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Response to The Humanimal Trust Essay of November 2017

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The Humanimal Trust recently published: "In response to recent allegations against our cause – November 2017." Some of the essay is reproduced below. This will be a long critique because 1) the original was long and 2) it takes far more space to refute falsehoods and accusations than it takes to make them.

The Humanimal Trust begins:

> The Humanimal Trust welcomes all constructive views on how to improve the wellbeing, welfare and quality of life of both animals & humans. We are ready and willing to engage in all conversations with integrity of purpose toward this goal in face-to-face open and transparent dialogue. We recognise the right of every individual to have an opinion on what is clearly a challenging and emotive topic, but we feel it is important to recognise that much of the information presented in recent posts on social media involves the selective use of scientific (and non-scientific) articles as supporting information. In particular, there has been a blurring of the lines between the related, but separate issues of One Health/One Medicine versus the broader issue of the use of animals in research and testing.

First, if The Humanimal Trust is willing to engage in "all conversations" we trust they will immediately support Early Day Motion 66, brought by members of the UK Parliament – citing For Life On Earth (FLOE) and Patients Campaigning For Cures (PCFC) – calling for a peer-reviewed (that is, properly moderated) public scientific debate, on the use of animals in human disease research and medicine development.

Second, the basis for using any animal species to model humans, such as is done daily in routine animal-based research and testing, is the same as the basis used by One Health/One Medicine and The Humanimal Trust to promote their idea. I do not know who has been *blurring the lines* between these concepts as there is no such clearly defined line to blur. The justification for the traditional use of animals as models for humans is merely restated by One Health/One Medicine. There is nothing new, scientifically speaking, in the position of The Humanimal Trust or in the position of One Health/One Medicine. See (Greek 2012b, Greek and Greek 2004, Shanks and Greek 2009, Shanks, Greek, and Greek 2009, Greek, Shanks, and Rice 2011, Greek, Pippus, and Hansen 2012, Novella 2017b) The reason animals cannot be used to model human response to drugs and disease is summarized by Trans-Species Modeling Theory (TSMT): "While trans-species extrapolation is possible when perturbations concern lower levels of organization or when studying morphology and function on the gross level, one evolved, complex system will not be of predictive value for another when the perturbation affects higher levels of organization." (Greek and Hansen 2013b) While I am not responsible for every statement from every person advocating for what amounts to TSMT, I do take responsibility for TSMT. The Theory of Evolution and complexity science are not examples of *non-scientific articles* or

concepts. Moreover, everyone uses references from nonscientific sources to support facts that are not scientific in origin. I do not keep up with all the discussion on social media regarding animal modeling but I suspect the nonscientific articles claim is a red herring.

Third, the wellbeing of humans and animals would be improved if everyone accepted the scientific facts upon which TSMT is based. Animal modeling, as advocated by The Humanimal Trust, does not help human patients or animal patients.

The Humanimal Trust continues:

> We do not feel that the social media platform is conducive to honest constructive dialogue for the betterment of animals

Then why do they use it? I agree, somewhat, and avoid social media whenever possible thus I engage in discussions like this very reluctantly. That said, the factual absurdities of One Medicine can be quite easily confirmed by any medical scientist free of its vested interest, but will not be so clear to many others. Thus, such claims cannot all be allowed to pass by but must be diligently arrested and corrected, to avoid muddying the waters of serious public scientific debate. Moreover, I have published my position in numerous articles in peer-reviewed journals as well as in book form. My position is straightforward and well established and yet it appears that many in the animal model community willfully misrepresent it. Such is inconsistent with purporting to welcome open dialogue.

> and would encourage organisations to come to the table if they wish to pursue meaningful progress toward the goal of a significantly better and fairer world for animals, and for humans too.

The reason many animal activists use social media is illustrated by the fact that the animal model community, including The Humanimal Trust, refuses to endorse or participate in the peer-reviewed public scientific debate platform called for by Parliamentary EDM 66. They are the ones who will not come to the table. We understand our position and we understand theirs. There is essentially no common ground in these opposing positions and we maintain that we have the factual science on our side. A peer-reviewed debate would be fair to all sides as experts - without a vested interest - would judge the science (see For Life On Earth (2016)). If The Humanimal Trust is unwilling to participate in an event that is this fair, open, and science-based, everything they say should be taken with a grain of salt. A better and fairer world for all is everyone's wish but used in this context is simply the fallacy known as *appeal to emotion*. It is also an example of poisoning the well as it makes it appear that animal activists who oppose The Humanimal Trust, do not want a fairer world for animals and thus society might be inclined to dismiss their science concerns.

> In the paragraphs that follow, we hope to be able to clarify the Trust's position on these issues, and to respond in a clear, concise and conciliatory tone to some of the unconstructive comments that have been made.

The Humanimal Trust has been exposed as lying about its agenda on Twitter:

> Hi Julieanne - for clarification, we do not experiment on animals and we will never support research where animals are used as experimental models.

For Life on Earth replied:

> 1/ Not true. Your evidence to Parliament's S&T Committee wholly supports the science of 'research where animals are used as experimental models' - as claimed predictive models of human patients in medicine & disease research: http://www.afma-curedisease.org/blog/2016/october/28/humanimal.aspx … @Protect_Wldlife @PeterEgan6
>
> 2/ From your animal testing page: 'We will collaborate with human medical researchers, including those conducting animal studies, as long as our involvement works towards replacing, reducing and refining that animal research'. http://www.humanimaltrust.org.uk/what-we-do/our-policies … @Protect_Wldlife @PeterEgan6

The Humanimal Trust then admitted:

> Regretfully we feel we are forced to recognise the regulatory requirements in regards to the current role of preclinical animal studies in defining the safety and technical feasibility of new medical treatments. We want to change that - & collaborate, to help make change happen.

I suggest you read the entire dialogue. But this is a long way from "we do not experiment on animals and we will never support research where animals are used as experimental models." At best, their statement was misleading and at worst, it was purposefully deceitful. The concept advocated by The Humanimal Trust is no different from the concept used by those who use animals as experimental models of humans. The Humanimal Trust is merely naïve or perhaps disingenuous in how to go about implementing the concept.

The Humanimal Trust continues with their essay:

> The concept of One Health and One Medicine is central to the charter for most veterinary schools, and is clearly stated in the manifesto of nearly all veterinary curriculums globally, for example; The University of Surrey (https://www.surrey.ac.uk/faculty-health-medical-sciences), The University of California, Davis https://www.ucdavis.edu/one-health/what-is-one-health/, and The University of Edinburgh https://www.ed.ac.uk/roslin/animal-biosciences-msc/one-biology-one-health-one-medicine. It is not a notion specific to The Humanimal Trust. To quote Rudolf Virchow, "Between animal and human medicine there is no dividing line – nor should there be. The object is different but the experience obtained constitutes the basis of all medicine."

This is a good example of incompetent science. Rudolph Virchow was a towering figure of 19th century biology but he was not flawless. He denied Darwin's Theory of Evolution and referred to

Darwin as an ignoramus. He also denied the Germ Theory of disease and opposed handwashing to decrease the rate of infection. (Glick 1988) We explained the ramifications of this anti-Darwinism in an article regarding the use of nonhuman primates (NHPs) in research:

> The modern foundation for animal use in research, be that research basic or applied, was the nineteenth-century creationist position that all animals were essentially the same, provided scaling for size was taken into account.123,124 LaFollette and Shanks state:
>
> > Bernard's particular understanding of hypothetico-deductivism, coupled with his rejection of all statistical laws, led him to assume that clinical medicine (including epidemiological studies) could never be a genuine science. Perhaps, though, he would have given more consideration to clinical medicine had he not believed he had a rigorous science ready to hand in the animal laboratory. However, Bernard believed in the interchangeability of species; he thus had reason to assume clinical hypotheses could be tested by laboratory experiments on animals.123
>
> The medical historian Elliot comments on the fact that the physiologist, and father of current animal-based research, Claude Bernard was a creationist:
>
> > Leading French biologists, such as Bernard himself and Charles Robin, were resistant to the Darwinian theory of evolution. … [Bernard and others] resisted these ideas because they saw them as the results of speculation unsupported by proper experimental evidence. The emergence of experimental physiology based on vivisection was therefore an integral part of a general trend in French science away from anything that could be interpreted as speculation towards a science based rigidly, too rigidly perhaps, on laboratory work and experiment.125
>
> Bernard was not a creationist in the current sense of the concept, the theory of evolution had not been fully developed during his time, but he was a creationist and this did influence his position.123 This position directly related to Bernard's stance as a strict causal determinist, meaning that if X caused Y in a monkey, then it would also cause Y in a human. Bernard states: "Physiologists ... deal with just one thing, the properties of living matter and the mechanism of life, in whatever form it shows itself. For them genus, species and class no longer exist."124 Bernard's position of causal determinism was also based on the Cartesian position of determinism, which led to the method of study in science known as reductionism. Reductionism basically means reducing the system being studied to its component parts, discovering the role of each part, and using that information in order to deduce the function or role of the whole system. Reductionism worked well for the physical sciences and the life sciences up to a point. Reductionism still plays a valuable role in science that studies simple systems; however, reductionism is not the only way, or even a viable way in some cases, to study complex systems. Times have changed, but underlying assumptions, unfortunately, have not changed sufficiently. Because of the close evolutionary relationship between humans and NHPs, the assumption is made that NHPs will provide a living intact system that more closely resembles humans. Therefore, by extension of this assumption, the study of gene

> function, drug and disease response, and basic neurophysiology is more likely to mimic that of humans. (Greek, Hansen, and Menache 2011)

I was raised by creationists and was taught that humans and animals were identical in terms of body parts and functions; the only difference was that humans had a soul. This was the foundation for animal modeling. The Humanimal Trust cannot simply throw up the name *Virchow* and expect everyone to accept their position. Science does not work that way. In defense of Virchow, many scientists of that era made the same mistake. But that only reinforces the fact that in science one has to prove one's position, preferably using a combination of accepted theory and empirical evidence (this is what TSMT does). Merely finding support among scientists is not sufficient to prove one's position.

Moreover, if such verbiage as in One Medicine exists in schools of veterinary medicine it is just that—verbiage. Veterinarians will be the first to point out that animals vary in the diseases they contract and in the ways they are treated. Cats are no more small dogs than monkeys are small humans. If vet schools are supporting the concept of One Medicine they either interpret it differently—all medical practice should be science-based—or they are doing so for monetary reasons and without the support of the actual practicing veterinarians teaching there. Both human medical and vet schools support nonsense when someone is paying them to do so. (Tsouderos 2011, COSA (The Clinical Oncological Society of Australia) 2013, McKenzie 2013, Crislip 2014, Gorski 2014a, b, Orac 2014a, b, Gorski 2015, Jones 2015, Novella 2015a, b, Orac 2015a, b, Gorski 2017a, b, SkepVet 2017, Novella 2017b)

The Humanimal Trust continues:

> It seems then that for individuals to endeavour to engage The Humanimal Trust on social media with the objective of abandoning the goals of the charity and its vision to improve global health for all animals and humans,

This is a strawman. No one that I read is trying to diminish the health of animals. Closing The Humanimal Trust would result in no philosophical loss to animal modelers, as the basis for The Humanimal Trust is the same as the basis for all their use of animals in general. It just is expressed more naively. The fact that The Humanimal Trust is relying so much on appeal to emotion, straw man arguments, and other fallacies implies they have no substance with which to advance their position.

> it would also require those same individuals to request that the majority of veterinary schools in the western world would abandon their platforms of One Health and One Medicine, which are the core principles on which the students are educated and that others in the wider scientific community comprehensively support (Mazet *et al.*, 2009; Zinsstag *et al.*, 2011; Gibbs, 2014)(http://www.onehealthinitiative.com/mission.php; http://www.oie.int/en/for-the-media/editorials/detail/article/one-health/; https://www.bbsrc.ac.uk/research/bioscience-health/).

Again, I have no idea what a majority of veterinary schools have written in a position statement or support document but I do have first-hand knowledge of both vet and med schools and

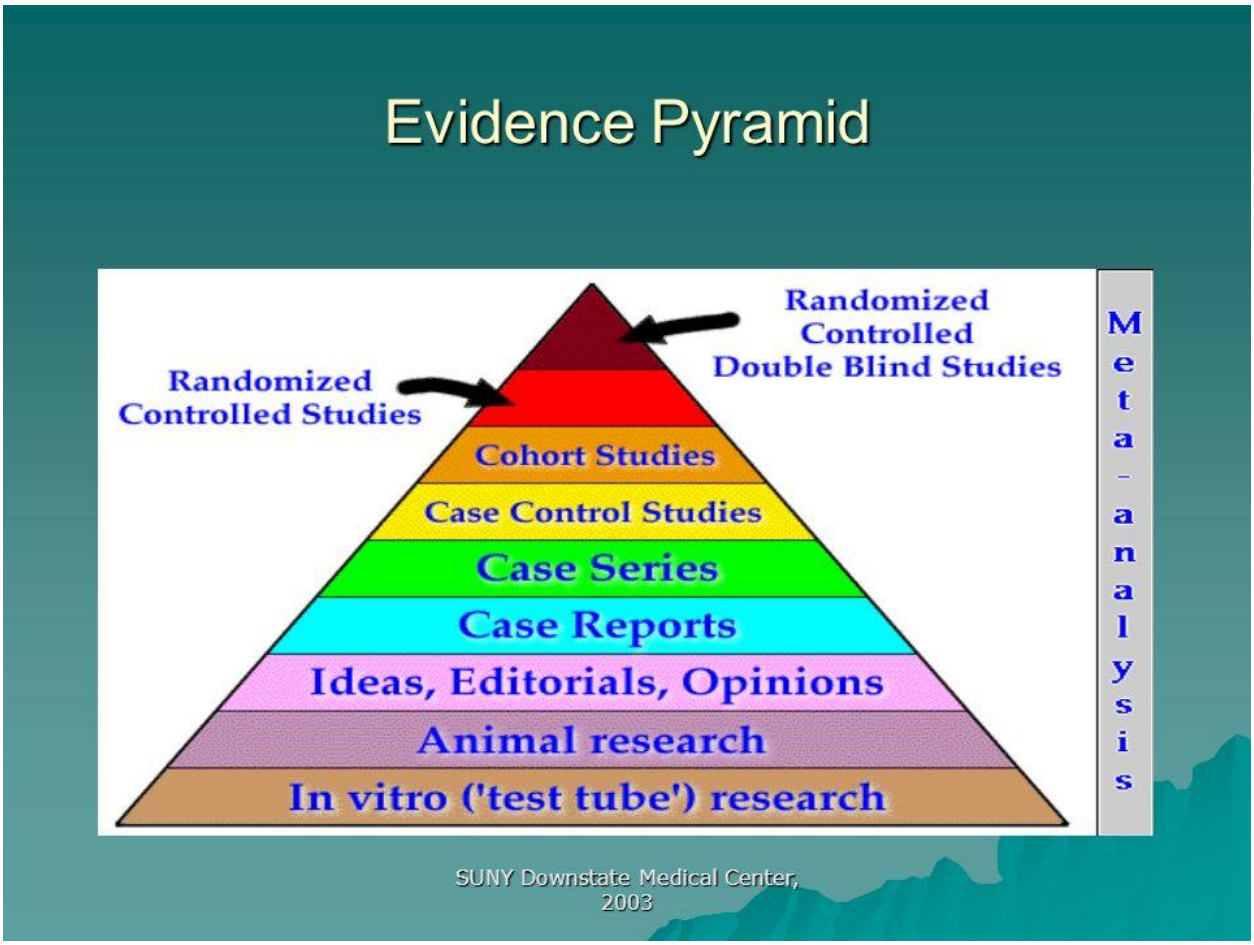
universities as a whole embracing nonsense when it pays them to. If The Humanimal Trust wants to make a scientific case for their position they should do so and refrain from using the *argument from authority* fallacy. Moreover, a pet peeve (pun intended) of vets in general is the popular assumption that cats are scaled down dogs. They aren't. They are complex systems with different evolutionary trajectories and this has implications for medical care. In summary, no competent veterinarian believes in the trans-species implications inherent in the position of One Medicine. (Greek 2012b)

> We emphasise that our endeavour is focussed on the good that can be achieved for animals in the context of medical advance.

Good intentions are not a substitute for good and correct science. The road to hell is paved with good intentions.

> We do not fund any research at all ever that involves the use of experimental or purpose-bred animals. We only fund studies that examine spontaneous and naturally-occurring disease in animals and, in doing so, our goal is to help animals. Disease will occur anyway; our intent is to lessen the impact of disease on quality of life of animals and study such disease so that all may benefit – animals and humans. By simultaneously studying naturally occurring disease in humans we seek parallels such that medical advance can benefit all species.

The above sounds good and let's take them at their word for the present. But let's also delve deeper into what this means. Evidence in medical science is ranked more or less as outlined in the figures that follow.


Evidence Pyramid
Randomized Controlled Double Blind Studies
Randomized Controlled Studies
Cohort Studies
Case Control Studies
Case Series
Case Reports
Ideas, Editorials, Opinions
Animal research
In vitro ('test tube') research
Meta-analysis
SUNY Downstate Medical Center, 2003

(Payne 2016)

Levels of Evidence for Primary Research Question

	Types of Studies			
	Therapeutic Studies—Investigating the Results of Treatment	Prognostic Studies—Investigating the Outcome of Disease	Diagnostic Studies—Investigating a Diagnostic Test	Economic and Decision Analyses—Developing an Economic or Decision Model
Level I	1. Randomized controlled trial a. Significant difference b. No significant difference but narrow confidence intervals 2. Systematic review[2] of Level-I randomized controlled trials (studies were homogeneous)	1. Prospective study[1] 2. Systematic review[2] of Level-I studies	1. Testing of previously developed diagnostic criteria in series of consecutive patients (with universally applied reference "gold" standard) 2. Systematic review[2] of Level-I studies	1. Clinically sensible costs and alternatives; values obtained from many studies; multiway sensitivity analyses 2. Systematic review[2] of Level-I studies
Level II	1. Prospective cohort study[3] 2. Poor-quality randomized controlled trial (e.g., <80% follow-up) 3. Systematic review[2] a. Level-II studies b. nonhomogeneous Level-I studies	1. Retrospective study[4] 2. Study of untreated controls from a previous randomized controlled trial 3. Systematic review[2] of Level-II studies	1. Development of diagnostic criteria on basis of consecutive patients (with universally applied reference "gold" standard) 2. Systematic review[2] of Level-II studies	1. Clinically sensible costs and alternatives; values obtained from limited studies; multiway sensitivity analyses 2. Systematic review[2] of Level-II studies
Level III	1. Case-control study[5] 2. Retrospective cohort study[4] 3. Systematic review[2] of Level-III studies		1. Study of nonconsecutive patients (no consistently applied reference "gold" standard) 2. Systematic review[2] of Level-III studies	1. Limited alternatives and costs; poor estimates 2. Systematic review[2] of Level-III studies
Level IV	Case series (no, or historical, control group)	Case series	1. Case-control study 2. Poor reference standard	No sensitivity analyses
Level V	Expert opinion	Expert opinion	Expert opinion	Expert opinion

1. All patients were enrolled at the same point in their disease course (inception cohort) with ≥80% follow-up of enrolled patients.
2. A study of results from two or more previous studies.
3. Patients were compared with a control group of patients treated at the same time and institution.
4. The study was initiated after treatment was performed.
5. Patients with a particular outcome ("cases" with, for example, a failed total arthroplasty) were compared with those who did not have the outcome ("controls" with, for example, a total hip arthroplasty that did not fail).

(Moore 2017)

(Belluz and Hoffman 2015)

The type of research that The Humanimal Trust suggests would be classified very low on any of the tables or pyramids. Note that animal-based research as it applies to humans only exists on one of the three figures above, ranking below *opinions* on the first pyramid. But even if we ignore the fact that The Humanimal Trust wishes to extrapolate data from one species to another, the very way this would be done also ranks very low according to the above figures. Case reports and case series have very limited value even when conducted using humans and what The Humanimal Trust is suggesting is more along the lines of anecdotes than either of those. Anecdotes don't even make the list. Feeding your dog the same food you eat and living in the same environment is not sufficient to draw conclusions about apparently shared diseases. Epidemiology does somewhat of the same thing and is a very good means of research but a) epidemiology studies humans when trying to relate cause to effect in humans and b) thousands of humans are needed in order to draw reliable conclusions. This is not the concept One Medicine and The Humanimal Trust are advocating.

The Humanimal Trust continues:

> The Trust is a signatory to the Concordat on Openness on Animal Research in the UK (http://concordatopenness.org.uk), an initiative that seeks to demystify and explain the studies that are being conducted in the name of scientific endeavour. Opponents of animal research are quick to identify examples where preclinical animal data has not been predictive of subsequent results in humans, using this as evidence for the lack of utility and relevance of the models. We agree with the notion that there are significant differences between species with regard to drug metabolism, just as there are idiosyncrasies in how individual human patients may react to a given therapy. Less

> attention is paid to success stories; perhaps this is the nature of things, but it is not the basis of a rational public debate.

I'll leave aside the issues associated with the Concordat on Openness on Animal Research in the UK for this essay. First, the different reactions among humans that are classified as idiosyncratic are relatively rare while the different responses among species are very common. Leading the reader to equate idiosyncratic reactions among humans with the myriad of different reactions among species is intentionally misleading, or another sign of scientific incompetence.

Second, stating that successes – when using animals to predict human response to drugs and disease – are given less attention, is intentionally seeking to lead the reader to the conclusion that the two outcomes are about equal and one side is just cherry-picking the data. In reality, animal models get it wrong far more often than they happen to get it right. When I have written about the predictive value of using animals to ascertain drug safety and efficacy I have shown that it is very low, especially when one considers that optimally anything attempting to predict human response, that is being relied on for treatment or diagnosis, should have predictive values over 0.9. Animal tests for efficacy and toxicity usually range from 0.0 to around 0.5. A value of 0.5 would be expected from tossing a coin under normal circumstances. As animal models of toxicity and efficacy result in a failure rate of around 90% of all drugs in clinical trials, the animal model is clearly inadequate as it offers no predictive value. See Shanks and Greek (2009) for more on probability. I have pointed this out repeatedly, as have regulators and scientists in drug development. This absolutely reveals "the lack of utility and relevance of the models." This is not analogous to the clinical observation that rare individuals have idiosyncratic reactions. Comparing one with the other is a false analogy because the analogy fails in all but trivial ways.

Third, there are no success stories. Occasionally, a species or more likely a strain of a species will mimic a human response, but most of the other species fail to do so raising the question: which animals can be believed? This is why we need a model with high predictive value. Otherwise animal models simply give conflicting results and we have no idea which species will be like humans in this particular instance. The species or strain reacting like humans is not a success of animal modeling, but rather what one would expect from random chance.

Responses to perturbations occupy a spectrum across species lines. Likewise, other traits and characteristics developed by evolution exist along a continuum.

A. Humans might have trait P and it is highly developed, while another species has trait P but it is much less developed and another does not have P at all. Likewise, humans might have enzyme ORS but another species might not have, while yet another has it but only in tiny amounts.

B. The presence of the trait or partial presence might have developed though the same mechanisms but it also might have developed through different mechanisms; for instance, the eye in humans and the eye in octopi.

C. So, using another species as a model might result in absolutely no knowledge gained about humans because of profound differences in the physiology of the trait, despite similarities in the

presence of the trait. For example, the animal might have only 10% of the enzyme activity as humans.

D. A more distantly related species though, might have developed the trait in more or less the same way as humans and might demonstrate the same response to perturbations that humans demonstrate. In this way, evolution is a random process and the responses to perturbations are apparently random as well. (They are not really random as we can find out why the response is what it is.) Moreover, the distance to our last common ancestor is not a reliable way to seek information about human responses to drugs and disease. This is exactly what we see empirically when using animal models. One species responds the same as humans but we can only determine this retrospectively as animal modeling has no predictive value. Retrospective prediction is an oxymoron. (Shanks and Greek 2009)

The current expectation that closely related species will better provide information regarding drugs and disease is called the *phylogenetic fallacy* or *Modelers phylogenetic fallacy*. LaFollette and Shanks state in *Brute Science*:

> Since phylogenetically related species, say mammals, have all evolved from the same ancestral species, we would expect them to be, in some respects, biologically similar. Nonetheless, evolution also leads us to expect important biological differences between species; after all, the species have adapted to different ecological niches. However, Darwin's theory does not tell us how pervasive or significant those differences will be. This again brings the ontological problem of relevance to the fore. Will the similarities between species be pervasive and deep enough to justify extrapolation from animal test subjects to humans? Or will *the biological differences be quantitatively or qualitatively substantial enough to make such extrapolations scientifically dubious*? (LaFollette and Shanks 1996) (Emphasis added.)

The causal/functional asymmetry theory states:

> although we cannot infer similarity of causal properties from similarity of functional properties, we can infer differences in causal properties from differences in functional properties. (LaFollette and Shanks 1996, 101)

Animal modelers in general constantly commit the Modeler's phylogenetic fallacy: *phylogenetic closeness implies underlying causal similarity*. (LaFollette and Shanks 1996, 137) Animal modelers who advocate for using primates use the fallacy more frequently than those who conduct research on mice, but both appeal to *similarity* obtained through the process of evolution to justify their research. Hau:

> Although one might be tempted to presume that extrapolation from an animal species to the human is the better the closer this species resembles humans (high fidelity), *phylogenetic closeness, as fulfilled by primate models, is not a guarantee for validity of extrapolation, as the unsuccessful chimpanzee models in acquired immunodeficiency syndrome (AIDS) research have demonstrated.* (Hau 2003, 3) (Emphasis added.)

Indeed, chimps are no longer available for research in the US. That fact alone should inform us regarding how valuable our phylogenetically closest animal model is. (Kaiser 2015) The reason chimps failed is because even though they have more in common with humans than other species, they are still *differently complex*. The notion that phylogenetic closeness should imply similarity in mechanisms and responses would be correct if humans and animals were simple systems, or if God created all of them using the exact same template. Using animals phylogenetically further from humans is not going to succeed any better than chimps for the same reasons. Regardless of how similar two complex systems are, as long as they are complex systems we cannot expect one to have predictive value for the second when the perturbation effects higher levels of organization. For more, see references to my publications throughout this essay.

E. In truth, more attention should be paid to the fact that animal models fail miserably when used to model human response to drugs. If that was the only empirical evidence we have it would be sufficient to abandon animal modeling. There are two reasons for this.

1. Medications exist for almost all diseases and there is no disease that animal model X has been shown to have predictive value for. Moreover, there is no animal model or combination of animal models that have been shown to have predictive value for toxicity. The main two reasons animal models are used in drug development are toxicity and efficacy—and multiple studies have proven conclusively that animal models fail to provide this information. Using animal models is like using a Ouija board. Rarely, the Ouija board will say a drug is toxic and it turns out that it is. But far more often reality has nothing in common with what the Ouija board predicted—be the drug safe and effective or not.

2. In order for animals to have predictive value for humans in other areas of research, without having predictive value for drug development, it would require evolution to use at least two very different overall processes - one for all the physiology that is relevant for drug development and another for all other physiological processes. This is obviously nonsensical as evolution works using multiple tools, but still the same general way throughout time.

The above is the basis for rational public debate. But since it does not allow supporters of the status quo to claim the scientific high ground they need, they must attack their opponents' character with lies, fallacies, bad science, and bad logic. It does not appear that The Humanimal Trust is seeking truth in order to help animals but rather that they are seeking to support the status quo in a misleading way. Or, they are just scientifically incompetent and picked what appeared an easy and popular cause to support that, unfortunately for them, demonstrates their incompetence.

The Humanimal Trust continues:

> One could reverse the argument and discuss how many times preclinical data from laboratory animals has prevented humans on clinical trials from being exposed to ineffective or potentially dangerous drug therapies.

This would be a great idea but cannot be done as it would be unethical. Currently, if a drug kills an animal in testing it will probably be pulled from development and forego testing on humans. All this proves is that industry pulled the drug on the *assumption* that it was dangerous. Given the track record of animals predicting toxicity for humans, it is far more likely that the drug would not have harmed humans (exceptions being drugs where the harm could have been predicted based on the physicochemical properties, presence of conserved processes, or the class of the chemical). (Greek and Rice 2012) So, no one knows whether, based on animal studies alone, animal models have ever prevented a tragedy. If they have it was not because of any predictive value they have, rather it was random chance.

What we can do, however, is look back in time at how drugs were developed and eventually marketed. When this happens we quickly see examples of a drug being safely and effectively given to humans when, had the developers waited for all the animal data, they would have abandoned the drug due to toxicity issues. This means a life-saving medication that is both safe and effective in humans would never had been available to human patients if the animal data had been available. Moreover, efficacious drugs would have been abandoned because they were not effective on animal models. Animals have no predictive for either safety or efficacy and do not prevent deaths except in a frequency that must be consider comparable to random chance. (Sitaram and Gershon 1983, Clemmensen and Hjalgrim-Jensen 1980, Clayson 1980, Anisimov, Ukraintseva, and Yashin 2005, Okita 1967, Jover et al. 1992, Anderson 1991, Bucher et al. 1991, Walker and McElligott 1981, Lagarriga et al. 1977, Editorial 2003, Engber 2011, Gura 1997, Sankar 2005, Dennis 2006, Editorial 2006, Lazzarini et al. 2006, Young 2008, Yukhananov 2011, Dayan 1981, Dunne 1981, 37)

The Humanimal Trust continues:

> The solution to these conflicting arguments should not be to abandon all animal models as being worthless, rather to improve our understanding of these inter-species differences, move away from using animal models that are not predictive, and focus energy and funding on those where there is clear evidence for translational relevance.

And this is why The Humanimal Trust is either incompetent in terms of science or very disingenuous. By explaining the fact that animals and humans are examples of complex systems with different trajectories, we have conclusively proven that animal models have never had predictive value, do not currently have predictive value, and never will have predictive value when the perturbation concerns higher levels of organization which is exactly where disease and drugs act. (Greek and Greek 2002, Greek and Pound 2002, Greek 2008, Shanks and Greek 2009, Shanks, Greek, and Greek 2009, Greek and Greek 2010, Greek, Hansen, and Menache 2011, Greek, Shanks, and Rice 2011, Greek 2012a, Greek 2012b, Greek and Hansen 2012, Greek, Menache, and Rice 2012, Greek, Pippus, and Hansen 2012, Greek and Rice 2012, Greek and Hansen 2013a, Greek and Hansen 2013b, Greek and Menache 2013, Jones and Greek 2013, Greek 2014) Animal models have the same probability of achieving high predictive value (and that is how they are presented to society) as bloodletting has of curing malaria and trephination (drilling a hole in the skull) has of curing schizophrenia. Conflicting arguments regarding science should be resolved according to the best science currently available. If that solution means one

side is completely wrong then so be it. But scientific facts should not be changed to accommodate the status quo.

If one wishes to increase understanding of interspecies differences, that is scientifically tenable and scientists wishing to accomplish this should state that is what they are doing and request grants accordingly. Such is not the case. Animal modeling is sold to society based on the promise of curing human disease and making the human drug supply safer and more effective. (Giles 2006, Katzner et al. 2009, Ringach 2009, National Science Foundation 2011, Rudczynski 2011, Devoy et al. 2012, Franco 2013, Novella 2017a, Ward 2004, Yorkshire Post 2011, BBC News 2012, Gibson 2012, McKie 2012, Chivers 2013, American Physiological Society 2017) If there was an animal model that had translational value in an area of medicine, everyone would be using it. But even animal modelers admit their models have little predictive value and need much improvement (see previous references to my publications). They have always said this and in the same breath promised better models soon. They roll out the next improvement in animal modeling, for example genetically modified mice, and find the new animal model still has the same problems. (van Zutphen 2000, 2001, Liu, Maas, and Aune 2004, Darlison, Pahal, and Thode 2005, Jankovic and Noebels 2005, Miklos 2005, Abate-Shen 2006, Kieburtz and Olanow 2007, Enna and Williams 2009, Geerts 2009, Lutz 2011, McArthur 2011) TSMT explains why this is the case and always will be.

The Humanimal Trust continues:

> Indeed, more than 400 genetically inherited diseases have been found in dogs that bear similarities to human diseases and over 40 naturally-occurring diseases found in dogs have mutations in a homologous human gene in relation to a similar disease process (Rowell, McCarthy and Alvarez, 2011).

This is irrelevant as on some level all life shares commonalities. What matters is whether there are causal analogies and whether they are consistent on all levels of organization and in the entire organism. This is not usually the case, and when it is the case, it is only noted in retrospect. (LaFollette and Shanks 1996)

> As we do not fund any laboratory animal studies,

To what extent this is true is currently in dispute. I will take their word for it in this essay. But they clearly argue in favor of animal modeling being scientifically tenable. As they are clearly advocating for a scientifically untenable position, their errors need to be pointed out.

> we have focussed on five areas where we can provide tangible evidence that naturally-occurring disease in animals can indeed be productively studied alongside human disease, specifically; infection, cancer, spinal disease, musculoskeletal disease and regenerative medicine.

This is cherry-picking. Anyone can find examples where animals and humans responded similarly to a perturbation and present that as the rule rather than the exception. What I have presented, in our papers, are studies on numerous drugs and diseases showing that animal models

have no predictive value for humans; and I have placed all of the evidence in the context of theory in the form of evolutionary biology and complex systems. This evidence is much more respected than anecdotes, or case reports or cherry picking the literature. Moreover, The Humanimal Trust and One Medicine lack a cohesive theory to explain where animal models should offer predictive value and where they should not. TSMT accomplishes this by using the Theory of Evolution and Complexity Theory.

> There seems little argument from anyone against the fact that naturally-occurring disease in both animals and humans needs treating to alleviate pain and promote quality of life and we respectfully submit that in all of these five areas, appropriately constructed studies can benefit both humans and animals.

That is attractive fiction. First, no one arguing in favor of TSMT suggests that humans and animals should suffer. Second, most new knowledge can be used to benefit the species that was studied in order to obtain the knowledge, but rarely does this benefit cross species lines. The exceptions are well known and predictable, see Greek and Rice (2012). The examples used by animal modelers are either cherry-picked, an example of *post hoc ergo propter hoc*, occur at levels of organization where the complex system can be treated as a simple system, or have been refuted. I have refuted many of their claims in my publications but do so only as examples to support TSMT. I am under no burden to refute every single example that pro animal modelers present, as such a list could be endless and picking a representative sample should suffice. TSMT uses empirical evidence and places it in the context of theory. This is how science is done. The burden of proof is on the claimant in science; and without making an argument for their claim—that discovery X proves animal models are viable or proves they have predictive value—the animal model community is left with just a claim. What passes for a proof among animal modelers is no different from what would be considered a mere claim in other areas of science, logic, and law. If I ever see real proof from animal modelers as to why example Y proves that animal models have predictive value, I will address it.

The Humanimal Trust continues:

> The Humanimal Trust endeavours to open the sharing of clinically relevant data between veterinary and human health care professionals, allowing clinical veterinary cases to benefit from a level of care previously the exclusive preserve of modern human medicine.

This reads like an article published prior to the scientific revolution in medicine. Veterinarians and physicians alike have access to the scientific literature. The difference between the way veterinary medicine and human medicine is practiced resides in the far greater amount of money available to be spent on human patients. If veterinarians had this resource available to them, the quality of their medical care would skyrocket overnight even without further research. Further research is always needed, but just with current knowledge the quality of veterinary medicine could equal that of human medicine very quickly if vets had the amount of money to spend caring for their patients that MDs have.

> Do we really want a world where medical advance is restricted to deployment in human patients alone and if we do move forward with veterinary medicine should not we share

> our experience for the betterment of all animals and all humans? By fostering a collaborative environment across veterinary and human disciplines, we are able to synergistically enhance the quality of care provided to human and non-human species alike.

This is like saying we should use all the knowledge we get from Ouija boards to benefit everyone.

As the examples provided next in The Humanimal Trust essay offer nothing to contradict TSMT I will skip analyzing them. The reason TSMT is of such value is that it obviates the need to analyze each case of animal modeling one at a time, in the same way that Darwin's Theory of Evolution obviates the need to analyze each new species discovered to ascertain whether it was created by God, or it evolved by natural selection and descent with modification. Please see previous references to our books and articles for more on this.

The Humanimal Trust concludes.

> **Our Vision**
> The Trust's position on One Medicine has been consistent and unwavering. We respectfully submit that studying and treating naturally-occurring disease in affected animals and humans makes both rational and scientific sense.

It does make sense superficially but science is about looking deeper and on closer examination the Pollyanna notion expressed above simply does not hold up to scrutiny.

> From the very outset, the Trust advocated for increasing collaboration between medical and veterinary professionals, with the goal being the betterment of health and healthcare delivery in all species. By treating animals with naturally-occurring diseases we are not making experimental scientific interventions on these patients, but treating them to the best of our knowledge and ability, from the currently available evidence base in the combined medical literature, to free them from pain and suffering.

Again, all this rests on the assumption that animals and human share causal analogies and ignores the fact that species are complex systems with millions of years of different trajectories.

> By sharing the information garnered from this treatment we can improve knowledge and therapeutic options for humans and aim to diminish the need for animal experimental models at all.

No. It can't "improve knowledge and therapeutic options for humans." (Greek 2012b) Moreover, society does not need animal models currently any more than it needs Ouija boards.

> The Trust is aligned with the principles of the NC3Rs (https://www.nc3rs.org.uk/the-3rs); Replacement, Reduction and Refinement, and advocates for a missing 4th R, Reciprocity, where animals benefit from medical advancement that they contributed to in the first place.

And this should settle the science issue for anyone knowledgeable about the Three Rs. The Three Rs community advocates for animal modeling because they say it is scientifically viable and offers predictive value for humans. (Greek and Shanks 2009) I say it is not scientifically viable and explain why in the books and articles cited above. This is a scientific issue and can be settled using scientific means. Parliamentary EDM 66 outlines a way to accomplish this.

> By engaging in open data sharing between veterinary and human healthcare practitioners we are able to ensure that the valuable information gained from the clinical application of these homologous treatments will lead to improved care for human and veterinary patients and that animals are not simply seen as stepping stones on an experimental pathway.

The above is naïve on many levels. MDs, PhDs, and DVMs communicate very well through the scientific literature and medical textbooks. There is no cure for cancer hiding in the charts of some general veterinarian in the UK. There is no One Medicine for all species. I wrote the following in my review of the book *Zoobiquity* (Greek 2012b) which touts the One Medicine concept and was written by Barbara Natterson-Horowitz and Kathryn Bowers.

> Woven in among all the verbiage describing the concern for animal health, "One Health" and "Many Species. One Medicine"™ purport that research using animals, regardless of how it is carried out, in the course of diagnosing and treating pets, or studying animals in the wild, or studying animals in laboratories, is directly translatable to humans and *vice-versa*. Natterson-Horowitz and Bowers confirm this, with an emphasis on animals in the wild, in saying: "We could improve the health of all species by learning how animals live, die, get sick and heal in their *natural* settings. . . . I wanted to break down the wall between physicians, veterinarians, and evolutionary biologists because together we are uniquely situated to explore the animal-human overlap where it matters most urgently—in the effort to heal our patients" (p10, 16) If this were not clear enough, psychiatrist and Darwinian Medicine advocate Randolph Nesse stated: "What Barbara is doing is very important. Not just to break down barriers between disciplines and to help us realize we are yet another species shaped by selection, but also because insights from diseases in other animals will be helpful in understanding, preventing and treating human diseases" [3]. Evolutionary medicine is an important and neglected area of study but the reasoning manifest in *Zoobiquity*, along with claims of direct applicability among species, do nothing to further its acceptance. . . .
>
> I found the attitude of the authors to be Pollyannaish, reminiscent of my own history, and wondered what other reviewers had written. To my surprise, almost every review was complimentary. The one exception that I found was from a veterinarian specializing in the care of animals in laboratories. She pointed out, correctly, that the concepts discussed in *Zoobiquity* have been appreciated and practiced for years by researchers and veterinarians who study animal models of disease. There is even a class of animal models referred to as *spontaneous*, meaning the study of animals that spontaneously suffer from the disease as opposed to *induced* models, meaning the disease must be artificially created in the animal. Indeed, the logical extension of *Zoobiquity* and One Health is the

> laboratory, where animals have been studied for decades but where there exists a profound lack of translation between species [5–7,9]. In short, while zoobiquity has been great in terms of comparative studies, it has been tried and has failed in terms of predicting human response to drugs and disease.
>
> The authors present myriad facts but most of these do not directly relate to the case they are trying to make. The interesting and true parts of *Zoobiquity* are simply comparative biology and are not ground breaking nor are they vital for medical advancement. The important aspects of response to drugs and disease require a deeper examination. Yes, animals and humans share traits such as the susceptibility to be infected by viruses and the presence of hearts that are susceptible to diseases. But these are merely surface commonalities or traits manifest on the gross level of examination and hence do not imply the same mechanisms, natural history, or etiology of a disease. Deeper examination reveals that the mechanism by which a virus such as HIV infects the cell differs dramatically among species, as does the resulting illness. "A zoobiquitous approach to cancer," advocated by the authors, has been the focus of the War on Cancer and has failed because species differ in cancer-causing mechanisms and this can be explained by the fact that animals and humans are evolved complex systems that are differently complex. Animal models of cancer, be they induced or spontaneous have not resulted in: "how oncologists might search for ways to cure it [cancer]" (p12). The fact that other species suffer from cancer is so well known as to be considered trivial in a book purporting to break new ground in the search for cures. (Greek 2012b)

The Humanimal Trust continues:

> Ultimately, non-animal models from *in silico* simulation will be possible using the information gained through sharing data and knowledge between professions.

In silico modeling is already in use and the downsides discovered have revolved around the fact that basing in silico testing on data obtained from nonhuman species results in good predictive value for that species, but not for humans. Mixing data from species will only result in poor predictive value for all the species.

> Whether in the context of osteoarthritis, cancer, stem cell research, infection or other diseases, the knowledge gained from studies in one species is highly relevant to our understanding of disease in other species.

Not only is this statement contradicted by history but also by evolutionary biology and complexity science. (See references to publications listed above.)

> It is not, as has been suggested, about seeing the vet as an alternative to a physician for dealing with human disease.

I do not know of anyone who seriously suggested that. I, along with others, have pointed out that the reason the One Medicine concept fails is precisely the same as why we take our pets to veterinarians not to physicians.

> It is not about advocating for a magic pill that can be given to all species to manage a particular disease condition. It is about understanding the interconnectedness of biological systems, recognising similarities when present, and applying knowledge and best practices across species.

These two statements are contradictory. Interconnectedness differs among species, hence the only way studying one species will yield knowledge that has a high predictive value for humans would be by magic. Species share commonalities, but the very small differences mean that knowledge from one species rarely translates into treatments for another. For more on the extent to which this is true see Greek, Menache, and Rice (2012).

> We share an ecosystem, and disease, as one part of that ecosystem, has implications for every animal and every human.

No, it doesn't. Some species are totally immune to diseases that kill other species. HIV/AIDS is a good example: infected chimps catch a cold while humans die if untreated. Moreover, different parts of the ecosystem can thrive while a species or many individuals of a species die. There is ebb and flow for all species in an ecosystem under normal circumstances.

> One Medicine seeks only to harness the knowledge created by scientific discovery and clinical human and veterinary practice, and to use the efficiencies of such an approach to improve overall healthcare.

Herein lies another problem and another example of why The Humanimal Trust appears scientifically incompetent. Science is not about gaining knowledge per se. Curd and Cover state:

> truth by itself cannot be sufficient as a characteristic of the goal of science. Why not? Because so many of the true statements we could make about the natural world have little or no scientific value. Imagine, for example, that a biologist wants to increase our store of scientific knowledge by counting the precise number of hairs on individual dogs at various times on various days, not to test a theory or experiment with a drug to prevent hair loss but simply to know the canine hair count for its own sake. Even if the information that the biologist collects is true it has negligible scientific value…Scientists are interested…in discovering truths about the world…in the form of general theories and laws with predictive power. These criteria of scientific excellence – generality and predictive power – and many others besides (such as explanatory power and simplicity) are among the cognitive values of science. They are not the same as truth. (Curd and Cover 1998)

Animal modeling has resulted in many new facts but these facts are not useful for the purpose the studies were undertaken, as the facts are species-specific and cannot be used for theories that have predictive value for humans. The same is true of knowledge gained from humans. It can be applied to humans but probably not your dog. The treatments that have crossed over from humans to animals have done so 1) because very few companies study animals in hopes of curing other animals and hence very few medicines specifically for animals are being developed

and 2) the ones that have crossed over have done so only after much trial and error using animal patients. Society only sees the successes. There is rarely a one-to-one translation between species. (Again, for an explanation regarding the exceptions see Greek and Rice (2012).) Because veterinary medicine is not plagued with the malpractice environment human medicine is, novel therapies can be tried and not only as a last resort. This is not necessarily ethically optimal, in my view, but it does explain the successful transfer of human medical care to animal medical care.

One must undertake research in the context of what is currently known. No knowledgeable person attempts to find a machine that will produce more power than it consumes. Likewise, no one should seek knowledge about disease and drug response in animals in order to predict what will happen in humans. Neither endeavour is scientifically tenable.

The Humanimal Trust continues:

> It is not only naive to think that the results from one species will necessarily translate across all species,

No, it is not naïve, it is what current science has discovered about life. At one time people thought it was naïve to think animals and human differed in their design. They were wrong. It is however, naïve to think that people with a vested interest, regardless of why they have a vested interest, will go against that interest.

> but also arrogant to assume that humans are so special for there to be no potential for knowledge transfer from other species.

On the superficial level, or the level where life can be treated as a simple system, we can and have learned things about humans by studying animals. No one denies this. For example, humans and mammals share basic characteristics including lungs, hearts and skeletons and in all these cases the heart pumps blood. But given the fact that animals and humans are both examples of evolved, complex system with different evolutionary trajectories, there is no reason to think responses to perturbations will be the same when the perturbation affects *higher levels of organization.* Empirical evidence supports this. It is not arrogant to accept rigorously proven science and to advocate for others to also accept these facts.

> We all accept that disease will happen anyway in both human and animal and we fervently believe that if we do not study animal and human disease in tandem with integrity and reciprocity, all medicine will be impoverished.

Comparative medicine will be slightly affected, not impoverished, but the search for future treatments of patients, be they humans or nonhuman will not be impoverished, it will flourish. Comparative biology and medicine simply seek the differences among species. While this is a very interesting and worthwhile scientific endeavour, it is not what leads to cures for humans or animals. Studying dogs will lead to better treatments for dogs but probably not cats or humans. Of course, we should study dogs, in my opinion in the same ethical way we study humans. But don't lie about it and claim studying dogs will lead to cures for human cancer.

> We strongly believe that the evidence supporting a growing global platform and paradigm of One Medicine is overwhelming and our unwavering endeavour is to contribute to this platform for the greater good of all animals and all humans.

What is overwhelming is the ends to which those with a vested interest will go in order to maintain the status quo. Animal modelers are not threatened by the One Medicine concept because they realize that the logical extension of it is what they do every day. Trans Species Modeling Theory recognizes that different levels of complexity exist; whereas not admitting such a hierarchy is necessary for those claiming One Medicine to be valid.

Finally, I should emphasize that as long as this essay is, it is not nearly long enough to explain and support every concept and fact I have mentioned. I have written books and articles that have been published in the peer-reviewed literature that accomplish this and cannot reproduce all of that in a single essay. Nor do I need to. If you want to learn about a subject such as this you will need to read a number of in-depth analyses of various aspects of the subject. You will also need to understand a number of related subjects so you can separate nonsense from scientific facts. I have alluded to the importance of critical thinking in previous publications as well as the importance of adequate knowledge about medicine and biology in general, evolutionary biology and evolutionary and developmental biology, complex systems, probability and statistics, as well as other fields. Without this background knowledge, it is not going to be possible to discern who has the science correct and who does not. I write to inform not to persuade. If the reader wants to understand this material on the level I understand it, or at least be competent on the topic, he or she will probably need to take some courses.

Moreover, I did not explain, in this essay, almost all of the *most important* facts and concepts I mentioned. In previous publications, I have explained the differences between a complex system and a simple system and how evolution works by very small changes in initial conditions. In order to understand this essay, the reader should have already read my previous publications. Again, I do not apologize for this because this is how science works. Every defense of a position does not go back and start by summarizing Newton. Then again, most criticisms of scientific positions do not use the shotgun approach or feign ignorance, as animal modelers and their defenders are prone to do, so an all-encompassing defense or explanation of well-accepted science is not needed. As I stated in the first paragraph, it takes more space to refute nonsense than to claim it.

This again brings me to Parliamentary EDM 66 and the idea of a peer-reviewed debate. We want the animal modelers to present, in a written document, their unified case for animal modeling and we will present our case against it in the form of Trans-Species Modeling Theory. Unbiased experts from all the relevant fields of science and other relevant fields of inquiry will then give their opinion, each on the aspects of the argument dealing directly with knowledge in their area of expertise. The scientist-experts will then render their judgement as to which side is correct. This type of thing happens routinely, such as when scientists meet to make a declaration on what is now known and what is unknown in a particular area. Guidelines in medicine, such as when to perform an intra-coronary artery stent placement, are another example. The judgement of the

experts should be accepted and acted upon by grant-giving institutions, including governments, and this should be agreed at the debate's outset.

It is unreasonable to ask average citizens to decide a matter that involves expertise in science, medicine, critical thinking, and other fields. A vast majority have no, or too little, education in any of these fields to make an informed decision. Asking unbiased experts to decide the matter is fair—and the only reason anyone could object to this proposal is fear of being exposed.

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