

## Response to criticisms from *Orac*

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### ***Introduction***

Recently, someone who goes by the pseudonym *Orac* published an [essay](#) on the use of animals in research. As some of the criticisms in the essay are not unique, I will respond to them here. Because the *Orac* essay is so long, >7400 words, and many of the accusations have been addressed numerous time in various publications (see (Shanks and Greek 2009) and (Greek and Shanks 2009) for a more complete explanation of our position), I will address only some of the criticisms here. I have grouped *Orac*'s criticisms into the broad categories in the table of contents above. The *Orac* quotes are from the essay linked to above.

### ***Animal-based research is not predictive***

*Orac*:

If you examine various websites or literature from animal rights extremists looking at the issue of animal use in medical research, the forms of the scientific arguments tend, when you boil them down to the very core of their essence, to take three main forms, which are related . . . Animal research **does not predict human physiology** or response to disease, or animals are "just too different from humans to give reliable results" (*i.e.*, it is bad science).

I agree with *Orac* when he says that some people, including us, take the position that animal models cannot predict human response to drugs and disease. Our book *Animal Models in Light of Evolution* (Shanks and Greek 2009) explores that very topic in depth and our other books and article address to a lesser degree (Greek and Greek 2004; Greek and Greek 2000; Greek and Greek 2002; Greek and Shanks 2009). For a thorough examination of the issue I refer the interested scientifically educated reader to *Animal Models in Light of Evolution*. Essentially everything I have to say here on the subject is a very condensed version of what can be found in *Animal Models in Light of Evolution*.

The use of animals in science can be criticized on essentially two fronts. 1. It simply does not work. For example, if one is trying to predict human response to drugs or

disease, animal models fail. 2. There are alternatives to using animals that work as well or in some cases better than using animals. The second criticism implies or explicitly states that the use of animals in certain areas *is* scientifically viable. If the animal rights movement wishes to remove animals from these endeavors then replacements must be found or animal rights as a philosophy must be accepted. Such is not the case with number 1, however. If a modality, be it a research method or weapon or means of transport, is ineffective it should be abandoned regardless of what else is available. No one argues, for example, that we should use Ford trucks to accomplish space travel as the Ford truck, a good product thought it may be (I drive one), is simply not viable for going to the moon or Mars. Orac, throughout his essay, conflates the viable use of animals in some areas of science and research with animal use in other areas where it is simply not viable. It appears this is done in order to justify using animals in the areas where it simply does not work—as predictive models—as that specific area is how animal experimentation is sold to society.

Orac is also right when he says 100% perfection is difficult to obtain. (Actually it is difficult to obtain in the biological sciences, but less so in the physical sciences.) Regardless, very few uses of animals in science demand 100% perfection. However, the use of animal models to *predict* human response requires a positive predictive value (PPV) and negative predictive value (NPV) that is very high (probably greater than 0.9). (For more on PPV and NPV see (Shanks and Greek 2009). For a brief review, see the Wikipedia [posts](#) and the links to sensitivity, specificity, and negative predictive value therein.) We have never criticized the use of animals as bioreactors because they failed to produce a 100% pure product or the use of pig valves to replace aortic valves in humans because they occasionally fail. I doubt many people have criticized them on this basis. I have criticized animal models as having a low PPV and NPV and thus not being predictive.

Orac criticizes the prediction argument in part because: “cell culture models tend to be even less predictive of many responses than animal models for many questions and because much physiology depends upon the interaction of different cell types in their native three dimensional matrix.” This reveals a fundamental misunderstanding of what prediction in science means and specifically the role of PPV and NPV in medical science. If a test or modality fails to have a high PPV and NPV then it is not used in medicine as a predictive tool. Medical science requires certain PPV and NPV values. Lives are at stake. Not all scientific endeavors require such high predictive values, but medical science does. (For more on this see *Animal Models in Light of Evolution* (Shanks and Greek 2009)). If other tests perform worse than animal tests, all that such performances signify is that the nonanimal tests are not predictive either.

Orac continues this theme:

. . . for a computer model to be adequately predictive, it needs (1) sufficient information to input and (2) sufficient understanding of the intricacies of the physiology and biochemistry. We don't have either.

This is a sweeping generalization. There are computer models (a very broad phrase by the way) that predict human response but Orac is correct in saying computer models *per se* are far from predicting human responses to drugs and disease. But then no one in the

*scientific* community (such as myself) is claiming computer models *per se* are currently capable of predicting human response to new drugs or diseases. The *future* of drug development however is in DNA chips (computer modeling of a sort) which, when science knows more about drug-gene interactions, will be used to predict the responses of individual humans. (This is being done to a limited degree already.) But the above criticism misses the point as once again just because modality A (for example computer modelling) fails to be predictive does not *ipso facto* mean modality B (for example animal modelling) is predictive.

Orac then states that: “Finally, physiology requires understanding at the macroscopic level of how organs interact.” Yes, but in the case of drug testing and disease research, the macroscopic level we are interested in is that of the human, not dogs, rats, or monkeys. How a drug performs in these animals or how a disease affects these animals is not predictive for humans. For that matter how one human reacts to a drug is not necessarily a good indicator of how another will (See section on personalized medicine in *Animal Models in Light of Evolution* (Shanks and Greek 2009) and or the following references (General Accounting Office 2001; Holden 2003; Weinshilboum 2003; Kaiser 2005; Penny and McHale 2005; Simon 2005; Mann 2006; Risch 2006; Couzin 2007, 2007; Spielman et al. 2007; Willyard 2007; Weiss et al. 2008; Bhatt 2009; Cosio, Saetta, and Agusti 2009; Shuldiner et al. 2009; Willyard 2009).) The fact that animal models cannot predict human response to drugs and disease is simply not controversial in scientific circles acquainted with the topic.

Orac:

. . . the problem inherent in this sort of argument is that one has to look at what the alternatives to animal research are and compare their usefulness, accuracy, and reliability.

This is simply not true when discussing prediction. Again, we are back to the use of a truck to achieve space travel. We do not justify attempting to use trucks to go to Mars by saying that using spoons and forks works even less well. If a modality is supposed to predict human response vis-à-vis a high PPV and NPV then failure to do so means the modality has failed; regardless of alternatives. The same argument Orac is making could be made for using a Ouija board to decide whether to market drugs. Someone could say that since no modality currently exists that can predict (via PPV and NPV) human response and if the Ouija board correlates with human response say 30% of the time and if this is the highest correlation of all modalities, then we should use it. The point is that 30% correlation, even if it is the highest of all modalities, is inadequate and should not be used, much less relied upon, when risking human health. Orac is setting up a false dichotomy between animal tests and nonanimal tests. Neither currently predicts human response. If society really wants safer medication *now* then the only solution is longer and broader clinical trials. That will work. Combine that with more research using DNA chips and matching drug response to genes and society will have safer, more effective, and *cheaper* medications. Personalized medicine (per the references above) via research on humans and human tissue is the way that is being, and will continue to be, accomplished.

Orac:

If one can't show that one's alternative is better than animal research, then all the complaints about the imperfections of animal research don't amount to much. It's still the best that we have, and, as such, it's bad science (and unethical, to boot) not to use it before trying therapies in humans.

Here Orac is saying the way animals are used in predictive research is actually useful for that purpose. For refutation of this see the above and (Shanks and Greek 2009; Shanks, Greek, and Greek 2009). *In this sense*, yes, I say such animal-based research and testing is *useless*. Conflating this instance of *uselessness* with the various other uses of animals, especially after we have said multiple times that such uses *are* viable, is disingenuous and casts doubts on everything Orac says. (I will address where animal use is viable in a moment.)

Orac:

I have yet to see a compelling argument that any alternative modality predicts human response to disease and treatment well enough that we should rely on it instead of animal models.

This statement assumes animal models are predictive. They are not.

Orac discusses the use of animals in the drug development process. The rationale for using animals is to weed out drugs that would harm humans or not be effective in humans and to assure the human subjects participating in the initial trials that the drugs are safe. All of these are examples of using animals as predictive models. In science there is no such thing as being *a little* predictive. If there were, then astrology and palm reading would qualify as being a little predictive. See (Shanks and Greek 2009) for more on this.

Orac:

Rather, animal studies should be best viewed as the first test of a new drug or treatment on a whole-organism level in order to look for unexpected, toxic, or other effects that might not be apparent in cell culture. In other words, animal tests are a *screening* process, not a substitute for human studies.

Yes, they are screens but screens for *humans*. Orac assumes prediction when saying animals are used to look for unexpected, toxic or other effects. The drug companies are not looking for toxic effects in rats, they are looking for toxic affects in humans and using the rats as predictive models. This point is not controversial nor is the fact that the pharmaceutical industry and the regulatory bodies acknowledge that animals fail in this process (Abbott 2005; Albani and Prakken 2009; Alonso-Zaldivar 2006; Barnes and Hayes 2002; Björquist and Sartipy 2007; Booth, Glassman, and Ma 2003; Browne and Taylor 2002; Butcher 2005; Collins 2001; Dixit and Boelsterli 2007; Eaton et al. 2007; Editorial 1997, 2003, 2005, 2005; Farde 1996; FDA 2004, 2006; Gao et al. 2006; Gura 1997; Harris 2006; Horrobin 2003; Hughes 2008; Hurko 2000; Kirkpatrick 2006; Kola and Landis 2004; Leaf 2004; Littman and Williams 2005; Lord and Papoian 2004; McGee 2006; Neubert, Webb, and Neubert 2002; Palfreyman, Charles, and Blander 2002; Roos 2002; Sankar 2005; Schachter 2007; Schnabel 2008; Seligmann 2004/5;

Smallwood and Richards 2003; Walton, Dorne, and Renwick 2004; Wang and Urban 2004). Pretending that scientists in the drug industry use animals for something that in the long run is other than prediction goes against what the industry itself says it uses animals for.

(If Orac wishes to pursue the claim that animal models *are* predictive in drugs and disease research, I suggest we take this discussion to the peer reviewed literature. I have been offered an opportunity to debate this topic in a Point-Counterpoint in an indexed, peer-reviewed journal and hope Orac will take this opportunity to make these claims in an arena where the rules of engagement, such as the need for references, are well known. I have already made this offer to another blogger-scientist ([David H. Gorski](#), MD, PhD, FACS a surgical oncologist at the Barbara Ann Karmanos Cancer Institute) that made [essentially the same criticisms](#) (the rhetoric is verbatim in places leading me to think Orac *is* Gorski) but he declined the invitation. To decline the opportunity to take this discussion to the peer review scientific literature for a proper scientific analysis speaks for itself.)

Orac uses as an example of the validity of animal models the use of animals in smoking research. If I were going to give examples showing the successes of the animal models I would not pick smoking and cancer. From *Human Epidemiology and Animal Laboratory Correlations in Chemical Carcinogenesis*.

For decades the clinical observation of an association between cigarette smoking and bronchial carcinoma was subject to unfound doubt, suspicion, and outright opposition, largely because the disease had no counterpart in mice. There seemed no end of statisticians craving for more documentation, all resulting in the fateful delay of needed legislative initiative. [(Clemmensen and Hjalgrim-Jensen 1980) p263]

Orac also uses as an example of the validity of animal models the use of animals in stroke research. Once again, if I were going to give examples of the successes of the animal models I would not pick treatments for stroke. Jonas et al.: “Agents claimed to be neuroprotective in animal stroke models have all failed in human trials (Jonas et al. 2001).” Stroke is one area even animal-based researchers use to point out the shortcomings of the animal model.

We demand from animal models the same thing we demand from any other modality that claims to be predictive—a high PPV and NPV. This is standard in medicine and medical care. It appears that what Orac is trying to do in the article is conflate basic research, which is not supposed to be predictive or even goal oriented with research that uses animals and frankly claims to be predictive. The use of animals in self proclaimed nonpredictive ways is not our issue. Our issue is with the claim that animals have a high PPV and NPV when predicting human responses to drugs and disease. By conflating the two areas of research, Orac can point to successes in one and claim the other is also valid.

But let me state again and for the record: no modality currently exists for predicting drug response in the individual human except where genes have been discovered that are responsible for certain effects. Read the pharmaceutical industry’s literature (cited above) and this will be confirmed. Indeed most of the references above mention this fact. The pharmaceutical industry is dying for lack of predictive models (Harris 2006). What we

are simply pointing out is that if you want to predict responses in humans you had better use human-based data.

The issue I have with this portion of Orac's position is very straightforward. We maintain that animal models are not predictive for human response to drugs and disease and the scientific literature supports this position. When Orac criticizes this position he either conflates using animals as predictive models with other uses or is disingenuous when defining prediction in medical science.

### ***The value argument***

Orac claims that some animal rights people maintain that animal-based research is useless, does not give society anything of value, and is misleading. This accusation is, at least in part, a straw man as no one in the scientific community that opposes using animal models on scientific grounds makes this claim. If I am wrong and there are qualified people who make this claim then they are simply zealots and should be treated as such.

But let's examine the claims one at a time. Orac claims that some people say: "Animal research doesn't teach us anything of value or even misleads us (*i.e.*, it is [bad science](#))." These two points are quite separate and distinct. It "doesn't teach us anything of value" is not something I claim. I have claimed that it "misleads us" and have given numerous examples where large numbers of lives were lost as a result of extrapolation from animal to humans. I am not alone in this accusation. The following is something I wrote for a blog that appears on [Opposing Views](#):

#### Research with animals is misleading

In our books (Greek and Greek 2004; Greek and Greek 2000; Greek and Greek 2002; Greek and Shanks 2009; Shanks and Greek 2009), we have said many times that research with animals is misleading. For example, drugs that would not have harmed humans did harm mice and were consequently not put on the market. The National Cancer Institute has stated that society may have lost cures for cancer because of animal testing. (Gura 1997) Researchers working with monkey models of HIV tested a vaccine on the monkeys and subsequently gave the vaccine to humans who were harmed as a result. These examples infuriate people in the animal-based research community. The following will too.

An article by Greber et al. (Greber et al. 2010) at the Max Planck Institute for Molecular Biomedicine in Münster reveals that work with stem cells from mice "are often pointless -- and sometimes even misleading"(Max-Planck-Gesellschaft 2010). This is not say mice and humans have nothing in common. Even their stem cells have things in comon. But it is the differences that are important when trying to extrapolate research results to a different species. "In other aspects, though, as scientists have known for some time now, human and mouse ES cells differ enormously. Certain signalling substances that can be used to turn mouse cells into liver, nerve or muscle cells, for instance, produce either no effect or totally different effects in human ES cells "(Max-Planck-Gesellschaft 2010). And there are more differences.

Hans Schöler, a co-author of the study, states "Ultimately, what this means is that many preliminary tests on animal cells -- particularly in medically relevant projects -- may not only be useless, but the findings from this kind of early testing may even be misleading . . . Particularly when we're talking about developing safe and effective stem cell therapies, we will still need human ES cells as the gold standard against which to compare everything else. In such cases, lengthy preliminary testing on animal cells risks wasting valuable time and resources." (Max-Planck-Gesellschaft 2010)

Society has faith that animal testing informs scientists about humans. Such faith is misplaced.

The fact that animal models can mislead scientists is not controversial in scientific circles acquainted with the topic.

But onto the value argument. *Value* depends on purpose. Counting the number of hairs on a dog is not science (Curd and Cover 1998). Counting the number of hairs on a dog suffering from alopecia in order to judge a treatment is science. One has scientific *value* while the other does not. Research with animals has many values. It brings in income for the university and the researcher, it generates knowledge, it might shed light on principles common to a set of living things and so on. But this is very different from being of value because the modality predicts human response to drugs and disease. This ties in to the below.

Orac furthers the *value argument* by accusing us of making what he calls the "argument from imperfection." Namely, that we claim that since animal models are not perfect they are therefore useless. First, there is a very big difference between what Orac here claims we say and what we actually say. It is spurious to lump concepts together so that if one is proven or disproven, then the reader will make the leap that all have been. We have consistently broken down the use of animals in science into nine areas:

(1) as predictive models for human disease; (2) as predictive models to evaluate human exposure safety in the context of pharmacology and toxicology (e.g., in drug testing); (3) as sources of 'spare parts' (e.g., aortic valve replacements for humans); (4) as bioreactors (e.g., as factories for the production of insulin, or monoclonal antibodies, or the fruits of genetic engineering); (5) as sources of tissue in order to study basic physiological principles; (6) for dissection and study in education and medical training; (7) as heuristic devices to prompt new biological/biomedical hypotheses; (8) for the benefit of other nonhuman animals; and (9) for the pursuit of scientific knowledge in and of itself. [(Shanks and Greek 2009) p30]

Even nine is too few but it makes an otherwise unmanageable topic manageable. In seven of the nine areas (#s 3-9) we readily acknowledge that animal use *is* scientifically viable hence useful. There is no argument from imperfection here. The point we consistently make is that one cannot analyze the use of animals as bioreactors (#4) and then make a claim about the use of animals as predictive models for drug testing (#2). There is no one scientific argument for or against using animals that applies across all nine areas. Attempts at conflation are not productive when the goal is to further mutual

understanding and increase education.

Orac:

In other words, because animal models have many difficulties and flaws and all too often don't predict human physiology or drug response as well as the critics think that they should, then by implication *all* animal research is bad science.

This is precisely the opposite of what we have said. For example:

This book is not intended to be a criticism of the use of animals in the context of basic biological research. There can be no doubt that careful studies of animals have prompted important hypotheses about basic biological principles, and there can be no doubt that studies of animals have contributed greatly to our scientific understanding of life, and there is little doubt that these studies will continue to illuminate these matters in the future (items (7) and (9) above). [(Shanks and Greek 2009) p30]

We are about to begin a detailed analysis of the roles played by animals in biomedical research. This is a good place to make clear, once again, what we are interested in, and what we are not. There can be no doubt whatsoever that if you wish to make discoveries about rats and mice you will be forced of methodological necessity to perform careful scientific studies of *R. rattus* and *M. musculus* respectively. In fact, in writing this book, we are the beneficiaries of the results of careful scientific studies of animals. There is no doubt that careful biological studies of rats and mice can help clarify the general contours of mammalian biology. Such studies can also play a valuable heuristic role by prompting new ways of thinking about human biological problems of interest. The issue we are concerned with is this: notwithstanding these cautions, are animal models predictive of human outcomes in, say, toxicology, drug discovery, and the study of the causes and cures of human diseases? (Ibid. p28)

We remind the reader once again that the target of our criticism of animal-based research is restricted to the practice of predictive modeling. We do not dispute that there are legitimate roles for animal test subjects in other kinds of experimental investigation—for example basic biological research aimed at increasing the sum total of human knowledge. Animal experiments in the context of basic research may enrich our knowledge of specific phenomena in mice, and, if painting is permitted with a broad enough brush, they may help delineate some of the important contours of mammalian biology, from which lessons about the Eukaryotes and even life itself might be forthcoming. (Ibid. p351)

Despite all we have written on the topic, the accusation that we claim that animal-based research teaches us nothing of value is not uncommon. Janet D. Stemwedel, a co-participant in a recent panel discussion at UCLA [wrote](#):

The next panelist to speak was Ray Greek, president of Americans for Medical Advancement. He asserted that animals are too different from humans to tell us anything useful about humans, and suggested that this is why so few basic research studies end up resulting in knowledge or therapies that are useful in treating human patients.

The refutation of Stemwedel's statement is easy as the readers can [view the panel discussion](#) and judge for themselves what I said. The reader can also read our books or attend one of my lectures where I frequently use the *Hox box* as an example of where research with animals was of great value in informing us about humans. In other words, it was useful. In any event, I can only conclude that the reason people consistently accuse us of taking this position, despite clear evidence to the contrary, is because they cannot refute the positions we do take.

Orac:

It is an example of demanding 100% perfection or certainty, a bar that no science can ever meet and of concrete thinking typical of extremists. (Creationists and "alternative" medicine mavens are particularly fond of this sort of argument against their hated "Darwinism" or "allopathic" or "conventional" medicine--usually said with a sneer--respectively.) In its most ridiculous form, [this argument](#) takes the form of claiming that cell culture and computer models, [among other modalities](#), can give us the same information without animals.

By lumping us together with creationists and believers in alternative medicine, Orac seeks to condemn us using *guilt by association* without actually proving his/her points. The actual claim that I make, I am not here representing others, is that animal models are not predictive for humans and that basic research of some types can be accomplished without using sentient animals.

Orac:

One example of this type of argument [that animal models are not predictive] I've seen comes from, of all places, a 2008 issue of [Skeptic](#), in which animal research opponents Niall Shank (a professor of philosophy who, oddly enough, authored a [book critiquing intelligent design](#)),

Niall Shanks is definitely *not* an opponent of using animals in science. His only issue with the process is the prediction issue which we discussed in the aforementioned article and elsewhere (Shanks and Greek 2009; Shanks, Greek, and Greek 2009). Shanks eats meat, wears animals and so forth. Shanks is about as far from an animal rights activist as one can be. This is a typical *ad hominem* attack and has no place in a scientific discussion. If Orac were conducting a scientific discussion in the scientific literature such attacks would not be allowed.

Orac:

Dr. [Ray Greek](#) (an anaesthesiologist and President of Americans for Medical Advancement, Europeans for Medical Advancement, and Japanese for Medical

Advancement, all facets of a [single group](#) that appears to be totally opposed to animal research in medicine),

AFMA et al. are indeed facets of a single group (although we have recently dropped JFMA) but are not totally opposed to using animals in research. Simply reading the website ([www.afma-curedisease.org](http://www.afma-curedisease.org)) would have informed Orac of that fact. The official position of AFMA is that while animals can be scientifically viable in certain areas of science they are not predictive models for human disease and drug response.

I will not give more examples or go into more depth regarding our position on this aspect of Orac's criticism, but rather refer the reader to any of our books or articles (Greek and Greek 2004; Greek and Greek 2000; Greek and Greek 2002; Greek and Shanks 2009; Shanks and Greek 2009; Shanks, Greek, and Greek 2009; Shanks et al. 2007). The above examples, which constitute proof, that what Orac claims we say has nothing in common with what we actually say should settle the question of whether Orac has an agenda in writing this essay and go a long way to proving that all other comments should be taken with a grain of salt.

I should take this opportunity to point out that Orac used some of the essay to respond to animal rights activists who, to the best of my knowledge, have no scientific credentials or training. While I respect the right of all to speak and comment on whatever they wish, I think anyone claiming to want a serious scientific discussion should address only positions taken by her scientific peers. On the other hand, perhaps people without scientific training should enlist the aid of those of us with such training rather than make statements they cannot legitimately defend. Both sides in this case seem to be motivated by emotion instead of critical thought.

Orac addresses two specific example of using animals in research and it is thus to heart surgery in infants and angiogenesis inhibitors that I now turn.

### ***The Blalock-Taussig operation***

Orac attributes the development of the Blalock-Taussig heart operation, performed on children suffering from a congenital anomaly known as Tetralogy of Fallot to operations on animals. He is not alone in this attribution. Animal model advocate Adrian Morrison stated more or less the same about the operation in his book *An Odyssey With Animals* (Morrison 2009). Orac specifically mentions the work in surgeon Blalock's lab of an assistant named Vivien Thomas.

The argument that operations on dogs made possible the operation on infants is an old one and relies heavily on an appeal to sympathy or the *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.

Cardiologist Helen Taussig was primarily responsible for planning the operation and she 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 and from autopsies. From our book, *Sacred Cows and Golden Geese*:

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.” (Taussig 1981) p159]

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.” [(Glaser 1961) p59]

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 the traditional argument that Orac and others make. First, the animal model advocates seem to be saying we ignored Blalock's ability to suture an arterial [anastomosis](#), which they claim was an animal-based breakthrough, and that that breakthrough 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. This was followed in the early 20th century by Alexis Carrel who perfected the technique of triangulation for vascular anastomosis. Vascular anastomoses were not new as some suggest. 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 also already been accomplished using arterial anastomosis.

That being said, the animal model advocates are correct in pointing out that it was Vivien Thomas, a Black female technician in Blalock's lab that was actually a master of performing the technique in dogs. However, while they are right in what they confirm they are wrong in what they deny. Specifically they fail to mention the fact that Thomas *stood by and watched* while Blalock operated on the child. Thomas's skills were not magically transferred to Blalock who, as his own colleagues acknowledged was: “not a

gifted technician” (Westaby and Boshier 1997). 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.

### ***Angiogenesis and angiogenesis inhibitors***

Orac addresses the work of Judith Folkman on angiogenesis so I will now comment very briefly on that topic. Angiogenesis is a complicated topic and, as this is an essay written for a general audience, my discussion will be far too superficial for experts in the area. The general points however, I believe, will stand up to scrutiny from honest evaluators.

In order for cancers to grow they must be supplied with the nutrients blood brings hence new blood vessels are required. These vessels are encouraged to grow by various chemicals including one called vascular endothelial growth factor (VEGF). If VEGF can be blocked or inhibited then the cancer will not receive the oxygen and nutrients it needs. It was this concept that drew Folkman’s attention. Holaday and Berkowitz:

Folkman observed that the tumors he removed from his patients were "hot and bloody" and highly vascular. It was the relationship between tumors, blood vessels, and blood supply that he chose to attack. (Holaday and Berkowitz 2009)

Already we are seeing that Folkman’s initial interest in this subject came from patient observation. That having been said, Brem and Folkman did use animal parts to show that angiogenesis factors occurred naturally in the body (Brem and Folkman 1975). The rabbit cornea was used as an assay but why human corneas could not have been used is not clear and in all likelihood they could have been thus calling into question the necessity of using animals parts in this instance.

Holaday and Berkowitz:

In 1971, he [Folkman] published a landmark paper (Folkman 1971), noting that the tumors were typified by new blood vessels. He reasoned that the tumors "recruited the vessels by sending out some factor that... was diffusible; these diffusible proteins would bring in the vessels, and *if you could turn this process off the tumors should stay... small*" (emphasis added). This hypothesis is considered today by most students of the field as a "cornerstone" concept (Figure 1), but at the time of its publication, it struck many as heretical. The search to identify pro- or anti-angiogenic factors as well as antiangiogenic drugs would be long, arduous, contentious, competitive, and expensive. In 1986, Folkman colleague Mike Klagsbrun reported the isolation and purification of the angiogenic factor known as basic fibroblast growth factor (bFGF) (Klagsbrun et al. 1986). In a landmark twenty-three million dollar grant and license agreement with Harvard, bFGF was licensed to Monsanto. The deal included both support and access to Folkman's discoveries, but three decades of research failed to translate bFGF into an angiogenic therapeutic. (Holaday and Berkowitz 2009)

The process that led to anticancer drugs and other angiogenesis inhibitors was “long and arduous.” Animals *were* involved in this process. Animals are involved in about every biomedical scientific process. But association does not imply causation. What one learns from an in depth examination of Folkman’s career and the development of angiogenesis inhibitors is that results from animal models sometimes correlated with humans but often did not. This gets us back to the *misleading* concept. Any analysis of historical events is colored by present knowledge. It is easy to look back and reconstruct history using only the times animal models correlated with humans to build a fictitious account of why animal models were vital to the process. It is also almost as easy to point out only the times the animal models misled scientists thus concluding that they were of no value. Both fictions would be wrong. But finding the truth of what role animal models played and what role they did not play is very difficult and one must navigate between the Charybdis of giving them too much credit and the Scylla of giving them none at all. (For a good example of this see [my essay on the making of the polio vaccine](#), which should be online sometime in 2010.)

The discovery of first angiogenesis inhibitor drug candidate was serendipitous. Holaday and Berkowitz:

In 1990, about the time that interferon alpha provided the first proof of concept that compounds with antiangiogenic activity could treat tumors in patients (White et al. 1989), Judah Folkman and Donald Ingber discovered their first antiangiogenic drug candidate in a sequence of events that was somewhat reminiscent of Fleming's discovery of penicillin. As Ingber was growing endothelial cells, one of his cultures became contaminated with a fungus that he reasoned might be releasing an antiangiogenic substance (Ingber et al. 1990). Ignoring a general rule that contaminated cultures were not evaluated, Ingber was intrigued and moved ahead with characterization of the antiangiogenic activity, re-discovering fumagillin, a fungal derivative originally discovered in the 1950s . . . However, in their follow-on studies, it was observed that the prolonged administration of fumagillin resulted in severe weight loss. Subsequently, in 1992, Takeda isolated an active component of fumagillin and synthesized an analog, TNP470, for further clinical evaluation. Unfortunately, after over a decade of research and development, TNP470 was not commercialized for human use, in part due to neurotoxicity, although fumagillin and its analogs continue to attract high interest, particularly for anti-parasitic uses. (Holaday and Berkowitz 2009)

Two of the early angiogenesis inhibitors that showed good results in animals were angiostatin and endostatin, neither of which made it to market. Many angiogenesis inhibitors went to clinical trials but never made it to the marketplace (Twardowski and Gradishar 1997). Perhaps other viable angiogenesis inhibitors were derailed because of animal models. Twardowski and Gradishar:

TNP-470 is an analogue of fumagillin, a naturally occurring antibiotic secreted by the fungus *Aspergillus fumigatus* fresenius. It was found to inhibit proliferation of

endothelial cells; however, the side effect of severe weight loss in treated animals limited its use. The synthetic derivative of fumagillin, TNP-470, was 50 times more active in its inhibition of endothelial cells and had no major side effects in initial laboratory testing. (Twardowski and Gradishar 1997)

Avastin (bevacizumab), which binds to and blocks human VEGF but not the mouse version, was approved for the treatment of colorectal cancer in humans in 2004 (Hurwitz 2004). In contrast to bevacizumab, two antibodies B20-4 and G6 bind and block both human and murine VEGF (Fuh et al. 2006). Had bevacizumab been tested for efficacy on mice and the results believed to apply to humans, we would never have had the drug. That notwithstanding, bevacizumab is the human version of A.4.6.1 and was derived from mice by immunizing mice with human VEGF. So mice did play a role in its development. (We have never said animals such as mice *cannot* be used as bioreactors.) However, researchers can discover new antibodies without using hybridoma technologies by using for example phage libraries. (Fuh et al. 2006)

Folkman himself admitted that mice are not humans when it comes to drug results. In fact in the first clinical trials angiogenesis inhibitors that had worked well in mice failed in humans. Not surprisingly, interspecies variability in metabolism was also found (Placidi et al. 1997). Cimons et al.:

Researchers note that as many as nine other drugs acting on the same basic principle--and that also cure cancer in mice--are in clinical trials in humans. So far, the results haven't overly impressed physicians. "This is not penicillin," said Dr. Lee Rosen of UCLA's Jonsson Comprehensive Cancer Center . . . "The history of cancer research has been a history of curing cancer in the mouse," said Dr. Richard Klausner, director of the National Cancer Institute. "We have cured mice of cancer for decades--and it simply didn't work in humans." . . . Dr. LaMar McGinnis, an oncologist and medical consultant to the American Cancer Society, agreed. "We thought interferon was 'chicken soup' in the early '80s," he said. "I remember how excited everyone was; it seemed to work miracles in animals, but it didn't work in humans." . . . The new miracle cure involves a phenomenon called angiogenesis. More than 30 years ago, a young physician named F. Judah Folkman at Children's Hospital in Boston discovered that tumors secrete chemicals that stimulate the growth of blood vessels into the mass of tumor cells, or angiogenesis . . . But he [Folkman] has been working with proteins obtained from mice. The Maryland company that he is collaborating with, Entremed, has been trying to produce the human form of the proteins, but is still short of that goal. "People do not understand how very far off this [clinical trials] is; these proteins are very difficult to make . . . and we are working very hard to make the human versions," Klausner said. "The mouse versions don't work in humans." Nevertheless, said Dr. Allen Lichter of the University of Michigan, president-elect of the American Society of Clinical Oncology, "I haven't had a single patient who hasn't asked me about this," he said. "It's certainly on everyone's mind. But I have to tell them, honestly, that I don't know if it will work in humans." (Cimons, Getlin, and Maugh\_II 1998)

It should come as no surprise that angiogenesis inhibitors are species specific, as well as strain specific (Rohan et al. 2000; Huszthy et al. 2006), as angiogenesis itself is strain specific (Thurston et al. 1998; Gao et al. 2002; Rohan et al. 2000).

*Forbes* magazine published an article in their December 27, 1999 (p190) issue about why new inventions and discoveries don't pan out. They singled out the failure of drug companies to find a drug to treat sepsis and cancer in humans in part on believing animal experiments.

Each [drug company] had a drug that targeted one or another link in the supposed chain – endotoxin, the irritant spewed out by invading bacteria; tumor necrosis factor, which the body deploys against bacteria; interleukin-1, a chemical signal by which the body marshals all its weapons. All seemed to help in animal models of sepsis and Wall Street entertained high hopes. Indeed, the main question for investors was not whether the drugs would work, but which would work first. None did. In several cases the drugs were so much worse than the sugar pill given as an experimental control that the trials had to be cut short... “We don't know what went wrong,” says R Phillip Dellinger, a specialist in critical care medicine at Rush-Presbyterian-St. Luke's Medical Center in Chicago, who headed a panel that investigated the problem. “The animal models may have been inappropriate; we may have been treating the wrong patients.”...[Speaking about the hype that accompanies discoveries] Sometimes, it's enough to just repeat yourself loudly – as, for instance, on the front page of the *New York Times*. Last year an article in that sensitive place informed readers that Judah Folkman and his company, Entremed, were going to cure cancer “in two years.” Aside from that appeal to authority, the article reported nothing that had not already appeared in an understated piece the *Times* had run months earlier, a summary from the British journal *Nature*. No matter that no controlled trials in humans had yet been completed. No matter that encouraging results in rodents had been found in countless cancer studies that ended up failing in humans.

Many discoveries, including discoveries impacting on the angiogenesis inhibitors, were made using animals or tissues from animals. There is no doubt some could have been made without using animals or animal tissue. For example:

In June 1989, Ferrara and Henzel reported the isolation of a diffusible endothelial cell-specific mitogen from a conditioned medium of bovine pituitary folliculostellate cells, which they named VEGF, to reflect the restricted target cell specificity of this molecule. NH<sub>2</sub>-terminal amino acid sequencing of purified VEGF proved that this protein was distinct from the known endothelial cell mitogens such as FGF-2 and indeed did not match any known protein in the available databases (Ferrara & Henzel, 1989). Subsequently, Connolly et al (1989) reported the isolation and sequencing of human VPF from a hepatocarcinoma cell line. (Ribatti 2005)

Exactly which discoveries would have been made without using animals can be analyzed but such an analysis regardless of what it revealed would not settle the matter for at least

one side in the debate; the side that perceived it had lost.

Finally, it should be noted that while angiogenesis inhibitors are of great value for some but they are not a panacea:

Antiangiogenic drug development is no exception, with data demonstrating that resistance to Avastin occurs within a few months after administration (27, 28). Indeed, over twenty different stimulators of angiogenesis exist, including various forms of VEGFs and FGFs. Blocking one of them with a specific antibody doesn't block them all, and some may be overexpressed when VEGF is blocked or neutralized. The molecular pharmacology and details of the specific pathways involved in antiangiogenic drug resistance are being increasingly characterized. (Holaday and Berkowitz 2009)

Several points can be made about the development of angiogenesis inhibitors, as well as about the development of most breakthrough drugs and discoveries.

1. Serendipity, *in vitro* research, human observation and various other nonanimal modalities played a vital role in the process.
2. The results from animal studies misled researchers many times and animal models did not predict human response to specific drugs.
3. Animals *were* involved in the process. But were the roles animals played vital? Could the breakthroughs have been made without animals? The answers to these questions are far less clear and propaganda exists on both sides of the debate. Another related point is the fact that if most of the research on the subject was conducted on animals then it should come as no surprise that most of the basic knowledge came from animals. If the primary method of mining used in the world was strip mining then most of the mineral brought up would be from that particular method. That is not to say that other less destructive methods could not have accomplished the same result. Merely that it would be a historical fact that strip mining had accomplished the extraction of the minerals. In the final analysis, the burden of proof in science is on the claimant, in this case the person claiming the breakthrough in question could not have been made without animals.

The role that animals are capable of playing and hence should play in current research efforts is not likely to be solved by analyzing past breakthroughs. 1. Historical analyses are fraught with revisionism and, if most of the major researchers are still alive, the financial factor (and ego) will rear its ugly head. 2. Technologies change as more advances are seen every year and this has a large impact on how research should be conducted. 3. The questions being asked also change. Today research leading to personalized medicine or gene-based medicine is probably the most important research being conducted. The linking of genes to diseases and genes to drug effects is a human-based endeavor.

Instead, research methods should be evaluated in terms of our current knowledge of the material universe and, something that has been historically neglected, against the background of evolution—which methods are in conflict with our knowledge of evolutionary biology and which are not? Such an evaluation would highlight the need for: 1. easier access to human tissues; 2. easier (with better safeguards for confidentiality so privacy assured) access to human medical records so researchers can use them; and 3.

better informed, more reliable, and more consistent Institutional Review Boards (IRBs). Many researchers that use animals admit the reason they do so is convenience as IRBs are notoriously hard to work with (Infectious Disease Society of America 2009) (Mansbach et al. 2007; McWilliams et al. 2003; Greene and Geiger 2006; Wagner et al. ; Byrne et al. 2006; Finch et al. 2009; Helfand et al. 2009; Kimberly et al. 2006; Green et al. 2006; Ravina et al. 2009) while Institutional Animal Care and Use Committees (IACUCs), the committees that oversee the use of animals are not (Plous and Herzog 2001).

I find discussing specific historical examples like angiogenesis inhibitors to be very unrewarding, in part because the *modus operandi* of science demands the claimant prove his case, in this example that animals were vital to the process and that the discovery could not have been made without them, and the claimant rarely does this. The claimant's argument usually goes something like this: "The following breakthrough could not have happened without using animals and this proves that animals are mandatory in today's research. Prove me wrong!" Engaging with someone who uses this type of reasoning does not usually lead to enlightenment. Again, I refer the reader to our books and article where we address issues like this and other historical cases in more detail.

The addition of angiogenesis inhibitors to the clinician's armamentarium is tremendous, but much work remains before clinicians can assure their patients that cancer is under control. This raises the question: Where would society be today in cancer management if instead of focusing on animals models we had studied humans? Perhaps angiogenesis inhibitors would never have been developed. Perhaps we would have something better. Anecdotally, all I can say is that if I am ever suffering from a terminal disease and hoping desperately for a cure, then I will be less anxious about my outcome if human-based research is the norm and not the exception.

### ***Alternatives***

Orac also criticizes us for saying that any study of humans and human tissue will at least give results that are applicable to the species in question and asking us to describe how to conduct experiments without using animals. If anyone believes studying dogs or tissues from dogs will give more reliable information about human drugs and disease response than studying humans and human tissue then we do not have enough in common to have a discussion. Note what I am *not* saying: Studying *Drosophila* gave us information about evo devo that could not have come from studying more complex organisms including humans. This is *not* what I am addressing. I am addressing the use of animals to determine disease and drug response and for that purpose humans and human tissue beats all else. For examples of this concept note any of the large number of drugs that have been pulled off the market in recent years. Yes, all of the recalled drugs went through human clinical trials but the trials were too short and conducted on too few and too homogeneous a population. And the trials themselves were and are influenced by the animal studies. For instance Gina Kolata reported in the *New York Times* September 16, 1997, on the diet drug fen-phen:

Why weren't these problems noticed before? Dieters in Europe had used Dexfenfluramine for decades. Dr. Friedman [an FDA official] said he

could only speculate. No one had initially thought to examine patients' hearts, he said, because animal studies had never revealed heart abnormalities and heart valve defects are not normally associated with drug use. (Kolata 1997)

Or examine the testing that led to TGN1412 being tested on humans. Six men who took TGN1412 were hospitalized in critical condition approximately 1 hour after ingesting the drug. The drug, an anti-inflammatory agent which was scheduled to treat conditions as varied as rheumatoid arthritis, leukaemia and multiple sclerosis, caused multiple organ failure. TGN1412 was tested in numerous animal species including rabbits and monkeys. *Nature* April 13, 2006 stated:

There was no warning from animal tests, but last month the experimental antibody drug TGN1412 put six British men in intensive care. "We were shocked and surprised to see what happened in humans," Hünig [an immunologist at the University of Würzburg and researchers at TeGenero] told *Nature*. In preclinical trials, monkeys got a dose 500 times that given to the human volunteers, and the monkey CD28 receptor is identical to the human one, says Hünig. This means that the effects in the monkey trial should have been comparable. (News 2006)

It turned out that monkeys and humans do not have identical CD28 molecules and therefore the reactions were very different (Vitetta and Ghetie 2006). Speaking of toxicity trials for new drugs in humans, an unnamed clinician quoted in *Science* stated, "If you were to look in [a big company's] files for testing small-molecule drugs you'd find hundreds of deaths." (Marshall 2000)

We have written books full of examples where the results from experiments conducted on tissue from humans differed from the results of the same experiments conducted on tissue from animals (Greek and Greek 2004; Greek and Greek 2000; Greek and Greek 2002; Greek and Shanks 2009; Shanks and Greek 2009). I need not multiply the above examples here.

As to Orac's criticism for not offering specific alternatives to using animals, in fact we wrote an entire book about this with the tricky title: *What Will We Do if We Don't Experiment on Animals?* (Greek and Greek 2004). But I will spend a moment addressing the issue in general. Orac criticizes us for saying that:

There are better ways of getting the information that do not use animals (*i.e.*, there is better science available than using animals.)

Yes, I make this claim. But even here I make the claim only with respect to very specific circumstances. For example, if you want to learn about human diseases then studying humans will accomplish that better than studying say, rats. Orac challenges this using transgenic mice give as an example. We have addressed the use of transgenic mice in research to predict human response in (Shanks and Greek 2009). There can be no denying the fact that transgenic mice can lead to new knowledge but this is a tautology and, again, this is not the point. The question we address is "Can they can predict human response?" Specifically can they predict human response to drugs and disease? But even

when genetically altered mice are used for so-called basic research, the results of gene manipulation does not mimic humans a large percentage of the time or even others strains of the same animal (Regenberg et al. 2009; Van Regenmortel 2004; Horrobin 2003; Jankovic and Noebels 2005; Noebels 1999). We address this more fully in *Animal Models in Light of Evolution*.

We have also addressed the issue of whether researchers, basic or otherwise, have available to them many modalities that do not involve animals and that have a good track record for discovering new knowledge that might conceivably lead to better treatments or more knowledge about human physiologies. We have never before felt obliged to prove that research, for example in the basic sciences of chemistry and physics, have produced such results because quite frankly no one questions this.

Orac:

They [animal models] are also a convenient tool that allows us to test hypotheses that we cannot test in humans, either for reasons of practicality or ethics. We can certainly argue about how good a tool or screening test animal studies can be, but it is disingenuous and incorrect to argue so strongly that animals are meant to be "substitutes" for human subjects.

This is a distinction without a difference when animals are used in drug development. Pharma experiments on rats and mice and monkeys not because they care what the drug does to rats and mice and monkeys but because historically they have been looking to predict what the drug would do to humans. As the above references will attest, Pharma now realizes this approach has cost them money and products without keeping dangerous drugs off the market and without protecting humans in clinical trials.

Animals are used at virtually every step of drug development precisely as human surrogates—the scientists want to know how the drug is going to affect humans. That is why drug companies exist—to make drugs for humans—not to find interesting drugs for rats. At every step of the process, historically, animals were used in hopes of ascertaining what would happen when humans consumed the drug. Determination of dosage and possible toxicities were among the things studied but so were efficacy, absorption, distribution, metabolism and elimination. This essay is too short to go into detail here but entire books have been written on this and numerous journals are devoted to the topic.

Here, I should again point out that the only test subject that can predict how a drug will affect you is *you*. All of Orac's essay must be judged in light of personalized medicine and pharmacogenomics. We cover this in the *Skeptic* article that he criticizes (an article for the general public not scientists) and to a degree in *FAQS About the Use of Animals in Science* (Greek and Shanks 2009) and in *Animal Models in Light of Evolution* (Shanks and Greek 2009) (a book written for the scientific community) in much greater depth. If a scientist wishes to go into the nitty gritty of our position, it is disingenuous to use as their source an article written for general public. Granted, any article should be true to the facts but criticizing such an article for not going into the depth necessary for scientists is unfair. We have written *Animal Models in Light of Evolution* for people who honestly want to have an in depth scientific discussion about animal models. The book had been out for six months when Orac wrote the article but Orac choose to criticize instead one of our articles from two years ago.

As for Orac's assertion that scientists can test hypotheses on animals that they cannot test on humans, this is true. Much research in neurophysiology falls under this category. This is pure basic research and is not meant to predict human response and we do not criticize it on that basis. What I have said is that society demands certain results when using sentient animals in this fashion and that the research community is inconsistent (and I would add disingenuous) when describing to society how their animals are being used as opposed to when they discuss such uses among themselves. (For more on this see Appendix 3 in *Animal Models in Light of Evolution*.)

### ***Conclusion***

Addressing criticisms takes space and this essay has not addressed all of Orac's complaints but has still consumed a lot of space. It only takes one sentence to accuse someone of a crime but many sentences for that person to acquit himself. In the final analysis, if a scientist or scientifically educated person wants to understand our views they should read *Animal Models in Light of Evolution* (Shanks and Greek 2009). That is our most thorough work and was written for scientists.

I claim that while animals have value in certain aspects of science and biomedical research, animal models can never predict human response to drugs and disease. This has important implications for how the Food and Drug Administration and the Environmental Protection Agency should regulate the approval process for new drugs and chemicals and how the National Institutes of Health should fund research.

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