Debate Between Dr. Ray Greek And Dr. Michael Festing

IV WORLD CONGRESS
SESSION C-1

THE MODERATOR: Welcome to the point counterpoint Session C-1 of the IV World Congress. This is the first major international meeting on alternatives to be held in this millennium. And it's quite fitting that at this time we stop for a moment, not just to think about reduction, refinement, and replacement, but to think about the need for animal research for scientific purposes at the present time.

What I hope we can do today is not to go over the past but to think about the present and where we might be going in the future. To do this today we have two speakers who are familiar and well-equipped by experience, qualification, and training to provide informed insights and analysis and a range of views sufficient, I'm sure, to stimulate discussion.

The format we'll follow here is that each speaker will have 15 minutes to set out their views of these issues. We will then veer onto time of 20 minutes discussion led from the floor, which I will moderate. And at the end we'll give each speaker five minutes to sum up what they think has been said and what they think the key messages are.

My role will be to keep to time. And unlike Jerry Springer, it will be to bring out the best in our speakers rather than the worst in them. And the intention is to generate light rather than heat. It's not to test the strength of people's views, the sincerity of those views, or the duration of time for which they've held those views. It's to actually hear and listen to the evidence and rationale for the views.

Our two speakers today will be known to some or all of you. Ray Greek is a medical graduate who was an anesthesiologist and a specialist in pain management. And in addition to his clinical practice, he has experience of research, both in man and animals. He is the president of the Americans For Medical Advancement, which advocates responsible spending on medical research of your tax dollars, if you're an American resident.

He's known best outside America, I think, from his publications and certainly the publication of *Sacred Cows and Golden Geese* attracted a lot of attention in Europe and farther afield. And his more recent publication *Specious Science* is also now receiving attention and comment.

The other speaker is Michael Festing. Michael is based at a UK medical research council unit at the University of Western UK. And he's known to me as a geneticist statistician and expert on experimental design. He is also a FRAME trustee and chairman of the FRAME reduction committee. And in addition, Michael and I touch base from time to time, as Michael is also a member of our animal procedures committee, the independent source of advice to government ministers on animals and science.

And with those relatively few words, I'll now ask Ray Greek to begin his presentation.

DR. GREEK: Okay, thank you very much. Can you hear me in the back? Can you hear me in the front? Do any of you even want to hear me in the front or the back, that's the question.

Well, thank you. Thank you all very much for coming today. Thank you, Dr. Michael Festing and the organizers of the IV World Congress, for scheduling this session. And again, thank you in the audience for attending.

Hopefully this session will shed some light on our respective positions. Some time ago I was asked by Dr. Festing to explain my reasons for believing that animals are no longer valid for modeling humans. During this debate I will try to outline those reasons, but as it will be impossible to address all areas in 15 minutes, I refer you to the handout, which is available on the back table, to AFMA's Web site, and to our books for a more detailed examination of this question and to the handout specifically for a response to Dr. Festing's critique of our first book.

It is easy to forget how far civilization has come in the past 300 years. Before Newton demigods ruled the universe, and if crops failed or sickness afflicted one's family, it was assumed to be caused by disfavor with God. Darwin's theory of evolution, electron microscopes, DNA, the study of genetics, chaos, and complexity were unheard of. And I think I can say without fear of contradiction, at least from this audience, that the philosophy of life, known as science, has been responsible for these changes and the advances that so separate us from our ancestors of just a few hundred years.

When society first started using science and animals in a serious attempt to learn about human disease and health, it made sense in a way. Grossly animals and humans have things in common, important things. Both were composed of cells. Both were affected by viruses and bacteria, responded to vaccines, had circulatory systems, lungs, livers, and so forth. So the initial idea of extrapolating results from animals to humans appeared valid. And indeed society did learn things from animals.

We can debate whether many of the great discoveries of old were dependent upon animals or whether the animal model even then did more harm than good, but that is not why we are here today. Today we want to have a science-based discussion about the animal model in 2002.

If one grants that initially animal models were useful, then the next logical question becomes, what has changed? Since this debate is science based, it may be appropriate to take a moment and remind ourselves what separates science from nonscience. In our books, the Web site, the handout, and as you will see in my portion of this session, I will present evidence based on science, evidence usually derived from peer-reviewed literature.

Science does not allow proponents to assume their conclusion but mandates they prove it. I will quote data from the scientific literature and stay away from what could only be called opinion, as is required by science. In science opinion counts for little, while references that can be checked are the currency of the day.

Of course, science also concerns itself with predictability and falsifiability. So the first question to be addressed is this. Is there a problem with animal models? Let's take ADMET as an example. First come facts.

Most drugs are effective only in 30 to 60 percent of patients. Adverse drug reactions are the fourth leading cause of death in the U.S. and the UK, and 15 percent of hospital admissions are caused by adverse medication reactions. Legal drugs kill approximately 100,000 people per year in the United States, more than all illegal drugs combined, and cost the U.S. taxpayer over 136 billion in health care expense.

Clearly, the probability of any given medication doing more good than harm is not optimal. And this, at least in part, is due to the animal testing that occurs prior to clinical trials.

Tom Patterson, the chief science officer at Entelos, likens the current practice of drug testing in humans during clinical trials to, quote, "making airplanes, trying to fly them, and marketing the ones that don't crash," not a good reflection of the efficacy of the animal testing that occurs prior to human clinical trials.

Barry Selick, formerly with Glaxo, said that for every drug that is withdrawn from the market, 10 remain available to people, even though they have ADMET-associated problems, and for every drug that is on the market with ADMET-associated problems there is an additional 10 to 50 that will fail before they reach the general public. All this despite extensive animal testing.

80 percent of new chemical entities, or NCE's, fail after Phase I clinical trials, and hepatotoxicity is the most common reason for this failure. Vis-a-vis hepatotoxicity, Mark Levin, Ph.D. and CEO of Millennium Pharmaceuticals, presented this slide at a Drug Discovery and Technology Conference in Boston one year ago. 28 potential medications were tested on rats. And 22 went to the tested on humans regardless of the rat results. Of the 11 that were shown to be hepatotoxic in rats, 6 actually tested liver-safe in humans. Of the 17 that rats predicted to be safe, 6 were shown to damage the human liver.

Levin concluded that this means that the rat data was basically as accurate as a coin toss. Not exactly the predictability we think of when we think of science. Clearly, the ADMET testing process, as it pertains to animal testing, is inadequate, as should be expected from a study of evolutionary biology and complex adaptive living systems.

Attempts to design drug tests that only equal the success rate of animal tests will be of no benefit to society. Pharmacogenomics and broader, longer clinical trials offer the

next step in the evolution of drug development. And that is where we should be focusing our resources. The fact that the three R's community continues to sing the praises of a failed modality while some in the pharmaceutical industry admit it's inadequacies is, in my opinion, significant.

This slide further illustrates the problems of complex systems and, hence, of extrapolation. Among 10 medications withdrawn from the U.S. market between 1998 and 2001, 8 were withdrawn because of side effects that occurred primarily in women. A recent study in *Science* revealed that one strain of mice could have a gene removed without obvious adverse effects, while a similar strain would die without the gene. If men cannot predict the effects of a drug for women and one strain of mice cannot predict what will happen to another if a gene is removed, perhaps we have reached the level of organization or complexity that defines one species from another and even defines one individual from another.

Evolution, the study of complexity, nonlinearity, and molecular biology combine to predict that animal testing should not work. And most importantly, empirical data, such as I have presented today and in our books, supports this. Most practicing physicians will tell you that the animal data is meaningless to them because it has no predictability, and hence they do not even read the animal experimentation literature. Likewise, physicians have complained for decades that longer and broader human clinical trials should be mandated.

In the old days people opposed animal experimentation for many reasons that turned out to be unsound. In the 1800's, for example, many who opposed the animal model also rejected science in general and anything associated with it, like the germ theory of disease and vaccines.

Today, the thing that many in the 1800's antivivisection movement rejected, science, provides us the best reason to reject transspecies extrapolation. Today the level of our study has changed from the gross level to the genetic. And at this level evolutionary biology predicts that the amount of data we can extrapolate from animals has diminished since the 1800's.

Even though humans may share 100 percent of their structural genes with another organism, say, mice, these two organisms can be as different as -- well, as a man and a mouse. By studying mice it is obvious that we can see only a piece of the puzzle, a mouse piece, not a human piece. And the rest of the pieces are usually ignored to the detriment of humans suffering from illness.

Evolution has not built each species from scratch but has added on, as Ptashne and Gann write about in their book *Genes and Signals*, to an already complex system. The use evolution has made of add-ons has resulted in living complex systems that behave like the complex adaptive systems that they are and, as such, differ significantly from their predecessors. Add-ons produce systems that are nonlinear. Small changes on the genetic

level, such as add-ons, can lead to very large differences between species. Indeed, that is what evolution is all about.

The claim that humans and mice are the same animal at the biochemical level just dressed up differently isn't true. Moreover, it is irrelevant to point to observed similarities in genetic makeup between species, since the details of the differences are in the interactions between the conserved genes, not in the genes themselves. It is as though humans and mice have a common genetic keyboard on which different phenotypic tunes are being played. What matters is not the similarity with respect to the keyboard but the differences with respect to the order and timing of the pressing of the keys.

Predicting human response based on an animal model is not an example of, quote, "applying a relatively simple set of well-established scientific principals," end quote. Living organisms are better examples of complexity theory than Newtonian physics. Using the example of a model airplane or an automobile, as so many defenders of the animal model do, is a good example of this. Studying a model of a 747 will allow the observer to demonstrate the basics of flight, just as studying a 1973 Vega will demonstrate the basic principles of an internal combustion engine. But if anyone seriously believes that the model airplane or the Vega can be or is used to repair a Ferrari or a 747, they are deluded. Just as animal model can be and were used to demonstrate very basic facts concerning anatomy and physiology, so a Vega and a model of a 747 can be used.

But today when we want to fix a Ferrari or repair a 747, we don't tear down a Vega engine, nor do we use a model airplane. And neither should we suggest to the public, who is paying for animal experimentation, that a cure for AIDS, cancer, stroke, and so forth will be derived from animal models.

A recent article in *New Scientist* said, quote, "Another key finding from both public and private genome efforts is that many human transcription factors are unique and a cut above those of the fly and the worm. Transcription factors and other regulatory proteins dictate which genes are switched on at vital stages of development as embryos form and organs take shape. It is they that orchestrate such amazing complexity from so few genes. Venter --" and this article is referring to Craig Venter of the Human Genome Project -- "Venter thinks all higher vertebrates have roughly the same genes. What is important is when they are switched off and on. He says," quote, "we have the same number of genes as cats and dogs but differently regulated."

Researchers, such as Marilyn Carroll and Bruce Overmier in their book *Animal Research and Human Health*, state that "animals are causal analogical models and thus can be used to study human disease and predict human response." Note this is different from using animals merely as heuristic devices. Causal analogies are a subset of analogy arguments in which causal assumptions arise based on the model. LaFollette and Shanks have explained how models are used as CAMs in their book *Brute Science*. Basically if a drug, Z, causes death in an animal model, animal experimenters will reason by analogy that it will also cause death in humans. Animals are thus used as causal analogical models. And this

reasoning process has resulted in immeasurable human harm, as we and many others have pointed out.

In light of our current knowledge of DNA, evolution, molecular biology, complex adaptive systems, and nonlinearity, I conclude that the burden of proof is now on those who claim animal models are predictive. They should produce prospective data gathered by investigators without a vested interest in the outcome that proves animal test A, B, and C and so forth is reliable. It is not incumbent upon us to provide any more data supporting the theory that animals are not furry looking humans. Darwin, Watson, Crick, LaFollette, Shanks, Kauffman, Collins, Venter and many others have provided more than enough data. Using animals as CAMs, causal analogical models, in 2002 makes a complete mockery of the scientific method.

In closing, I would ask Dr. Festing these four questions: Are animal models used as CAMs in drug testing and the study of human disease? And if so, why do they fail so miserably in ADMET? And if not, how are they used in drug testing, as they can certainly not be considered heuristic. If you claim they are heuristic, why does big pharma and other vested interest groups claim they are CAMs?

Number two, how specifically do we know which findings and which animals can be extrapolated to humans? For example, most species are unharmed by thalidomide, ritalin, Fen-Phen, Opren, practolol, and so on. And why do interspecies variation, as predicted by evolution and complexity theory, allow for this extrapolation?

Number three, can you produce peer-reviewed data proving that animal models are predictive by comparing prospectively obtained animal modeled results from all species tested to the actual human results?

And finally, number four, if the purpose of the animal model in biomedical research is to aid in easing human suffering, how do you explain the fact the two leading causes of death in developed countries, a high-fat, high-cholesterol diet, and cigarette smoking, were both deemed safe in animal models, that the animal model influenced French scientists to allow HIV-infected blood to be transfused, and that the animal model delayed the implementation of life-saving modalities, such as artificial heart valve, cyclosporin, penicillin, Lasix, the statins, the SSRIs and so on. In other words, what ratio of harm to good is acceptable in a model?

Thank you for your attention. And I welcome any questions during the Q and A.

(Applause.)

DR. FESTING: Right. Can everybody hear me?

About 18 months ago, I think I was, I received a letter from an animal welfare charity in the UK inviting me to go along and meet Ray and Jean Greek where they would be answering questions about their book *Sacred Cows and Golden Geese*. Now, I must admit

I'd never heard of the Greeks until that time, and I was interested in what they might say in their books. I went and got a copy. And to be honest, I was completely horrified by it because I think they had completely attempted to rewrite history and they had clearly failed to understand exactly how medical research is done and how animals are used as models and how alternatives, indeed, are used as models in the process of biomedical research.

So I went along to the meeting, and we had a very interesting free and frank discussion, I think it would be called. And as a result of that, I came back and tried to find whether anybody'd written a review of the book. Apparently nobody had, so I set down and -- sat down and wrote a book (sic), and it was a highly critical review of the book, which I think was justified.

Ray, following that, wrote an extensive rebuttal. He wanted it to be published in the same place, FRAME News, but as it was twice as long as my book review, FRAME said no. And as a result of that, Ray challenged me to a dual, which is why we're here now. This is the modern equivalent of a dual.

Okay, so what basically do they say in their book? They say humans and each species of animals differ. Nothing new there. Everybody can agree on that. Therefore animals can never be scientifically valid models of humans. And this is their basic thesis, because of the difference between animals and humans we cannot use animals as models of humans.

Animal research, they claim, has never contributed to human welfare, and in doing this they've rewritten history. The only proper model of humans is humans, and therefore, the only proper model of animals in vet research is other animals of the same species. So if you want to develop -- if you want a drug for dogs, you've got to do research in dogs and so on.

Now, straightaway you can see the weakness if we just consider this last point. Dr. Jean Greek is a vet. Now suppose one day she gets a call from the local zoo, "Can you come along and help us? We've got a tiger who's sick."

And so she goes along and she sees this tiger, and it's got maybe a splinter in its paw. What does she want to do? She wants to give it a tranquilizer so she can then anesthetize it and maybe give it a dose of antibiotics, clean up the paw, and so on. What can she do? Nobody has used tigers to develop drugs and anesthetics and tranquilizers for tigers. There are no drugs developed on tigers.

So what would she do? Of course she would go and see what drugs and anesthetics and so on are available in other species. Now, I don't say that she could necessarily use them all just as they are, same doses used for other species. But she, with caution, she would almost certainly find that she could treat her tiger with the available drugs available in the veterinary sphere.

Okay. So now what we really want to question is, given that humans and animals differ, how can animal research ever be scientifically valid? What I will do is show how and why

animals and alternatives can be used as models, even though they do differ indeed from animals (sic). I'm not going to discuss all the major achievements of animal research because there simply isn't time to do that.

I will accept that each animal research project must be scientifically and ethically justified, because of course it is only too easy to do the experiments. There is no doubt at all about that. I will show the philosophical justification for the use of animals as models and for the use of the alternatives as models is in fact identical. And if we say that we can't use animals as models of humans, philosophically we would have to say also that we can't use any of the alternatives that you are all developing, because after all, a test tube full of even human cells is not the same as a human.

Okay, so where do we go from here? Mark Switavski (sp?), an American philosopher has written a book on models where he says "Theories, hypotheses, models, and analogies I take all to be species of a genus. And my thesis is best stated directly by characterizing this as representation. So we use animals as representations of humans." He goes on to say, "There is additional trivial truth which may strike some people as shocking. Anything can be a model of anything else. This is to say no more than between any two things in the universe there is some property which they both share. So there can be a vast asymmetry between the likenesses and the dislikeness between a model and the thing they're modeling."

And I want to use an analogy to explore this in a little bit more detail. My grandchild lives in New York. And last summer we took her to Brooklyn Botanic Gardens. And when you go into Brooklyn Botanic Gardens, they give you a map. Now, a map is a model of Brooklyn Botanic Gardens, clearly is a model, a representation of Brooklyn Botanic Gardens.

My six-year-old granddaughter immediately took control of it, and we had to tell her where we wanted to go, and she showed us how to get there taking control of the map. Of course, when you come to think of it, children immediately know all about models because we supply them with models as toys, model dolls, model humans, model trains, and so on.

What is a characteristic of this model? How is is similar to the real Brooklyn Botanic Gardens? Well, it's only got one similarity, a spatial orientation, or a spatial relationship among features on this maps are similar to the real Botanic Gardens. There are millions of differences. Think of Brooklyn Botanic Gardens, which has insects, plants, soil, buildings, and so on. So there are millions of differences. And just because there are millions of differences, that doesn't mean to say it's not a useful model.

The other thing is that the scales are different here. This is an important point about models, that models do not -- sometimes the differences between the models and the thing we're modeling is very useful. You can imagine a map which was full scale of Brooklyn Botanic Garden covering several acres would be totally useless for our particular purposes.

Okay, the next point is that maps are useful only for a specific purpose. And this again is the point about our models. We don't use them to model everything in humans. We use each model specifically to model a particular characteristic. And in those circumstances we can indeed use them for prediction. A model, of course, has to be validated. And in the case of this particular map, we would validate it by looking to see whether, when we enter the gate at the top left-hand corner, whether we see a long avenue of trees with grass. If we didn't see that, of course we would begin to think that we had either got of wrong map or we didn't know where we were.

And of course you must have the right map. If you have the wrong map, then catastrophe could ensue. Last week, was it, eight -- or last month eight miners in this country were given the wrong map, as a result of which they nearly broke -- they nearly lost their lives because they broke through into a tunnel which was flooded. So you need the wrong (sic) map.

And models can provide new information. I mean the moment I was given that map, I knew a whole lot about Brooklyn Botanic Gardens without having to go and explore it and find it all myself.

Okay, so what we're going to do is look at a couple of models Ames test. Here is an in vitro model, chemicals which disrupt DNA may cause mutations and cancer in humans. Bacteria and mammals, both have DNA, so doubt about that. Mutagenesis in bacteria is easily tested; therefore, the bacteria in Ames test can be used as a model of human response to chemicals which may or may not cause cancer, may or may not be carcinogens. So the Ames test has been validated to some extent. It's not a hundred percent valid. It's accuracy is in some doubt, I must admit, but it's still regarded as quite a useful test.

As an animal model, we look at the rabbit response to an injection of insulin. Insulin reduces blood glucose in both rabbits and humans; therefore, rabbits can be used to model humans in testing the potency of insulin preparations. There is no doubt about that. That's a predictive model. It has been valid repeatedly because it's been used for more than 60 years in testing the potency of insulin preparations. It's no longer a necessary model because nonanimal assays have now been developed. But it is still a scientifically valid model.

Okay, what about animal model in the development of drugs and vaccines? Well, just four very quick -- three very quick examples. Antirabies vaccine developed in about 1885 by Pasteur using dogs and rabbits. The point about the use of the dog here is that rabies is a virus which affects both humans and animals; and therefore, animals could be a model for developing a vaccine. And in fact, having developed a vaccine against rabies which was effective in dogs, Pasteur found that the same vaccine was equally effective in humans.

Salvarsan for treating syphilis. Ehrlich screened more than 600 arsenic compounds in rabbits. He was able to do this because a colleague had developed, discovered that rabbits could be infected with syphilis, so he was able to screen a large number of compounds to

see whether they were effective against syphilis, and he found one of them, salvarsan, wich was.

And indeed, this sort of process has been used repeatedly in drug development. Of course one needs, following discovery of a drug which will cure the disease in rabbits, of course one needs clinical trials. That stands to reason. One needs clinical trials, and some of them will fail. Nevertheless, it is one way of developing drugs. And so far no better way really has been developed. Although maybe in the future we will develop better ways.

Penicillin was isolated in 1929 by Fleming. He couldn't isolate it. Chain and Florey did so. And this is a good example of the use of an in vitro model, because of course penicillin will kill bacteria in vitro, in a test tube, and therefore they didn't need to use an in vivo model in the isolation of penicillin. But they did need to use it in testing the efficacy and whether it was toxic. And we know in that case they used mice.

So we now have a whole lot of vaccines that have to be tested still in animals. And until such a time as we have alternatives, we will have to continue to use these animals to test the safety of these vaccines. For example, polio is a live vaccine, and it's notorious for reverting to virulence. If we did not test it in animals, then every so often we would give a batch of polio vaccine to children who would then get polio. And as a result of that, people of course would stop vaccinating, and they would lose confidence in the vaccination process, and polio would come back as a serious disease.

Now I'll give you an example of a model developed for a very specific purpose. In -- at Lester (ph), a young surgeon working with terminal liver cancer patients. They had tumors in their liver. You can't excise those surgically, but what he has is a new probe about the size of a pencil, which he can put into the tumor and give a dose of microwaves and cook it.

So the question he asked is, what dose of microwaves could be needed to cook a tumor of a given size? And does cooking a tumor sitting in your liver harm the patient? Now, he couldn't test this on patients because really it would not be at all ethical to do so. The models he used was pig's liver from a butcher. He tried this first. But of course pig's liver from a butcher is not the same as pigs liver or human liver, live liver, because there's a considerable blood flow through liver.

So he used second 13 pigs given various dose levels. The lesion diameter was recorded, and the fate of the lesion was recorded. After a couple of months it had shrunk away. And he was then able to test -- to treat so far nine terminally ill patients who were expected to die. And as a result of this procedure they are now living.

So okay, but Christopher Columbus didn't have a map. Sometimes we need to explore things a little bit. The procedure is quite straightforward. We study another life form because it's easy, practical, and often ethical. We find the phenomenon that -- likely to be of medical importance. We say is it also seen in humans? If it is, we've got new knowledge. If it's not, then we don't have new knowledge.

So I'll just very quickly give some examples. Mendel's laws were developed use peas. Now, Mendel was not aware that he was developing a model for the mode of inheritance of cystic fibrosis in humans. So in that sense is was an orphan model. He'd developed the model, but he didn't quite know what it was a model of.

Muller in 1927 discovered that irradiation caused mutations, using drosophila. There are some other examples there, which I think I'm going to skip over because I'm running out of time.

I'll just come to this last model here, human obesity. This is a major problem. Here is a genetically obese mouse. We don't know how appetite is controlled. And this mouse maybe gives us an opportunity to learn that. It's been around for about 40 years. Recently it was cloned. We didn't think it was a model of any human disease. Because of course, human obesity we thought was never controlled by a single gene.

But lo and behold, once we cloned it and discovered that it coded for a protein called leptin, a human family with this particular deficiency was discovered. So straightaway as an animal model and a human equivalent. The same mutation, as I say, is found in humans. And now this gives a stimulus to explore what are the genes that control appetite and how might appetite be controlled.

And you might have seen there was a paper last week in *Nature* in which the hormone PYY 336, which is secreted in the intestines was given to mice, rats, and humans in a controlled double-blind trial. And it was shown to reduce appetite very substantially.

So let me just finally add this -- which is not strictly relevant, but it is important to remember that if you live an average lifetime of 75 years in the UK -- we've got very good statistics on numbers of animals used -- your total usage of animals will be about four. You will use, as it -- well, other people will use on your behalf 2.4 mice, .4 of a fish, .8 of a rat, and .4 of other animals. So that is a total requirement, as it were, for you for a lifetime's medical research.

So I will conclude here, yes, we still need animals in medical research until we can develop alternatives. Animal and alternative models have the same philosophical justification. They do not need to be like humans in every respect. They do of course need to be validated. Models can provide new information. I might come back for the 747 model a little bit later. Scientific validity alone, of course, does not justify use. Each project needs separate and scientific and ethical justification.

Thank you.

(Applause.)

THE MODERATOR: Thank you, Michael, and thank you again, Ray.

I plan to have discussion and comment from the floor till around 2:00 o'clock. Then I'll allow each speaker five minutes to sum up. And then we'll make way for the next session in here which starts at 2:15.

Bob, do you have a question or a comment?

QUESTION: Yes. I have a question (inaudible) Michael. I obviously have put my cards on the table. I'm sorry (inaudible). And I'm having (inaudible) question (inaudible) the question is very simple. Do you hold your views that animals are still required in experiments because you are a trustee at FRAME and because FRAME gets funding from industry, as is implied from this document?

DR. FESTING: Absolutely no. I don't get any funding from industry. I'm an independent person, and I speak my own views, not the views of FRAME. And of course not.

QUESTION: Dr. Festing, do you consider validation by virtue of use -- I'm speaking specifically about animal tests now -- to be proper validation?

DR. FESTING: It depends on the circumstances. For example, the example I gave of testing batches of insulin preparations for potency. That in a sense is validation by use. It goes on over many, many years. And therefore I would say that is reasonable validation.

There are other circumstances where maybe it's not. So I think each case has to be judged on its merit.

QUESTION: Could I just follow up with a question?

DR. FESTING: Yes.

QUESTION: Would you -- would you support proper validation under the current standards that were arrived at in (inaudible). Would you support those validation criteria for new animal tests or revised animal tests?

DR. FESTING: Again, it depends on circumstances. I mean, you look at the example I gave you of the liver tumors where a microwave probe was used to develop a new treatment for liver tumors. In a sense this -- the validation of that was when it was first used in patients. So there's a very, very short period from the development of a technique to its actual use.

But of course in drug development this takes years and years and years. So I don't think you can give a general answer to that.

QUESTION: Sorry.

THE MODERATOR: You have to come and sit up here.

QUESTION: Is there -- can you give me an example of an animal experiment that you would not support simply on ethical grounds?

DR. FESTING: Well, anything that is trivial, anything that is badly designed. I mean, I am personally quite critical of much of biomedical research. And if you'd like to come to my symposium immediately after this, you will hear that I will give some critical comments. So anything that is not scientifically valid and anything that obviously creates excessive amount of pain for a trivial gain I would say I wouldn't support.

QUESTION: That was (inaudible)

THE MODERATOR: Any other comments or questions?

QUESTION: My name is Ken Shapiro, a psychologist for the ethical treatment of animals. And at an earlier symposium I made some comments about use of animal models. And both of you have emphasized that the issue of whether or not the model and the model are similar or different. And my thesis is that that kind of discussion, the (inaudible) model and models are similar and different is not the bottom line problem.

If validation simply means discovering similarities and confirming similarities, then that's not very helpful bottom line criteria. A better criterion is do we learn anything new? You validate the stuff that you knew to be in the target and find it in the model or vice versa. And that's not having learned anything.

You also can learn from differentness -- differences. So we need other criteria besides validation. One of those criteria is do we learn anything? Second is do we gain an effectiveness for treatment? And there are simple ways of ascertaining these considerations. One is the citation analysis. Did the animal model in literature receive citation levels comparable to other studies? Did they receive citation levels in those relevant clinical specialties where they're supposed to be applied?

We can also do surveys of the relevant clinical specialists. Do they know about these animal models? Do they find them useful?

So it seems to me that this discussion of similarities and differences goes on forever. It's half empty; half full. Ray says they're different; you say they're similar. Back and forth. You go to different levels, analysis, biochemical, and so forth and so on. That's not where it's at.

Where it's at is do we learn anything? And was it -- do we gain in treatment effectiveness? And there are simple social scientific analytic tools to determine that. What we need is researchers to go out there and study particular animal models, find out the level of citation, interview the appropriate clinical people, and find out whether they learned from them. That will give us good scientific argument about the science and use here.

That's of course (inaudible) ethics, which I don't do. I think it's unethical to do this research. But that's not the discussion here.

DR. GREEK: Can I comment? I agree with you, Ken. And I think if you read one or both of the books --

QUESTION: I have read them.

DR. GREEK: -- I -- then you know that I quoted that study, that citation study that I think you're referring to. And I think it's in the second book in the neuropsych chapter. So I agree with you.

But this, without getting into the old M.D. versus Ph.D. argument, you know, is basic research good in and of itself? Or does it have to produce something? Okay, without going down that direction, what we tried to do in book two especially was do both things, okay.

Kind of coming to you today as a clinician primarily and someone who has taught in two medical schools, I can tell you point blank a vast majority of my colleagues think the animal model is a waste of time. And this goes across party lines. It goes across all ethnic groups, male, female. I mean it's just a joke.

And if you really want to see some people get upset, talk to some physicians who have recently had relatives or a close patient die and tell them how much money went for breast cancer or Alzheimer's, you know, for the animal model.

So I agree. I'm very happy to see empirical data. And indeed a vast majority of book one is empirical data. And furthermore, I would also say -- you're shaking your head. You don't think a vast majority of book one is empirical?

QUESTION: No, it isn't empirical data that I am talking about. It's simply descriptions and show differences. It doesn't say whether those similarities (inaudible)

DR. GREEK: Okay. That leads me to the second point. The second point is why are you doing the research? Okay, the examples that we use and will continue to use are examples where the animal model failed. They're peer-reviewed references, et cetera. Et cetera.

Now, if you're doing animal experimentation in order to help human beings, then show me the data. Show me the data that says it helps. And I think that's where you and I are agreeing on this. I'm saying that when I quote studies out of the *New England Journal* and *JAMA* that show that based on an animal model of stroke, 38 people died in the experimental group and 14 died in the control group that didn't receive the treatment, that's as good as it gets.

Now if you, you as a psychologist, want to then go into the kind of psychological, sociological domain and ask physicians, I agree. AFMA, even as we speak, is sponsoring

a very large poll in the United States and is asking those exact same questions. But as a scientist, I don't really care what my clinicians say. I want to see the peer review data. And if 198 drugs are released and 102 are relabeled or recalled, that's significant.

And I'll let Michael disagree.

DR. FESTING: Well, it rather depends what level we're talking at. I mean we heard this morning about how many species have now been sequenced and how useful it was to, as it were, explore the genomes of different species and get new information from them. And these are basically, therefore, being used as models of humans. And I think that sort of exploratory research is excellent and very good.

And I tried to make the point that quite a bit of animal research is exploratory in nature. We are looking at things like mutations in that obese mouse to try to find out what happened. Sometimes this will give us information which is extremely useful for humans. In the case of the obese mouse it tells us that there is a compound, leptin, which is produced by the white adipose tissue which controls appetite. And we can go on to discover other genes that control appetite, as is being done now. And maybe one day we will find a way of controlling human obesity.

And this is the sort of research that goes on extensively using animal models, using not only vertebrate models, of course, but lower animal models. People are not pumping lots and lots of money into research on the worm C. elegans because we want a better world for C. elegans. They're doing it because it will tell them, tell us a lot about humans.

For example, in my institute we're studying apoptosis. Apoptosis is programmed cell death. Cancer is a disease not only of multiplication of cells but a failure of cells to die. We want to find out how we can cause cells to die. C. elegans maybe will help us because a lot of the genes that are responsible for cell death in C. elegans have been identified in humans. So that sort of model I think is extremely valuable.

THE MODERATOR: Time for one more question.

QUESTION: I have one comment to make. I didn't hear anything about the validity that we distinguish in (inaudible) research, that the construct validity or the face validity (inaudible). And I think you are mixing these constantly. And then you can compare them. Construct validity means that you have the same biochemical basis. And face validity is that a disease looks the same in humans and in animals. You should put these two apart and not mix them up like you did with the airplanes and the engines.

DR. GREEK: I don't think I mixed them up. I think that complex adaptive systems have causal functional dissimilarities. And I think that in and of itself invalidates the extrapolation. I also think that causal system disanalogies exist, which also invalidate animal models.

And again, I think -- and Michael can feel free to disagree -- but when I participate in discussions like this, what I hear are two entirely different conversations. Okay. If you want to have a conversation about whether or not animal models are heuristic, that's fine. We can have that conversation.

That's not what I'm having today. What I'm telling you is that they don't help me as a physician. Now, I'm telling you that animal models are not CAMs, they're not causal analogical models, which the animal experimentation community maintains that they are.

Now, look, there's a lot of things that are debatable in this venue. But there are some things that are not debatable. And until both sides of this issue can come together and agree on the fundamentals, you're never going to make any real progress. And as long as people continue to confuse HAMs and CAMs, which is what you're accusing me of, by the way, no, it's not going to happen.

But if you're talking about biomedical research on animals in the hopes of curing human disease and, by god, especially if you're talking about drug testing, that is the use of animals as CAMs. There's no way you can say that's heuristic or anything else. If it kills the mouse, it doesn't go to human trials. Okay? And that's what I'm telling you is doing far more harm to my patients than good. And if you disagree, show me the data.

Sacred Cows has about 5-, 600 references. *Specious Science*, plus or minus the same. I figure half of them are from peer review sources. So I think there is a huge amount of data supporting my position.

And I would just note -- I was going to save this for the last five minutes, but I would just note in my presentation today you saw reference after reference after reference. *Nature, Biotechnology, Nature Medicine.* I think the oldest one was 1996. I didn't see any in Dr. Festing's.

DR. FESTING: You didn't see a reference to --

DR. GREEK: I didn't -- I couldn't see it.

DR. FESTING: There was a reference to *Nature* last week.

DR. GREEK: Last week. And how many references did you have in your presentation?

DR. FESTING: Oh, I don't know. That's not relevant.

DR. GREEK: Okay, I -- I couldn't see the screen that well. But my point remains, and I make the point also in the handout, if anyone cares to read it.

THE MODERATOR: Ladies and gentlemen, we're about to enter the last phase of this point-counterpoint discussion. I would like to invite each speaker in five minutes each to

expand on what they said in their opening remarks and to comment and explain on anything that they've heard either in the discussion or the opposing speakers say.

And on this occasion Michael Festing will speak first.

DR. FESTING: Okay. Standing up here and really not quite sure what I'm going to say, Ray's paper really didn't tell me anything at all. He uses quite a lot of long words like "CAMs" and "HAMs." I think LaFollette and Shanks introduced these terms.

They use quite a lot of what I call straw men. In other words, they say scientists believe such and such, and then they tear down what it is that scientists, they say, believe. But in fact scientists don't believe those things. They are straw men. They are not -- they are not what scientists do.

Again, I think again with the LaFollette and Shanks in their book, they are two philosophers. They have used the terms of philosophy to investigate how biomedical research is done. Now, what is the raw material of philosophy? The raw material of philosophy is what people have said. So what they've done is to look to see what people have said, and they've taken selected quotes from wherever they wish and tried to build a philosophical argument.

What they haven't done is to go and look at original publications. And I would suggest at some extent Ray Greek has not done that. Because in his book a lot of the references are simply to antivivisectionist literature, and much of that is quite unreliable.

So I ought to respond to one or two things that he's said. Again, the 747 model is something that LaFollette and Shanks have brought up. They say that models can't produce anything new. Because a model of a 747 is produced as a result of copying a 747, we can't learn anything new from it, because it's got all the information from the 747. Well, that's simply not true. I'm sure all of you know that if you want to develop an improved 747, say, better streamlined, less air resistance, what you do is you use a wind tunnel model of a 747 to try to improve it. Now that is use of model to predict a better 747.

And if you want to teach a pilot how to fly, what do you have? You have a model of a cockpit, a simulation. And you teach the pilot how to fly using that model. Those are perfectly valid models, and they will give new information.

So it's simply not true to say that models cannot produce any new information. They certainly can because there are circumstances where we simply can't use a 747 to train pilots. At least they might well crash them.

So I don't think Ray has produced anything in his talk that I can respond to in particular, and I don't think he's produced anything new. So I'll stop at that.

DR. GREEK: All right, let's see if I can get the computer to work.

This, I think, came from *Science*. This is a quote from the atmospheric scientist Stephen Schneider of the National Center for Atmospheric Research. And he said that "to do that" -- and this is to communicate the risk to reduce the possibility of disastrous climate change. He's a big antiglobal warming guy -- "we have to get some broad-based support to capture the public's imagination. That of course entails getting loads of media, so we have to offer up scary scenarios, make simplified dramatic statements, and make little mention of any doubts we might have. This double ethical blind that we frequently find ourselves in cannot be solved by any formula. Each of us has to decide what the right balance is between being effective and being honest."

Now, quite frankly, that statement offends me. But what offends me more is that Stephen Schneider won the AAAS award for the public understanding of science for his work that led to that statement.

The book, the first book, has been criticized out the wazoo by people who, A, don't practice medicine and, B, who don't understand the difference between a publication in *Nature* and *Science* and something that's written for the general public. People simplify. And that's not a sin. Every day when I talk to patients or when I did talk to patients I simplified things. And if you really wanted to go get down to the nitty-gritty, some of the things I simplified to the point of, like Schneider said, we have to draw this double ethical blind.

But let me tell you something. When I go in to have a hernia operation, the surgeon simplifies when he tells me what he's going to do. And when he asks me to put him to sleep for an operation, I also simplify. Okay? So I stand by every word we wrote in the book.

Now, if you want to have a book that's written to the standards of *Nature* and *Science*, I'm happy to do it, as long as you find me a publisher, and that's not going to happen. And again, what we tried to do in book one was give people enough references -- and, hey, take all the references to the AV societies out. That's going to be maybe one percent of the references. And I would ask you to judge the book just on the references in, you know, the top ten peer review journals of our time, *Science, Nature, Nature Biotechnology*, and so forth.

With regards to what Dr. Festing had said, I think with the tranquilizer issue and my wife going to see a tiger, that's one reason why we have veterinarians today who specialize in exotic medicine. And I'll give you an example. When big game, lions, tigers, et cetera, are tranquilized, they use a tranquilizer called carfenta. And they have two people that drew it up. One person stands by the other person with a syringe of narcan. Because if one drop, one drop, of carfenta gets into your system, you will probably die of respiratory arrest and/or paralysis.

Now, again, there are huge differences. And I think that once you understand complexity and chaos -- and for our definition complex adaptive systems are very similar to chaotic

systems. And that is, a very small change initially can result in huge changes on down the line.

By the way, Neil Shanks is a Ph.D. in physics*, and he teaches molecular biology at a university in the United States.

So and also when we decided to have this debate, this debate is about what's ongoing in the year 2002. Rabies, insulin, syphilis, penicillin, those are all examples that we've disagreed on in the past.

So again, I would just point out, if you want to know where we stand on these issues, read the books, read the handouts, and by all means, check the references. And I still will stand by everything that we've said in both books. And I'm happy to talk to anybody about it afterwards.

And thank you again for coming.

(Applause.)

THE MODERATOR: Ladies and gentlemen, it only remains for me to invite you to thank the organizers of the IV World Congress for inviting Ray and Michael to speak today and to thank them for coming and sharing their thoughts with us today. Thank you.

(Applause.)

* Actually Shanks studied physics as an undergraduate and went on to earn a PhD in the History and Philosophy of Science.