifically invalid, their use could be banned immediately. Unfortunately, the Greeks are wrong."

Once again this is not what we say. We and AFMA vice-president Niall Shanks have gone to great lengths to recognize the fact that animals can be used as heuristic models. (See *Animal Models in Light of Evolution* (Shanks and Greek 2009) and "Two Models of Models" (LaFollette and Shanks 1995) for more on this.) Our issue is and always has been that animals are not predictive for humans.

The Greeks present the same distortions of medical history as those presented by other individuals discussed in this chapter. Their effort consists of an entire book that ranges over many areas of medicine. *Sacred Cows and Golden Geese* is full of myths, twisting of meanings, and illogic, as exemplified in the book's introduction. Although the book's argument is that animals differ too much from humans to be *useful* in research, (emphasis added)

We address what people mean when they use weasel words like *useful* in *FAQs About the Use of Animals in Science* (Shanks and Greek 2010) and in *Animal Models in Light of Evolution* (Shanks and Greek 2009). Suffice it to say here that *anything* can be useful if by useful you mean it pays your mortgage or, being more charitable, that it adds knowledge to the world. Useful does not equate with predictive and being predictive is how animal-based research is sold to society.

the Greeks cite the problem of mad cow disease as a warning against using animal parts in restorative surgery. Eating the meat of such cows can result in the passing of altered prions (proteins that can "infect" cells and damage them) to humans, which leads to brain degeneration. How can this be possible, we must ask, if animals are so different from humans?

Being different enough to undermine prediction doesn't require them to be Martians or alien lifeforms. Trucks can flatten cats and cardboard boxes, cats not the same as cardboard boxes. Cows cannot do higher math, people can, people with Alzheimer's cannot. As we say in many places, animals and humans have things in common but that does not mean animals can be used to make the drug supply safer vis-à-vis predicting

human response or that they can be used to predict the mechanisms of human disease. Morrison is here using the either-or fallacy; either things are similar or different. The fact is they can be both. Humans and mosquitoes, for example, are both similar in some respects and different in others. The *Anopheles* mosquito can transmit malaria to humans but that does not mean we can use it to predict the effects of drugs.

Penicillin

Morrison:

As for myths, especially those handed from one animal rights publication to another, the Greeks claim that penicillin kills guinea pigs. They proceed to ignore or downgrade the literature establishing the fact that penicillin is very effective in other laboratory species, that early adverse effects on guinea pigs were due to impurities in the penicillin administered, and that in later experiments some guinea pigs died after administration of a certain strain of penicillin containing a dangerous bacterium. The bacteria interacted fatally with the microscopic organisms naturally found in the herbivorous guinea pig's ample gut, thereby upsetting their digestive tracts." Other examples of distortion and selective quoting abound in the book.

Morrison's toxic rhetoric here hardly makes a rational case.

Accusations of distortion and selective quoting is, without detailed evidence, a tack to immunize Morrison's views from evidential refutation. His read of the literature is right while anyone else reading the same literature and coming to a contrary view is wrong. Fact: the literature does not provide a unified front when it comes to Morrison's views on its significance (he ignores what we emphasize).

That being said, penicillin is a good example to seriously examine.

There are as many stories about how penicillin came to be as there people who have written them. The hows and whys of the discovery and development of penicillin are a hotly debated story. Such is true of most medical and scientific discoveries; especially ones that occurred almost a century ago. There are some details, however, that seem to be factual:

1. Fleming *re*-discovered penicillin in 1928.
2. He then tested it *in vitro* and *in vivo* on rabbits and mice (he mentions the rabbits in his original paper). The *in vitro* results showed promise, as did topical application on rabbits. But when given systemically, the rabbits metabolized it too rapidly and led Fleming to believe it would be useless for humans when administered systemically. (Hence it was considered ineffective.) He therefore abandoned developing penicillin as a therapy for systemic infections in humans.
3. Fleming continued to grow penicillin and even administered it, topically, to humans in the 1930s and into the 1940s. Through a student of his, G. G. Paine, Fleming gave it to 4 humans suffering from ophthalmic neonatorium, 3 of whom responded well (Henderson 1997; Florey et al. 1949).
4. Florey and Chain conducted research with penicillin and produced a purified product using basic chemistry.

5. The purified product was eventually tested on mice who responded well.
6. The purified product was also given by Fleming to a friend of his who was dying. His friend recovered due to the antibiotic. Simultaneously penicillin was administered to a cat that subsequently died.
7. Publicity surrounding Fleming's patient led to funding to develop the drug. Fleming went down in history, rightly or wrongly, as the person primarily responsible for penicillin.

We did not claim, nor did we pretend, to give the definitive historical account of penicillin. Rather, we simply presented what seems clear: that regardless of how one views the history of penicillin, species differences resulted in one species leading researchers down the wrong path while another species reacted as did humans. This draws into question the notion of trans-species extrapolation.

The fact is that penicillin *does* kill certain animals, was ineffective (or considered ineffective in other animals), and was very effective in other animals. There is nothing controversial about this. Back in 1966 Theodore Koppanyi and Margaret A. Avery wrote an article about species differences, observing:

If it [penicillin] had been screened in guinea pigs (Harare et al. 1943) or Syrian hamsters (Schneierson and Perlman 1956), penicillin might have been discarded. (Koppanyi and Avery 1966)

Hau, in the *Handbook of Laboratory Animal Science* wrote:

Uncritical reliance on the results of animal tests can be dangerously misleading and has cost the health and lives of tens of thousands of humans, as in Ciba Geigy's cloquinol scandal, the Opren disaster of Distra Products Ltd., or ICI's Eraldin calamity. Such counteraction in interspecies reactivity is bilateral: what is noxious or ineffective in nonhuman species can be innocuous or effective in humans. *For example, penicillin is fatal for guinea pigs but generally well tolerated by human beings*; aspirin is teratogenic in cats, dogs, guinea pigs, rats, mice, and monkeys but obviously not in pregnant women despite frequent consumption. [(Hau 2003) p4] (Emphasis added.)

Schneierson and Perlman:

Observation of the unique toxicity of penicillin to guinea pigs as compared to mice and rabbits was first made by Hamre et al. (1) and has since been amply confirmed (2-8). (Schneierson and Perlman 1956)

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The toxicity of penicillin to the gut of the guinea pig was well known by the 1960s (Toshkov 1965; Kaipainen 1960). Hamre et al. had first described it in 1943 (Hamre et al. 1943).

While researching *Sacred Cows and Golden Geese*, we easily discovered that Fleming used a rabbit in his early research and concluded from it that penicillin would not be effective in humans.

Francis Diggins, another of Fleming's associates, wrote to us:

Hello, nice to hear from you! Yes, he tested the crude broth extract on rabbits and mice. These were described in his original paper, sent to the *British Journal of Exp. Path.* on 10 May, 1929 and published in June 1929. Ref: Fleming A, *Brit J Exp Path.*, 10 : 226, 1929. I have not got a copy of it (although I have almost every book published on the discovery, many of them with rubbish in them!) but you will find quotes from it in the book by Ronald Hare, "The Birth of Penicillin", George Allen & Unwin, 1970, p 90. "Twenty cc. injected intravenously into a rabbit were not more toxic than the same quantity of broth". Also "Half a cc. injected intraperitoneally into a mouse weighing about 20gm. induced no toxic symptoms". (Diggins 2002)

With regard to the role of cats and rabbits, the facts are on our side and are well described. V. D. Allison (a student, lab worker, and protégé of Fleming's), wrote in *The Ulster Medical Journal* in 1974:

Subsequent events are well known—the short life of the mold extract, its lack of damage to blood cells and tissues, its ability to cure certain [topical] infections in rabbits, and topically in the human eye and skin infections . . . He [Florey] asked Fleming not to use it (the penicillin) until he (Florey) had injected some into the spinal canal of a cat to see if it was innocuous. However the patient was moribund with all hope given up, so Fleming decided to inject the crude penicillin into the patient's spinal canal on the evening he received it. Fleming slept at the hospital that night and early next morning, Florey phoned Fleming and told him the cat had died. [Fleming's patient made a complete recovery because of the penicillin.] (Allison 1974)

Alison also mentions that the only disagreement Almroth Wright and Fleming ever had was over a statement that Fleming wanted to include in his original paper stating that penicillin may be useful for infections in humans. The statement was left out because of Wright.

Allen B. Weisse, Professor of Medicine at the University of Medicine and Dentistry of New Jersey, and author of *Medical Odysseys: The Different and Sometimes*

Unexpected Pathways to Twentieth-Century Medical Discoveries, (Rutgers University Press, 1991), wrote in *Hospital Practice* August 15, 1991:

[Fleming was discouraged about penicillin's possible use because first...] Third, after injection into an ear vein of a rabbit and with blood samples taken periodically thereafter for testing, it was found that penicillin was rapidly removed from the bloodstream. Samples taken at 30 minutes were found almost completely devoid of activity. Of what use might be an antibacterial agent that took several hours to act but was removed from the body within 30 minutes and inhibited by the blood with which it would obviously be mixing? (Weisse 1991)

Craig H Steffee of Bowman Gray School of Medicine, writing in the *North Carolina Medical Journal* states:

Flemming considered penicillin a potential chemotherapeutic agent, but his early in-vivo investigations were discouraging. In rabbits, serum levels of penicillin dropped rapidly after parenteral administration, too fast to allow the several hours of contact with bacteria required for an effect in vitro. (Steffee 1992)

Steffee defends Fleming's laying penicillin aside based on the rabbit work stating:

...how many therapeutic modalities with the poor in vivo results of Fleming's early penicillin trials would be offered continued funding today? (Steffee 1992)

Note also, that Weisse defends Fleming's decision not to use more animals:

One might well wonder why, given the uncontrolled devastation of bacterial diseases, no further experiments on animals or humans were undertaken. The rapid disappearance from the blood has already been mentioned . . . Even the choice not to use animal experiments more extensively, a routine practice of investigators on the continent, could be defended by Fleming and his group. After all, there might be differences between humans and other animals in resistance or susceptibility to different infections . . . In August 1942, a close personal friend of Fleming had contracted streptococcal meningitis. When conventional therapy failed and death seemed imminent, Fleming turned to Florey for help. The latter personally delivered his remaining supply of penicillin to Flemming and instructed him in the initial use of it. A dramatic cure was obtained, even the more so since penicillin was administered into the spinal canal for the first time to enhance its effectiveness. This "miracle" at St. Mary's was reported in the *London Times* and the following day a letter from Almroth Wright identified Fleming as the one on whose brow the laurel wreath should sit. (Weisse 1991)

Human observation also encouraged Florey to continue the penicillin purification process. As John Warren Henderson wrote in the *Mayo Clinic Proceedings*:

About that time, Florey who had been at Sheffield before his appointment at Oxford, recalled Paine's (previously mentioned) successful topical treatment of ophthalmic neonatorium [in humans] with a crude broth of penicillin. All these factors gave Florey and Chain hope that systematically administered penicillin might have therapeutic potential in humans. (Henderson 1997)

Granted, Fleming obtained the more pure form of penicillin, which he gave to his friend in 1942, from Florey who tested penicillin on mice. But that is irrelevant to our point. To say that the purification process, which produced the penicillin, was dependent upon testing it in the mice is another example of fallacious reasoning, a *non sequitur*. The purification process was classic *in vitro* research, based on knowledge of chemistry. If Florey gained the confidence to proceed, based on tests in mice, that does not mean that animals were necessary for the development of the drug. If he had used guinea pigs, who knows what would have happened?

The point of our passage is that Fleming received data from rabbits, which led him to abandon penicillin as a systemic antibacterial agent. Many references support this. The general public does not understand the differences between $t_{1/2\alpha}$ and $t_{1/2\beta}$ and $t_{1/2\pi}$ (and perhaps neither do some of our scientist readers) but the nonscientific audience does understand what is meant when someone says, "it did not work" which is what we said about the rabbit tests. We stand by our statement. We do not deny that penicillin can be used in many species. We do deny that animals can be used as predictors for humans because, as the penicillin story illustrates, animals vary in their reactions and a reaction in animals does not mean the same will occur in humans. Where is the human signal in all the noise generated by variable animal test results? There is no answer from Morrison or others who have made similar criticisms.

The fact we reported that generated so much controversy was that penicillin has been seen to kill guinea pigs and Syrian hamsters. This was and is true. Morrison explains, in part, why this is true implying that since we now know why it is true we should excuse the fact that the species differences were misleading in applying animal results to humans; penicillin does not in fact kill humans the way it kills guinea pigs and Syrian hamsters. The point we were making was that using animals as predictive models is fraught with so many hazards and there are so many example of where the practice has damaged human health that the practice should be abandoned. (Had Fleming ethically tested penicillin systemically on humans society would have had it a decade before it otherwise did. How many lives were lost because of that animal-based mistake?) Penicillin illustrates a very important question about using animals in research: how do we know, prospectively, which animal to believe? Mice or guinea pigs or rabbits or cats in the case of penicillin? Mice or rabbits in the case of thalidomide? No one has ever answered that question.

In addition, other questions we would like to see answered are: Why do Drs. Morrison and Festing and others, who give unqualified support to animals as predictive models for humans, ignore the above facts? Why do Morrison and Festing refuse to address the lack of predictability of animal models? Neither do these individuals address the quote attributed to Fleming by his student, "How fortunate we didn't have these animal tests in the 1940s, for penicillin would probably never have been granted a license, and possibly the whole field of antibiotics might never have been realized (Parke

1994).” They also ignore the statements of Florey, who emphasized species differences when he stated: “Mice were used in the initial toxicity tests because of their small size, but what a lucky chance it was, for in this respect man is like the mouse and not the guinea-pig. If we had used guinea-pigs exclusively we should have said that penicillin was toxic, and we probably should not have proceeded to try and overcome the difficulties of producing the substance for trial in man (Florey 1953).”

Penicillin is an outstanding example of why animals are not predictive for humans.

Cancer

Morrison continues:

In the chapter on cancer research the Greeks include a quote from Nobel Laureate Renato Dulbecco: "If we wish to understand human cancer, the [research] effort should be made in humans because genetic control seems to be different in different species." This statement followed a familiar premise by the Greeks: "Each creature has different physiologic and pharmacological responses."³ In an earlier part of the article containing Dulbecco's statement, however, Dulbecco described the developments from studying cancers by different methods in various species that led him to the following conclusion:

We are at a turning point (in 1986) in the study of tumor virology and cancer in general. If we wish to learn more about cancer, we must now concentrate on the cellular genome. We are back to where cancer research started, but the situation is drastically different because we have new knowledge and crucial tools, such as DNA cloning.

He went on to suggest a strategy that included sequencing the human genome and performing "cancer research with cells in culture or in immunodeficient mice [my emphasis]." In other words, as any scientist would tell the Greeks, we will use the most appropriate method(s) at this stage of our knowledge to solve this particular problem.

We acknowledge that there are many research modalities for studying disease and advancing medical knowledge and treatments. We wrote an entire book about that topic (Greek and Greek 2004). The question is not, “Are there many methods that can be used?” but rather, “What is the role of animals in cancer research?” “Can they predict human response?”

Morrison offers no proof that what we said was wrong. Namely that each creature has different physiologic and pharmacological responses in general and to cancer in particular. For example, 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.)

For more on cancer and animal models see (Shanks and Greek 2009) and (Shanks and Pyles 2007).

Immunosuppressives and drugs in general

Morrison:

In another chapter, "The Pathetic Illusion of Designer Drugs," the Greeks argue that inconsistencies in experiments with various species *delayed introduction of cyclosporin and FK506 (tacrolimus) as immunosuppressive antirejection agents*. These are life-saving medications used in transplant patients and others with autoimmune disease. The same mystifying claim appeared in a letter they wrote to the editor of the Journal of the American Medical Association. My friend Charles Nicoll of the University of California at Berkeley doubted the Greeks' claim and wrote to Sir Roy Calne in England, the author of one of the studies discussed by them. Sir Roy responded with an *unpublished letter* to the editor, which he has given me permission to quote here:

I wish to point out that Dr. Ray Greek's letter in the Feb 9th issue of *JAMA*, re the Medical News and Perspectives article, *takes out of context quotes from the literature*, and this results in the distorted view of the relationship of animal experiments to progress in medicine. As any reasonably educated person knows, *virtually every effective medicament and surgical procedure available in modern medicine only reaches the clinic because of preliminary investigations in animals*. In particular, if cyclosporin had first been used in man it would never have been licensed because of its nephrotoxicity in man, whereas it wasn't nephrotoxic in animals and we would have lost the chance to use this extremely valuable drug. As far as FK506 and our own work is concerned, the fact that this agent was toxic in some of our animal experiments but not in others was an important observation that led to a cautious approach to dosage in the clinic and again the availability of an extremely valuable immunosuppressive agent. (All emphasis by Greek.)

Morrison, and others who have criticized our work, make liberal use of personal communication between themselves and other scientists. The value of these quotes is questionable as the statements are obviously not peer-reviewed and, even if they were, are merely opinions. Granted when a researcher who makes a discovery comments on that discovery, his statements should be considered, but more weight should be placed on critical thought, science, and scientific studies than on appeals to authority. For more on this see (Shanks and Greek 2009) and (Shanks and Greek 2010). Further, if current statements that are self-serving contradict previous statements delivered in the peer-reviewed literature then those previous statements should take precedence. One of the reasons for peer review is to ascertain the credibility of claims made. Beyond the realm of peer review one could claim the moon is made of green cheese – even possession of a Nobel Prize will not make it true.

However, let's begin by analyzing “every effective medicament and surgical procedure available in modern medicine only reach the clinic because of preliminary investigations in animals.” This is a true statement in as much as the FDA requires animal testing but the statement raises the question: “Is the relationship between reaching the clinic and the animal studies casual or causal?” Sir Roy obviously is insisting it is causal but is this reasonable?

In the US, and most developed countries, medications and surgical procedures used on public are required by law to be tested on animals first, the claim here is *post hoc ergo propter hoc* (after this hence because of this) and confuses legal necessity with causal and medical necessity. The scientific community, the pharmaceutical industry, and others have admitted animal models are misleading when used to predict human response. The data from testing six drugs on animals was compared with the data from humans [(Suter 1990) p71-8]. The animal tests were shown to have a sensitivity of 0.52 and the positive predictive value was 0.31. The sensitivity is about what one would expect from a coin toss and the PPV less. Not what is considered predictive in the scientific sense of the word. (See (Shanks, Greek, and Greek 2009) for more on this.) Because of data like this animal modelers will occasionally use the phrase *concordance rate* or *true positive concordance rate* when judging animal tests. These terms are not in the normal prediction-relevant statistics lexicon and are usually used to mean correlation, which has nothing to do with prediction. (Concordance usually equates with sensitivity, a measure of how well a test recognizes true positives. See appendix for more on this.)

Two studies from the 1990s revealed that: (1) in only 4 of 24 toxicities were found in animal data first [(Heywood 1990) p57-67]; and (2) in only 6 of 114 cases did clinical toxicities have animal correlates (Spriet-Pourra, Auriche, and (Eds) 1994). The positive predictive value (PPV) and negative predictive value (NPV) of animal models based on these studies are obviously suboptimal.

A 1994 study of 64 marketed drugs conducted by the Japanese Pharmaceutical Manufacturers Association found that 39/91 (43%) clinical toxicities were not forecast from animal studies [(Igarashi 1994) p67-74]. (This study, as do many others, counted as a positive prediction when any animal correlated with the human response. Without knowing the raw data it is impossible to calculate a true PPV and NPV but even taken at face value, 43% wrong/57% correct is not predictive).

Butcher (Butcher 2005) Horrobin (Horrobin 2003) Pound et al. (Pound et al. 2004) and others (Dixit and Boelsterli 2007; Uehling 2006; Littman and Williams 2005;

Editorial 2005; LaFollette and Shanks 1996) have questioned the value of using animals to predict human response.

In the 2006 report “The use of nonhuman primates in research” written by a committee chaired by Sir David Weatherall, the authors state: “It’s undoubtedly the case that all animal models are limited in their predictability for humans [(Weatherall 2006) p92].”

The National Institute of Allergy and Infectious Diseases acknowledged at a summit they held in 2008 following the failure of a Merck AIDS vaccine in 2007 that the rhesus macaque system now used to test potential vaccines is not predictive and in fact has not been working out well for researchers. The Merck vaccine failed to protect against HIV infection in humans despite doing so in monkeys(Kaiser 2008).

In an editorial in *Nature* 14 December 2006 we find the following remarks:

Animal research saves lives. That is the mantra often used to counter verbal and physical attacks on animal researchers and their institutions by animal-rights activists. And it is unquestionably true: animal research has made many valuable contributions to medical science.

However, the simplicity of the slogan barely does justice to the complexity of the issue. From a scientific point of view, for example, it is clear that certain animal models are useful: the neural prosthetics that promise to restore some independence to paraplegics, for example, arose from curiosity-driven studies of the primate brain (see *Nature* 443, 122; 2006). But others are imperfect: certain mouse models of cancer, for example, do not accurately mimic the disease in humans, and may even have hampered the development of some drugs (see *Nature* 442, 739–741; 2006). (Editorial 2006)

Wall and Shani observe:

We conclude that it is probably safer to use animal models to develop speculations, rather than using them to extrapolate. (Wall and Shani 2008)

Curry points out:

The failure, in the clinic, of at least fourteen potential neuroprotective agents expected to aid in recovery from stroke, after studies in animal models had predicted that they would be successful, is examined in relation to principles of extrapolation of data from animals to humans. (Curry 2003)

Lindl et al., have tried to quantify the clinical utility of animal models:

According to the German Animal Welfare Act, scientists in Germany must provide an ethical and scientific justification for their application to the licensing authority prior to undertaking an animal experiment. Such justifications commonly include lack of knowledge on the development of human diseases or the need for better or new therapies for humans. The present literature research is based on applications to perform animal experiments from biomedical study

groups of three universities in Bavaria (Germany) between 1991 and 1993. These applications were classified as successful in the animal model in the respective publications. We investigated the frequency of citations, the course of citations, and in which type of research the primary publications were cited: subsequent animal-based studies, in vitro studies, review articles or clinical studies. The criterion we applied was whether the scientists succeeded in reaching the goal they postulated in their applications, i.e. to contribute to new therapies or to gain results with direct clinical impact. The outcome was unambiguous: even though 97 clinically orientated publications containing citations of the above-mentioned publications were found (8% of all citations), only 4 publications evidenced a direct correlation between the results from animal experiments and observations in humans (0.3%). However, even in these 4 cases the hypotheses that had been verified successfully in the animal experiment failed in every respect. The implications of our findings may lead to demands concerning improvement of the licensing practice in Germany. (Lindl, Voelkel, and Kolar 2005)

Marincola in the *Journal of Translational Medicine* 2007:

It is surprising how often a manuscript is dismissed by reviewers as "just descriptive", regardless of the novelty of the reported observation. On the other hand, we have not once received a negative comment on a "mechanistic" study, even if it lacks proof of the validity of the experimental model and its relevance to human disease. Such studies are automatically given the benefit of the doubt based on predictable rationalizations vaguely offered in the introductory paragraphs. As a consequence, innumerable conflicting results are published, each one a reflection of its own experimental bias. For example, in animal models, Interleukin-23 can either promote or hamper cancer growth [1-6]; yet, information about its bio-availability in human cancers and its modality of expression, information that can potentially provide insight into the interpretation of such models, is limited. (Marincola 2007)

The notion that animals cannot predict human response certainly appears widespread in the scientific literature. (For more on this see (Shanks and Greek 2009).)

Sir Roy then states:

In particular, if cyclosporin had first been used in man it would never have been licensed because of its nephrotoxicity in man, whereas it wasn't nephrotoxic in animals and we would have lost the chance to use this extremely valuable drug.

The above makes no sense. Is Sir Roy actually saying that because animal models failed to predict nephrotoxicity cyclosporin made it to humans where it was nephrotoxic? Borel and Kis reported that the initial toxicity screening in animals found cyclosporin very safe:

A few weeks later, however, the Vienna Group reported the fungistatic activity of 24-556 in animals as only modest and restricted to relatively innocuous fungal

strains such as *Candida albicans*. Our colleague there added: "Not even toxic whatsoever!" (Borel and Kis 1991)

Sir Roy is in essence saying *when animals and humans correlate that is useful and when they do not that is also useful*. Useful depends on purpose. If one is using animals to predict human response, then their failure to do so is not *useful*. For basic research, sure, anything can be useful. Would Sir Roy say that it was lucky that thalidomide passed animals tests because today we use it for treating cancer? That is essentially what he is saying about cyclosporin. This is unfortunately a common misuse of logic when animal experimenters attempt to justify their work in the face of failure.

Cyclosporin is nephrotoxic to humans and was initially thought to be uniquely so (Thomson et al. 1981). After this fact became known it was possible for scientists to reproduce it in animals (Collier et al. 1986). Thomson et al.:

In most animal studies in which therapeutic doses of CsA [cyclosporin A] have been used to prolong allograft survival, little or no side effects of the drug have been reported. However, several untoward effects observed in patients, in particular nephro- and hepatotoxicity and the appearance of lymphomas, tremor and hirsutism, have prompted more detailed investigations of the toxicity of CsA in various laboratory species, including primates. Perhaps of greatest interest have been efforts to produce an animal model of CsA nephrotoxicity - the most important clinical side effect of the drug. In addition, the effects of CsA over a wide dose range, the consequences of long-term treatment and the reversibility or otherwise of the toxic changes have been investigated [11, 141, 143, 158, 160, 181] . . . Whereas in animal toxicity studies the effective immunotherapeutic dosage of CsA appears to be significantly below toxic levels of the drug, in man these appear to be much more closely associated. This may reflect differences in absorption or drug metabolism between species. (Thomson, Whiting, and Simpson 1984)

The interaction of cyclosporin with other drugs leading to kidney failure as well as the dose optimal for humans was likewise worked out in humans (Editorial 1986).

Calne:

As far as FK506 and our own work is concerned, the fact that this agent was toxic in some of our animal experiments but not in others *was an important observation that led to a cautious approach to dosage in the clinic* and again the availability of an extremely valuable immunosuppressive agent.

All drugs should be given to patients for the first time with caution! The notion that if scientists see adverse effects in animals they precede with heightened caution is ridiculous. Maximum caution is always taken otherwise the physician supervising the clinical trial is guilty of negligence. Even the complete absence of adverse effects in any tested animal species, is no assurance of safety in humans.

As to our statement about FK 506 that Calne says we took out of context, what we actually said in *Sacred Cows and Golden Geese* was:

FK 506, now marketed as Tacrolimus, an antirejection agent, was almost shelved before proceeding to clinical trials.⁸⁰ After experimenting on dogs, researchers stated, ``Animal toxicity was too severe to proceed to clinical trial."⁸¹ Subsequent research with baboons yielded different results, once again proving that we cannot extrapolate results from one species to another. Test enough species and you are bound to find one that gives you the results you want. Scientists, experimenting on animals, also suggested that the combination of FK 506 with cyclosporin might prove more useful.⁸² In fact, just the opposite was true in humans.⁸³ [(Greek and Greek 2000) p72]

In our *JAMA* letter (Greek and Greek 2000) we said:

FK 506, now called Tacrolimus is another anti-rejection agent that was almost shelved before proceeding to clinical trials. Researchers stated, “Animal toxicity was too severe to proceed to clinical trial”.[We referenced (Calne et al. 1989)]

Calne said:

The fungal product, FK506, is immunosuppressive in animals with organ grafts.² We confirmed the immunosuppressive effect but animal toxicity was too severe to proceed to clinical trial, although such a study is now underway in the USA. (Calne et al. 1989)

[Reference cited]

2. Collier DSJ, Calne R, Thiru S, et al. FK506 in experimental renal allografts in dogs and primates. *Transplant Proc* 1988; 20(suppl 1): 226

(NOTE: I was unable to find this reference but did find: Collier DS, Calne R, Thiru S, Friend PJ, Lim S, White DJ, Kohno H, Levickis J. FK-506 in experimental renal allografts. *Transplant Proc.* 1987 Oct;19(5):3975-7 and other similar references.)

It appears we quoted Calne exactly. Now we will examine context. The article is very short, four paragraphs total. Here are the first two paragraphs:

Rejection and infective complications of immunosuppressive treatment are the main causes of failure in organ allografting in man. To minimise the individual side-effects, azathioprine, corticosteroids, and cyclosporin are combined in small doses. Cyclosporin is the most powerful agent of the three, but can be nephrotoxic. No other immunosuppressants are useful clinically because of toxicity and/or lack of efficacy.

The fungal product, FK506, is immunosuppressive in animals with organ grafts. We confirmed the immunosuppressive effect but animal toxicity was too severe to proceed to clinical trial, although such a study is now underway in the USA. A compound with structural similarities to FK506, rapamycin, was investigated on the basis of a report that it inhibited experimental allergic encephalitis, adjuvant arthritis, and the formation of humoral antibody in rats. Rapamycin is a lipophilic macrolide produced by *Streptomyces hygroscopicus* with both antifungal and antitumour properties. (Calne et al. 1989)

The article then goes on in the next (and last) 2 paragraphs to describe experiments with rapamycin. There are no disclaimers in the article outlining why animal tests here were not predictive but why they usually are. The context here was simply that of scientists describing past and current experiments. I do not see how anyone can seriously accuse us taking this quote out of context.

There is no controversy about the toxicity of FK506. Starzl et al:

Cyclosporin has been an essential factor in the expansion of transplantation services during the past decade. [1] However, its nephrotoxicity and other limitations have stimulated a continuing search for alternative agents. We report here the first clinical trials in liver recipients of a new drug that is not related chemically to cyclosporin or to other standard immunosuppressants. FK 506, a macrolide produced by *Streptomyces tsukubaensis*, as discovered in 1984 in Japan during a search for new immunosuppressive and cancer chemotherapeutic agents. It was shown to be immunosuppressive in vitro by Kino et al [2] and in rats by Ochiai et al [3] and by numerous others (see ref 4) throughout 1987. A major divergence of opinion quickly surfaced about the potential clinical value of the agent. From our studies of heart, kidney, or liver transplantation in rats, dogs, and subhuman we judged it worthy of a clinical trial. *In contrast, workers at Cambridge University reported unacceptable toxicity including widespread arteritis.* [10] However, we [8] and Ochiai et al [11] have shown such vascular lesions to be present in non-immunosuppressed dogs after whole organ transplantation and in dogs treated with other agents including cyclosporin. Arteritis has not been a feature in baboons treated with FK 506 [9] or in formal toxicology studies. [8] [When examining its effects in man we did not feel justified in conducting potentially dangerous pharmacokinetic studies in normal volunteers, as is the usual practice in drug development. Instead the agent was given, in the first instance, to patients in desperate plight because their liver grafts were being rejected despite conventional immunosuppression.

Later, it was combined with low doses of steroids as primary antirejection treatment for high-risk recipients of livers, kidneys, and in one case a pancreas . . . (Starzl et al. 1989) (Emphasis added.)

The introduction of FK506 certainly appears to have been delayed because of animal studies.

The principal toxic effects of CsA and Cyclosporin's immunosuppressant affect were likewise difficult to ascertain from animal studies [(Altman 1998) p32] [(Reines) p56]. Since animals did not receive the same immunosuppression anticipated in humans, its effectiveness looked doubtful. Cohen:

The immunosuppressive effects of cyclosporine have, thus, differed considerably between species, limiting any direct inference that may be made regarding use in human organ transplantation, and precluding formulation of a unifying concept explaining the observed diversity of actions. (Cohen et al. 1984)

Another significant discrepancy between animals and humans was absorption of the drug. Researchers administered cyclosporin orally to animals, but found that humans varied considerably in how well they absorbed the drug into their bloodstream. In other words, neither cyclosporin's success nor its side effects were predicted by animal tests (Cohen et al. 1984; Editorial 1986; Bennett and Pulliam 1983). The most life-threatening of these effects is kidney damage, which led researchers to state: "... failure to produce renal dysfunction experimentally [in animals] that is similar to that seen clinically [in humans] may result from species differences in metabolism (Bennett and Pulliam 1983)." Professor A D Struthers, Professor of Clinical Pharmacology at the University of Dundee and Consultant Physician, writing in the magazine *MRC News* in December 1992:

[Regarding the toxicity of the immunosuppressive drug cyclosporin] We decided to tackle this problem by studying man rather than animals since the study of animals was proving inconclusive and because there is no sure evidence that what is found in animals can be applied to man. (Struthers 1992)

Scientists also suggested that the combination of FK 506 with cyclosporin might prove more useful (Starzl et al. 1989). In fact, just the opposite was to be true in humans (Neuberger 1991). Starzl et al:

In the early cases we examined the effect of FK 506 on the pharmacokinetics of cyclosporin and observed increases in cyclosporin blood levels with associated nephrotoxicity. The results discouraged us from trying combined therapy . . .

In many of the first investigations with FK 506, the possibility was entertained of combining small doses with agents such as cyclosporin, with which it is synergistic in vitro [15-16] and in animals. [5,6,8,11] Our experience so far has not encouraged such combination therapy. The FK 506 may have increased the toxicity of cyclosporin, possibly by raising its blood concentration. FK 506 was so potent and free of side-effects that the simplest expedient was to use it alone.

[Select references cited]

5) Murase N, Todo S, Lee PH, et al. Heterotopic heart transplantation in the rat receiving FK-506 alone or with cyclosporine. *Transplant Proc* 1987; 19: 71-75.

6) Todo S, Demetris A J, Ueda Y, et al. Canine kidney transplantation with FK-506 alone or in combination with cyclosporine and steroids. *Transplant Proc* 1987; 19 (suppl 6): 57-61.

8) Todo S, Veda Y, Demetris TA, et al. Immunosuppression of canine, monkey, and baboon allografts by FK 506 with special reference to synergism with other drugs; and to tolerance induction. *Surgery* 1988.; 104: 239-49.

11) Ochiai I., Sakamoto K, Gunji Y, et al. Effects of combination treatment with FK506 and cyclosporine on survival time and vascular changes in renal-allograft-recipient dogs. *Transplantation* 1989;48:193-97. (Starzl et al. 1989)

References in book

Morrison continues:

Based on the number of references listed at the back of *Sacred Cows and Golden Geese* (949-some of them titles from the animal rights literature),

The references from animal protection organizations were of a historical nature or were themselves references to scientific works. References to newspapers and so forth were also used but again were not used for scientific proofs but rather used for their appropriate value.

Morrison in his book and article references Botting 1991, which is a paper published by the Research Defense Society, an outspoken support group for all animal-based research, thus calling into question his assertion that anything not published in peer-review journals is disreputable. (Indeed RDS was the official representative for animal experimenters in England. It has since merged with another organization.) Of course I am sure he would say his side of the debate is reputable and the animal rights side is not, but that is the kind of thinking one studies in courses on critical thought and logic—in this particular case it is called question begging. Combine the above with Morrison's reliance on personal communications and the weakness of his case is obvious.

the book seems scholarly on the surface. But legitimate works were disingenuously cited in the book to bolster an argument even if the author of that work would not support the Greeks' overall point of view.

The issue here is not whether the authors we quoted agree with our overall point of view but whether they said what was reported. Morrison can not make his case by misrepresenting our position. Because the accusation of taking things *out of context* is considered such an odious act in scholarly circles further comments are warranted.

The strength of many of the quotes Jean and I have used in numerous books and article lies in the fact that true believers in using animals to advance medical knowledge and predict human response have, perhaps in an unguarded moment, perhaps in a moment of honest reflection, admitted that there are limitations to using animals – which we think for theoretical reasons need to be given more space and consideration. The fact these comments come from *animal users* strengthens our case since it would be easy to find statements of limitations from dimwitted animal activists. We took the high ground. If we were to say in an article we wrote that animal models were excellent predictors for humans and should be used religiously, that statement could be used to call into question other statements we have made which conveyed the opposite position. This is not science *per se* but merely common sense.

Many of the scientists we quote are speaking very specifically about an area or example that falls directly within their expertise. When they comment that animal models failed in some way, *in their area of expertise*, their claim carries weight. When they are confronted by a colleague with our quoting of them and they then speak out in favor of using animals in research in general, something that is outside their area of expertise, their words carry less weight. Not to mention the fact that if anyone else tried to justify such a flip-flop they would be called on it and rightly so. That experimenters fail to see what the limitations they point to really mean – their broader significance – is neither here nor there. They have been trained to work under the paradigm that says animal

models work. This is perhaps inevitable. We try to rethink the admitted limitations by locating them in evolutionary context – a theoretical perspective only dimly appreciated by researchers who pay lip service to it.

Morrison and others seem to be saying that: 1) we quote scientists who have, for a vast majority of their career, held the position that animal models are excellent predictors of human response or were used in virtually every medical advance in history; 2) when we quote these scientists as saying anything that calls such a position into question, we are quoting them *out of context*. Thousands of politicians who, thinking the microphone was turned off, flip-flopped on an issue and hundreds of thousands of people convicted of a crime because they confessed to it wish this were a valid argument.

The out-of-context accusation is disingenuous because the FACTS of species differences are not at issue. What is at issue are the INTERPRETATIONS authors place on the facts they refer to. We are justified in citing facts while rejecting interpretations. We cite many examples of the same phenomenon (species difference) to establish that it is a more or less agreed fact. Our point is not to get involved in an endless ding-dong about examples but to suggest that there are other well-established ways to deal with what we see (i.e. evolution). It matters not to us that those referring to the facts of species differences are also ardent advocates of animal experimentation (no doubt some of them also play golf). What matters are the facts. Science is as much driven by disputes about the meaning and significance of facts as it is about the facts themselves. We have nothing to apologize for in this regard.

Antihypertensives

Morrison:

For example, they refer to an article by the late Paul Beeson, a distinguished professor of medicine at several universities including Yale and Oxford, to support the notion that animals played no role in the development of drugs for high blood pressure. Beeson made no such claim, but rather found it "interesting to note that three of the four major classes of hypertensive drugs now in use were not known to affect blood pressure until they were given to patients for other indication."

Nor did we say that he did. We merely listed as one reference among many his article as supporting our claim, which was: "The development of the anti-hypertensive medications not only was not dependent upon using animals, it would have been impossible using them (p169)." We readily acknowledge that animals may play a role in research without being predictors. Morrison is here making an error in confusing the roles.

Further to accuse us of saying animals played no role in the development of antihypertensives is also wrong. We readily acknowledge that basic knowledge of the circulatory system came from animals. But basic knowledge was not what we were describing. We were discussing using animals as predictive models and in that respect we stand by our statement that "The development of the anti-hypertensive medications not only was not dependent upon using animals, it would have been impossible using them."

And this is supported in the book by the references we give and the quotes of scientists familiar with the discovery process; including Beeson.

In other words, medical science forges ahead on many fronts, benefitting from the observations of alert physicians treating their patients in addition to the experimental work stemming from laboratory research. The occurrence of one medical advance made without the direct contribution of animal research does not negate the value of all research conducted with animals.

Once again, the fact that there are many research modalities has nothing to do with whether animal models are predictive and what role they played in the past. What we actually said:

The fact that there are so many animal models for hypertension and atherosclerosis indicates that none of them is completely satisfactory. Identical observations can be made for the other severe cardiovascular pathologies: coronary ischemia, cerebral ischemia, cardiac insufficiency and rhythm disorders.⁷⁹

Medications

Dr. Franz Gross, a HTN researcher remarked,

It has to be admitted that the antihypertensive effect of some drugs such as the diuretics, clonidine or the beta-adrenergic blockers was first observed in man, and only later studied in animal experiments with respect to their blood pressure-lowering activity.⁸⁰

Dr. B. Pritchard was a physician who was administering a beta-blocker to a human patient suffering chest pain when he noticed the blood pressure decrease. His observation led to anti-angina medications such as propranolol, metoprolol, atenolol, and others being used for hypertension. Animal studies had predicted previously that they would not lower blood pressure.^{81,82,83} [82 is the Beeson paper] "Nothing in our work on animals predicted the slowly developing antihypertensive action of pronethalol which Pritchard and Gilliam have described."⁸⁴

Dr. B. Fitzgerald comments on Dr. Pritchard's clinical observation, "Pritchard's tenacious studies on the hypotensive action of propranolol eventually paved the way for the extensive use of beta-blockers in hypertension, even though this therapeutic application was not predicted from animal studies."⁸⁵

Today, millions of people use beta-blockers as treatment for HTN. Even animal experimenters admitted the failure of animal models of hypertension in this regard. Many other anti-HTN medications such as alpha-methyldopa, calcium channel blockers, and clonidine were not predicted based on animal studies.

Conversely, once researchers attempted to "validate" the usefulness of beta-blockers, these animal tests did not foretell beta-blocker side effects such as heart failure, bronchospasm, fatigue, and others.

Unwanted effects such as bradycardia slowing of the heart rate, hypotension, heart failure, bronchial spasm, cold extremities and easy fatiguability are attributable to known actions of beta antagonists. With the exception of

bradycardia, none of these was predicted from the initial animal studies.⁸⁶ (Emphasis added.)

We can also credit the diuretic treatment of HTN entirely to clinical experience.⁸⁷ As long ago as 1937, doctors noticed that patients who took medications to increase urine output began to breathe better. As a patient's heart fails, fluid fills the lungs and he or she essentially drowns. Diuresis allowed the congested lungs to get rid of excess fluid; thus patients could breathe easier. The scientists then modified the medication's chemical structure to isolate the diuretic effect and the thiazide diuretics were born. Lasix is one commonly used example. The substances were never tested on animals. Ray Gifford, MD, a major contributor, acknowledged, "We had no protocols, no informed signed consents, no statistical consultation. We just gave the drugs in any combination we thought would reduce blood pressure and minimize side effects."⁸⁸ Dr. Karl Beyer stated, "We did not assess the activity of chlorothiazide in hypertensive animals prior to clinical trial."⁸⁹ Dr. Gifford added, "I can't help but wonder how long it would take to get hydralazine or chlorothiazide on the market today?"

Although those who earn their living by experimenting on animals will try to convince you that all medical miracles arose from calculated experiments on animals in controlled laboratory environments, clinical initiative is how discoveries actually emerge. Many more such examples abound, more than the vested interest groups would like to reveal. The development of the anti-hypertensive medications not only was not dependent upon using animals, it would have been impossible using them. Dr. F. Gross states in the textbook *The Scientific Basis of Official Regulation of Drug Research and Development*,

The antihypertensive effect of diuretics does not occur in normotensive animals and is difficult to obtain in hypertensive rats or dogs. Similar problems have to be faced with respect to the antihypertensive action of beta-adrenoreceptor blocking drugs. The beneficial effect of phentolamine, of prazosin, or of hydralazine in the treatment of heart failure is hardly demonstrable in experimental animal models. The predictive value of the results of numerous preclinical animal tests or experimental models for the therapeutic uselessness of a drug is at best uncertain, and the predictability will not be improved by simply increasing the number of tests. One of the most widely studied examples of a disease model is experimental hypertension, but for the development of new drugs for the treatment of high blood pressure the various types of experimental hypertension are dispensable tools.⁹⁰

Morrison continues:

(Actually, Beeson criticized Brandon Reines, a veterinarian whose work is discussed below, for "citing a statement of mine that seems to align me with the antivivisection movement.")

We do not as relevant how Beeson or Morrison or others *feel* about how others interpreted their words. All that matters is what was said as a matter of fact, and what was

said, in this case was consistent with and emphasized our point. This debate is not about misrepresentation of vivisectors as proto animal rights folk. We don't care what they believe. The issue is one about species differences and clinical versus animal medicine.

If you criticize X and someone who believes Y (which you do not) finds your criticism useful, that does not make you a supporter of Y. If we accepted this constraint of Beeson's we should be unable to conduct a rational conversation with anyone we disagree with. The only relevant point here is whether Reines cited Beeson accurately. If he did then Beeson should either be more careful in choosing his words or take responsibility for them. If Reines misquoted him then shame on Reines. (The paper Reines was citing was P. B. Beeson, *Am. J. Med.* 67, 366 (1979). To the best of my recollection, we did not cite that paper. We cited Beeson, P. B. 1980. How to foster the gain of knowledge about disease. *Perspect Biol Med* 23 (2 Pt 2):S9-24.)

Furthermore, Beeson's 1980 paper was actually arguing the importance of creating an environment that would attract additional young clinician scientists, obviously needed for their special insights. (I say essentially the same thing to my students "Keep your eyes open and your mind clear because you may discover something important that was under everyone's nose.") As such, Beeson's comments were taken out of context to support the entirely unrelated argument made by the Greeks that animals stand in the way of medical progress.

What Beeson actually said:

It is fair to assert that our understanding of cardiac function and cardiac failure has been advanced more by clinical investigators than by physiologists [animal experimenters] during the past fifty years. New concepts regarding support of the failing heart by digitalis preparations, diuretics, aldosterone antagonists, and agents to alter the peripheral blood flow are presently being evolved, based on intensive studies that can only be carried out in man. Much of our understanding of the importance of thromboembolic disease, and its prevention or treatment, falls in the realm of clinical investigation. The entry of cardiac surgery into the treatment of valvular and congenital heart disease, as well as of diseases of the larger blood vessels, undoubtedly constitutes an advance which will always have to be listed among the major events in the history of medicine. These measures, together with effective long-term control of hypertension by pharmacologic means, must be major factors in the apparent decline in mortality rate from cardiovascular diseases that has occurred within the last quarter-century. With regard to hypertension, it is interesting to note that three of the four major classes of antihypertensive drugs now in use were not known to affect blood pressure until they were given to patients for other indications.

Beeson's entire article sings the praises of clinical research. Our point, in part, was that clinical research on humans was more predictive for humans than animal-based research. Not surprising since humans are of the same species while animals are not. To accuse us of quoting him out of context, when the article was about the value of clinical research, is ludicrous. Morrison continues:

Furthermore, in his article in which he presented some of the challenges inherent in clinical research, Beeson noted the difficulty of knowing how a particular disease might begin, because patients come to a doctor only after a disease has progressed, adding that “only when it is possible to devise an animal model of the disorder under study is the clinical scientist able to investigate the early phases of a process.”

Indeed that is what he said. It is incorrect but it is what he said. Investigation of early stages of disease has been accomplished using humans for centuries. But that was not the focus of our referencing Beeson. Beeson agreed that clinical research and observation were important for antihypertensive development. The role animals played in their development was minimal and based on research designed to find basic things about living organisms. Animals were not used as predictive models nor could they have been. That was our point and we stand by it.

Another reference misused by the Greeks to support the case against a role for animal research in the development of antihypertensive drugs is Julius Comroe’s *Exploring the Heart* a delightful but scholarly history of the experimentation that led to achievements in cardiovascular medicine and surgery.

The Greeks quote a statement made by a scientist in Comroe’s book “We did not assess the activity of chlorothiazide in hypertensive animals prior to clinical trial.” Comroe reveals, however, that the scientist, Karl Beyer, had a long history of research in renal physiology in animals, first working to find a way to retain penicillin in the body, which later led him and others to the development of diuretics. He was convinced that “the substance worth developing was one that would eliminate sodium, chloride, and of course water, but not bicarbonate.” His chemist colleagues created a number of substances similar to sulfanilamide, each of which had to be tested in animals for their diuretic effect. One of the most promising substances was altered chemically and “chlorothiazide (Diuril) was born.”

Beyer’s conviction that a diuretic would be beneficial in the treatment of hypertension was clearly backed up by years of work in renal physiology in animals, so the Greeks’ quotation is misleading. Beyer moved directly to patients (which would be impossible today) because of his long experience and strong hunch-not because the use of animals was unnecessary for the development of Diuril.

The following speaks for itself:

We did not assess the activity of chlorothiazide in hypertensive animals prior to clinical trial (p. 169).

As we have said many times and in many places, research with animals can certainly reveal basic functions and processes. However, predicting the response to drugs is not a basic process. A careful review of the history of antihypertensives, which we but briefly

did in *Sacred Cows and Golden Geese* proves beyond a reasonable doubt that animal-based research did very little to demonstrate to researchers that various drugs could be used to lower blood pressure. The references we used speak for themselves on this point. Almost any clinically relevant breakthrough can be traced back to some research that involved animals. But it is disingenuous to conflate any research with animals that was generally in the same area with research that actually led to the breakthrough in question. All modern-day Noble Prize winners have ridden in cars but riding in cars did not cause, in any way, the winning of the Nobel Prize.

Pediatric heart surgery

Morrison:

Another statement lifted out of context is the following: "The experiments are suggestive but not very conclusive. But if you are convinced the operation will work, I am convinced I know how to do it." This was surgeon Alfred Blalock's response to Dr. Helen Taussig's request that he operate on one of her desperately ill "blue babies." The Greeks quoted Blalock's isolated statement and interpreted it as proving that "Blalock's animal experimentation was a flop."

Taussig's little patients were blue because they were cyanotic, the scientific term for a bluish cast to the skin. This appearance results from low oxygen levels in the circulating blood. Oxygen in the blood corpuscles reddens the skin. The abnormal condition results from various developmental anomalies of the heart and the large vessels coming from it, such as narrowed pulmonary arteries that reduce the flow of arterial blood to the lungs where oxygen is transferred to it. Among the "inconclusive experiments" of Blalock and his super technician, Vivian Thomas, were those in which they had been trying to create cyanotic dogs for further studies on the benefits of a shunt they had devised. The shunt would bring additional blood to the lungs from an artery normally going only to the arm, the subclavian artery.

But Dr. Taussig had a little patient who could not wait for additional animal experiments to prove the efficacy of the shunt. So Blalock proceeded, actually guided by Thomas, who had done most of their experiments in dogs in an attempt to develop methods for anastomosing (suturing together) arteries. They were not yet certain, without further testing on dogs, of the physiological effects the shunt from the subclavian to the pulmonary artery would have when a surge of blood entered a cyanotic human infant's lungs. This is why Blalock thought his experiments were not yet conclusive. The effect was wonderful for the child. "Her condition was considerably better than it had been before the operation." Again, the Greeks' attempt to force the conclusion that animals cannot contribute to new advances in human medicine does not reconcile with the facts. Would any surgeon attempt such a drastic operation without considerable practice in suturing arteries together in animals, a new technique at the time? Blalock's team had already mastered this, thanks to their practice on dogs.

This is an appeal to sympathy or *ad misericordiam* fallacy. Bringing up sick children is a ploy to divert the reader's attention from the problem at hand (in this case the role of animals in an operation) to the plight of the child.

Taussig had been looking for someone to attempt this operation for some time. Many patients had been seen over that time and Taussig had learned more about the disease from them. From *Sacred Cows*:

Other surgical procedures, designed to correct congenital heart anomalies rather than conditions brought about later in life, ran amok because of the animal-model. Pro-vivisectionists cite the surgery for Tetralogy of Fallot (TOF) to justify funding more animal experimentation. Babies with insufficient oxygen in the blood to provide the healthy pink skin color are called "blue babies." In infants with TOF, blood bypasses the lungs, receiving no oxygen because of a malformation of the heart. Cardiologist Helen Taussig suggested a surgical correction of the problem to Alfred Blalock, a surgeon at Johns Hopkins. She based her suggestion on clinical observation and autopsy findings on the affected infants. Dr. Blalock attempted to simulate the condition in dogs by cutting out lung tissue. His results were poor, to say the least. Many animals became paralyzed. Trying to surgically mimic what is a naturally occurring disease in humans, Blalock's animal model was fundamentally flawed from the start. Dr. Blalock's experience led him to state to Dr. Taussig, "The experiments are suggestive but not very conclusive. But if you are convinced the operation will work, I am convinced I know how to do it."167

Despite his lack of success, Dr. Blalock felt the operation might be possible in humans based on Taussig's observations and his surgical expertise. Contrast his actual statement above with this quote from those profiting from animal experimentation, "The (animal) experiments were so successful and confirmed Dr. Taussig's theory so completely that Blalock felt he could venture to operate on one of the poor children."168

Typically, though Dr. Blalock's animal experimentation was a flop, promoters still credit it for the success, and throw in the plaintive term "poor children" for good measure! One of the animal experimentation lobbies' historical battle cries, "Which would you rather save--one blue baby or one brown dog?" refers to this sloppily rewritten version of history.

What we wrote was and is true.

There are several points to be made about what Morrison said above. Morrison seems to be saying we ignored the ability to suture an arterial anastomosis and that that ability was the key to the success of the operation. This is neither the historical fact surrounding the operation nor what we said. The operation as a whole was new, never before attempted in human babies. That was why it was dangerous. The Blalock-Taussig shunt was performed on November 29, 1944. Vascular anastomoses had been performed since 1897 when the first one was performed in humans by John Murphy. In the early 20th century Alexis Carrel had perfected the technique of triangulation for vascular anastomosis. Vascular anastomoses were not new as Morrison suggests. The first *subclavian to pulmonary artery anastomosis* was performed by Blalock in this operation but the

significance of this was the result, not the act. The actual suturing of the arteries was the same as it had been for decades. Successful repair of the condition known as coarctation of the aorta had already been accomplished using arterial anastomosis.

That being said, it was Vivien Thomas, a Black male technician in Blalock's lab that was actually a master of performing the technique, in dogs. He stood by and watched while Blalock operated on the child. Blalock himself was: "not a gifted technician" (Westaby and Bosher 1997); technician in this sense meaning *talent or skill with the use of his hands*. If one had wished for someone already a master of surgery in general or of suturing arterial anastomoses in particular, one would not have chosen Blalock. In fact, according to Nuland, Blalock had never performed the procedure in the dog lab relying on Thomas's experience instead (Nuland 1995). Nuland goes on to say that despite Thomas's success in the lab: "Whether or not such an increase of blood flow to the lungs would sufficiently help a cyanotic child would have to await the operations first trial on a real patient."

Another point is simply that a surgeon performs an operation, not a team. Yes, a team is needed to allow the performance of an operation; a team including an anesthesiologist, scrub nurse, circulating nurse, pump technician in the case of many heart surgeries, and other operating room personnel. An operation could not be performed without all these and many other people. But the surgeon does the actual cutting, dissecting, repairing, and suturing. How many times the surgeon's laboratory technician has performed the operation does not count as training by the surgeon. Such skills are not magically transferred. Blalock performed this surgery with no prior experience on dogs. To credit dogs for his ability to perform the operation on human babies borders on the mystical.

Conclusion

Due to the rather broad nature of some of Morrison's criticisms I cannot respond in sufficient detail to convince those that do not want to give a fair hearing to our position. I cannot even respond to all his points, as that would require a book in and of itself and this essay is too long as is. For those who desire a more in-depth explanation of our position we refer you to *Animal Models in Light of Evolution* or, if your background in science is meager, then *FAQs About the Use of Animals in Science*. *Animal Models in Light of Evolution* is not for the general public as was *Sacred Cows and Golden Geese* but for scientists and as such should be used by scientists when they criticize our position as it explains our position better than any lay-oriented book we have written. We also refer the reader to "Are animal models predictive for humans?" (Shanks, Greek, and Greek 2009)

Morrison's assertions are suspect or outright untenable for the following reasons.

1. The scientific literature, history of science, or our actual words does not support Morrison's assertions. Morrison is simply factually incorrect in many of his assertions and claims.
2. Upon analysis some of Morrison's criticism boils down to *I do not believe the Greeks*. Morrison has staked his reputation, career, and ego on the validity of using animals in research and drug testing. I seriously doubt there is any evidence that would convince him of the fact that animal models have been harmful in the past and have never been predictive for drug and disease response in humans.

3. Morrison uses fallacious reasoning including *ad hominem* attacks in making his points. This is inauspicious for the validity of his other arguments. Confusing facts with personal views betrays scientific objectivity. The issue of animals and science is not about personalities its about evidence.

4. The fact that Morrison makes use of personal communication for some of his reference material raises the question of why he would do this instead of relying on the scientific literature.

5. Finally, his definition of *out of context* does not stand up to scrutiny.

In the final analysis what all this really comes down to is the truth as can be ascertained from the scientific literature and critical thinking. We invite the reader to critically evaluate our words and the references they are based on and decide for yourself.

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Appendix

In biology many concepts are best evaluated by using simple statistical methods involving probability. For example, in medicine physicians can use a blood test to determine whether someone has liver disease. In order to ascertain how well this test actually determines the health of the liver we calculate the sensitivity and specificity of the test along with the positive predictive value (PPV) and negative predictive value (NPV). The sensitivity of a test is the probability (measured on a scale from 0.0 to 1.0) of a positive test among people whose test should be positive—those who do in fact suffer from liver disease. Specificity is the probability of a negative test among people whose test should be negative—those without liver disease. The positive predictive value of a test is the proportion of people with positive test results who are actually positive. The negative predictive value is the proportion of people with negative test results who are actually negative. This is all quite straightforward. Very few tests have a sensitivity or specificity of 1.0 or a PPV and NPV of 1.0 but in order for a test to be useful given the demanding standards of medical practice, in this case tell us if the patient actually has liver disease, it needs to be have PPV and NPV in at least the .90 to 1.0 range.

		Gold Standard	
		S+	S-
Test	T+	TP	FP
	T-	FN	TN

T+ = test positive

T- = test negative

T = True

F = False

P = Positive

N = Negative

S+ = standard positive

S- = standard negative

Sensitivity = $TP/TP+FN$

Specificity = $TN/FP+TN$

Positive Predictive Value = $TP/TP+FP$

Negative Predictive Value = $TN/FN+TN$