DEBATE: RAY GREEK VS. ERIC SANDGREN
Are Animal Models Predictive for Humans?
University of Wisconsin, Madison
September 26, 2007

(Introduction.)
ZWEIFEL: My name is Dave Zweifel. I'm the editor of the Capitol Times, which is sponsoring this debate as a public service. I have with me tonight one of our staffers, Susan Troller, and her husband Howard Cosgrove, who will assist me.

I want to thank you you all for coming. And I'm sure the next two hours will be informative and contribute to our understanding about animals and research and allow us to formulate our own views on the subject.

First I want to emphasize that this is a debate aimed at giving vent to the two sides on this issue. I know that emotions over animal research are high on both sides. But please, let's be courteous to the people who have agreed to give of their time and spend the next two hours and enlighten all of us.

And to do that we have with us two esteemed experts in their respected fields. First, Ray Greek, on my left and your right, who is president of Americans and Europeans For Medical Advancement, is here from California to argue his case. Dr. Greek, an anesthesiologist and an expert in pain management, has written and coauthored with his veterinarian wife three books that argue that animal research is cruel and unnecessary.

He has also authored several major pieces on the subject for major magazines and newspapers and is in demand throughout the country and globally to discuss animal research. We are indeed fortunate to have Dr. Greek here this evening.

Next, Dr. Eric Sandgren on my right has dealt with this topic for years in his position at the UW Mass's veterinary school and his position as chair of the All-Campus Animal Care and Use Committee. He did his undergraduate work here at the UW. He got his veterinary degree and Ph.D. in genetics at Penn and then joined the vet school here in 1993.

In his research studying pancreatic and liver cancer, Dr. Sandgren uses genetically modified mice. He is keenly knowledgeable in animal researches, and we indeed too are fortunate to have his participation here tonight.

We will conduct this debate as follows: Dr. Greek will start off. He will have 30 minutes to present his case. Then Dr. Sandgren will have 35 minutes to give his side. And Dr. Greek will come back with five minutes of rebuttal.

Following those presentations we will spend the remainder of the time, approximately 45 minutes, on questions and answers. All members of tonight's audience are invited to submit written questions using the paper and pencils I think that you received when you came in the door. And Susan and I will in turn direct those questions to the two doctors. We will not take questions verbally from the floor.

Drs. Greek and Sandgren will each have two and a half minutes to answer the questions that you have asked. Neither debater will be allowed to interrupt the other. Susan and I will keep time and give warnings before cutting off either debater at the time that their time expires.

And again, please be courteous. No matter how strong the feelings, no interruptions from the floor, which would only spoil our ability to hear the arguments.

We will now proceed.

Dr. Greek, you're first.

DR. GREEK: Is my microphone working? Everybody hear me okay? Does everybody want to hear me? I think that's probably the more pertinent question.

ZWEIFEL: Can you be heard in the back? Just raise your hands. Okay, good.

DR. GREEK: All right. Well, thank you very much.

Before I get started, I'd like to thank the Wisconsin Historical Society for allowing this debate to be held in their auditorium. I'd like to thank the Capitol Times for sponsoring the event and Dave Zweifel for moderating. I'd like to thank Rick Bogel and the Alliance for Animals for organizing the event. And of course I'd like to thank Dr. Eric Sandgren for agreeing to participate.

Eric, you did not have to do this, and I appreciate your participation.

And finally I would like to acknowledge and thank the National Antivivisection Society, whose generous grant allows Americans for Medical Advancement to continue to function.

Can everybody see the cartoon?

Well, suffice it to say that we're going to take the road to the left tonight and look at some unquestioned answers.

Now, before I begin I need to set out some disclaimers. Number one, I cannot cover everything in one brief lecture. So please understand that there will be some necessary omissions. For the details and more information, I recommend the numerous references and books discussed on our Web site.

Number two, I am not here to convince you of a concept that may be totally foreign to you. Rather, I am here to ask you to question some old assumptions. We have been taught from high school on that animals must be used to ensure the safety of drugs and discover the cause and cures of disease. We respect our teachers and our mentors, like we should. And hence, it is difficult for us to question some of what they taught us.

But in scientific pursuits before a claim can be established, it must be proven. There are many instances of the scientific community accepting a concept that later proved false or rejecting one that later proved true. Usually such mistakes were corrected because a few scientists stayed true to the scientific method and accepted the evidence regardless of the consequences.

The paradigm of science demands skepticism and is antiauthoritarian. Opinion does not count. Evidence counts. Before accepting a concept, scientists expect to see evidence, usually in the form of supporting documentation from the scientific literature. I will list on my slides, as I'm sure Eric will, references from the scientific literature supporting what the slide says.

It is important to note that documentation, as is relevant to our discussion this evening, does not consist of anecdotes. One very impressive correlation or even multiple correlations between animals and humans is not scientific evidence of predictability. A multiplication of anecdotes does not equal evidence. It is still anecdotal.

Rather, when trying to decide if a research modality, such as the use of animal models, is predictive for humans, one must produce data and studies that compare what the animal model revealed in many cases many times with what actually happened.

For example, if one wishes to evaluate the animal model of testing drugs for their ability to cause heart attacks, one should look at drugs that caused heart attacks in humans and then look at the animal species that were tested and see what happened in them. If five animal species were tested and only one showed heart damage, it is incorrect to conclude that that animal model predicted heart attacks in humans. To focus only on one animal species in one test would be anecdotal.

I will give examples of scientific evidence in my talk, and I will contrast that with anecdotes. On the other hand, proving a modality is not predictive is actually much easier, as sufficient scientific studies can invalidate a hypothesis, for example, that animal models are predictive for humans.

Number three, I claim that animal models are not predictive for drug testing and disease research, and the predictability of animal models is the topic for tonight's debate. My organization and I do not deny that occasionally an animal will react to a drug or a disease in the same fashion as a human. But this is anecdotal. It does not imply predictability.

Retrospective analysis will usually find an animal that mimicked human reactions to drugs or disease or whatever. But again, this is not the same as prediction. Retrospective prediction is an oxymoron.

Now, obviously animals can be used in many scientific pursuits, some of which I have listed on the slide. And again, obviously humans and animals have things in common, and, hence, animals have been used in the past for many things, such as to demonstrate the germ theory of disease, to demonstrate that blood flows in a circle, and to learn about very basic physiology. But that is not where science is today.

Today we are studying humans at the level where the differences between species outweigh the similarities. Claiming past successes justify current use is like using a canoe to travel across the Pacific Ocean. Yes, it was done at one time, but today we use airplanes.

And lastly, Americans For Medical Advancement is in favor of anything that leads to cures or safer drugs. If animal models were predictive, we would not oppose them. We are not an animal advocate group. We accept funds from animal advocate groups and individuals, but we would gladly accept funds from the American Physiology Society or WARF, if they offered to give us any.

Our position is very straightforward. We reject the animal model as a predictive modality for humans while acknowledging their scientific viability in other areas.

So our debate tonight focuses on predictability. So I'd like to take a moment and define that word. I looked up various definitions in various dictionaries and so on, and I thought this was a very representative one. And I think I got this one from Wikipedia, actually. It says, "A prediction is a statement or claim that a particular event will occur in the future in more certain terms than a forecast. In a scientific context, a prediction is a rigorous, often quantitative --" and this is an important term to remember -- "statement forecasting what will happen under specific conditions typically expressed in the form 'If A is true then B will also be true.'"

Now, outside the rigorous context of science, prediction is often confused with an informed guess or an opinion. Occasionally getting the right answer is not the same as predicting it.

This is a little two-by-two table that anybody who has ever studied statistics is far more familiar with than they probably would like to be. And but this is how we test a test. This is how we decide if the test actually does measure what it is we want it to measure. And there is little math formulas that we can go through. And we can calculate sensitivity and specificity, and so forth. Tonight we're going to focus on positive predictive value, since that's kind of what we're talking about.

Now, before I get to the scientific evidence, I want to give you examples of how scientists who use animals use the word "prediction." Now this is from a toxicology textbook in

2007. It says, "Biomedical sciences use of animals as models is to help understand and predict responses in humans in toxicology and pharmacology." It goes on to say, "By and large animals have worked exceptionally well as predictive models for humans. Animals have been used for models for centuries to predict what chemicals and environmental factors would do to humans. The use of animals as predictors of potentially ill effects has grown since that time.

If we correctly identify toxic agents using animals and other predictive model systems in advance of a product or agent being introduced into the marketplace or environment, generally it will not be introduced."

This is from a 2006 Cancer Research Journal. It says, "Genetically engineered mice closely recapitulate the human disease and are used to predict human response to a therapy, treatment, or radiation schedule."

And finally this is from the New York Academy of Science in 2003. It's an abstract of a paper. And it says, "The failure in the clinic of at least 14 potential neuroprotective agents expected to aid in recovery from stroke, after studies in animal models had predicted that they would be successful, is examined in relation to principles of extrapolation of data from animals to humans."

Now, all of these examples are viable ways that the word "prediction" is used in science. And I think this is very clear as to how these people use the word. Well, why is this important? In an editorial in Nature in 2006, the editor said, quote, "In the contentious world of animal research one question surfaces time and again, how useful are animal experiments as a way to prepare for trials of medical treatments in humans? The issue is crucial, as public opinion is behind animal research only if it helps develop better drugs. Consequently, scientists defending animal experiments insist they are essential for safe clinical trials--" in other words, that they are predictive -- "whereas animal rights activists vehemently maintain that they are useless."

Now, I'm not going to maintain that they're useless, but I am going to maintain that they are not predictive.

And let me just delve a little bit further into this word "prediction." Let's assume that there are 200 faculty and staff at the University of Wisconsin in the history department. I have no idea how many there are. I just made that up. Well, it's football season and eventually we will have a bowl championship series and we'll have a champion in the Division 1A football. And let's assume that the 200 people in the history department all wager on who will be the ultimate No. 1.

Now, it's highly probable that at least one person will get the correct answer. So can we say then that the history department always predicts the winner of the BCS? Well, no we can't, because if the history department were predicting, they would only get one pick, not 200. And this is a classic fallacy known as the fallacy of composition. It confuses a collective and distributive forms of a word.

But the animal model community is prone to use words in this fashion. For example, thalidomide is a drug that caused birth defects in humans in the late '50s and early '60s. And the drug caused the exact same birth defects in a particular rabbit. Now, some people would say that therefore the animal model predicted thalidomide would be dangerous.

The problem with that is that there are over a hundred species and strains of animals that were tested, and very, very few of them mimicked the human response. Over 90 percent of the animals tested did not suffer birth defects from thalidomide. So you really cannot say that the animal model per se is predictive. Neither can you say that the rabbit predicted the response. In order to say that the rabbit predicted this, you would have to see what the rabbit did when tested with other known teratogens, drugs that cause birth defects.

Now, if the rabbit mimicked humans nine out of ten times, 19 out of 20 times, that's not bad. I would accept that as being a pretty good predictor. But in point of fact, rabbits are very, very poor predictors. And this is just an example where they happened to correlate with human data.

Well, the reason that we know that rhino horn is not an aphrodisiac, aside from the fact that I took a whole lot of it in college, is because of the scientific method. Okay, the scientific method is the best method we have of understanding the material world. And we can do studies, and we can actually find things out. And it's really neat.

Now, teratogenicity is to see if drugs cause birth defects in humans. Teratogen means birth defects. And there are approximately 1500 chemicals that cause birth defects in animals. Of those, only 40 have been shown to cause birth defects in humans.

Now, we're going to use our little two-by-two table up here, and we're going to calculate the positive predictive value of animal tests for birth defects. And as you can see it's about three percent. Not stellar.

This is a study published in 1990 where six drugs that were in clinical trials were studied for their side effects, and then people retrospectively looked back at the animals that were tested to see how everybody compared. And what they found was that animals and humans shared 22 side effects. And we call those true positives. Animals incorrectly identified 48 side effects that in fact did not occur in humans. And the animals missed 20 side effects that in fact did occur in humans.

Now, again, if we use our little box down here in the right-hand corner, we're going to find that the sensitivity of that test is about the same as flipping a coin. And we're going to find that the positive predictive value of that test is 31 percent. Again, not a number that I would want to hang my life on.

This is not my slide. This is a slide from Mark Levin, the former CEO of millennium pharmaceuticals. He showed this data at a Drug Discovery meeting in 2001 in Boston. And his company looked at 28 potential drugs and tested them all on rats to see if it

damaged the rat's liver. That's what hepatotoxic means, liver toxic. And in rats 17 of the drugs were safe and 11 damaged the liver.

Levin said let's test pretty much all of them on humans and just see what happens. Very small doses. They weren't going to kill anybody. And what they found was that of the 11 drugs that were toxic in rats six of them were safe in humans. And of the 17 that were safe in rats, six of those were toxic in humans. Now, what Levin concluded from this -- and this is -- well, it is my conclusion, but it was Levin's conclusion first -- is that the rat data was about as accurate as a coin toss.

For those of you who don't have a science background in the audience, this is the type of graph we call a scattergram. And in this study that was published in 2002, the authors compared animal bioavailability of drugs, which is on the X axis, with human bioavailability of those drugs, which is on the Y axis. And they looked at primates, rodents, and dogs and compared that data with humans. And as you can see, there is absolutely no correlation whatsoever in this data.

This is a meeting that I attended one year ago this week that was sponsored by the CBI. And it was a really neat meeting. It was a closed meeting. And I only got invited through a fluke. But it was comprised of people from the pharmaceutical industry, the NIH, and the FDA. And like I said, it was a closed meeting, and it was pretty neat because pretty much everybody who was in the audience was also a speaker. Again, except for me.

And the premise of this meeting was that animal models are not predictive for humans. Okay. That was the given. And it was -- again, it was neat because the pharmaceutical companies came together and shared data.

So Pfizer's up there saying, "We don't have anything that predicts what a drug is going to do in humans." And it's predictive ADMET. A stands for absorption, D for distribution, and so forth. And these are the parameters that we try to use animals to determine, okay. ADMET is what it's called for short.

So Pfizer gets up and says, "Here's what we're doing. It doesn't work. But, you know, does anybody else have any ideas?"

And then the scientists from Merck get up there and say, "We know animal data doesn't work. We're trying this computer method." And so on and so on and so on.

But it really kind of floored me after ten years of going around the country and saying the animal model is not predictive to have representatives of NIH, FDA, and, you know, the big pharma up there agreeing with me. I wondered what I was going to do when I went home.

Well, let's talk a little bit about diseases. Now, I've been focusing on drugs. And drugs are very easy to measure. It's a very easy thing to quantify. You can get very nice statistics from them, et cetera. But let's look at some diseases.

Now, this is a quote from a textbook in 1980. But this is a quote that summarizes hundreds of studies, okay. So this quote by itself would be considered anecdotal. But the fact that it summarizes hundreds of studies I think speaks for itself.

And it says, "For decades the clinical observation of an association between cigarette smoking and bronchial carcinoma was subject to unfound doubt, suspicion, and outright opposition, largely because the disease had no counterpart in mice. There seemed no end of statisticians craving for more documentation, all resulting in the fateful delay of needed legislative initiative." The tobacco companies rode that puppy for decades before they had to put that little label on the side of the cigarette carton.

This is from a text book in 1948. And again this summarizes hundreds of studies. And the authors say, "There is no satisfactory evidence that the incidence of atherosclerosis bears any relation to the concentration of cholesterol in the blood."

Now, in the old days, you know who used to advertise cigarettes? Doctors. I have a whole slide show of ads showing doctors recommending menthol Cools or whatever. And this is very similar because today, if you have a heart attack, we strongly recommend that you cut back on the fat in your diet and try and lower your cholesterol. In the '40s and '50s we put you on a high-fat diet. Okay. That's not good.

And this is a study, again, that summarizes scores of studies that were done on asbestos. This was published in 1965. It says, "A large literature on experimental studies has failed to furnish any definitive evidence for induction of malignant tumors in animals exposed to various varieties and preparations of asbestos by inhalation or by intratracheal injection." And that kept asbestos on the market for a long time.

Okay, a little more recent example, this is HIV. This is what some of the blood values do in humans when humans are infected with HIV. And as you can see, it's either completely opposite or not correlated to what the same blood parameters do in chimpanzees. And just FYI, we don't, the scientific community doesn't even use chimpanzees for HIV research anymore, despite the fact that they are our closest relative.

Now, Van Zutphen -- I think that's how you pronounce his name -- is an animal modeler himself. And he wrote an article in 2000 in Comparative Medicine and said that animal models can be used to find out which genes cause diseases in humans. Okay, that's fine. Then he goes on to say this, "However, results to date suggest that the predictive value of a candidate gene established in such an animal model is rather low. Thus far only few genes have been allocated as causative factors for corresponding disorders in man. In fact, it can be questioned whether the use of animal models is the most effective way to detect candidate genes for complex human disorders. Due to the complexity of the genotype

environment interactions, the pathways that lead to an aberrant phenotype often differ between man and animal."

And this is an article from 2004 EMBO Reports. It says, "Knockout experiments in mice in which a gene that is considered to be essential when activated or removed are widely used to infer the role of individual genes." That's true. "In many such experiments the knockout is found to have no effect whatsoever despite the fact that the gene encodes a protein that is believed to be essential.

"In other cases the knockout has completely unexpected effects. Furthermore, disruption of the same gene can have diverse effects in different strains of mice --" not different species, different strains. "Such findings question the wisdom of extrapolating data that are obtained in mice to other species," like humans. "In fact, there is little reason to assume that experiments with genetically modified mice will necessarily provide insights into the complex gene interactions that occur in humans."

Okay. So since we're at a liberal arts college, let's bring in a little liberal arts and quote Lewis Carroll. And Lewis Carroll says through Humpty Dumpty, here he says, "When I use a word," Humpty Dumpty said in a rather scornful tone, "I mean just what I choose it to mean, neither more nor less."

"But the question is," said Alice, "whether you can make words mean so many different things."

I've given you a definition of what prediction means. Again, I think that's really self-evident. But I've nonetheless supplied you with definitions. Let me tell you what prediction does not mean. It does not mean that the animal model gives us a general idea or points us in the right direction or makes us think or lets us know if we were on the right track. Occasionally getting the answer right is not the same as predicting it.

Now, you frequently hear people say, "We tested 25 species, and one ended up giving the same results as humans; therefore, it was predictive." No, it wasn't, not unless you can show me studies of, you know, 20 or 30 tests with different drugs that that animal also got right.

And you'll also hear people say that for any given drug an animal can be found in retrospect that mimicked human response; therefore, the animal model per se is predictive. And again, this is like saying the history department always predicts the winner of the BCS.

Everybody see the cartoon? Okay.

So we have to put all this in context. Today the buzz word in medicine is personalized medicine. For example, we know that men and women react very differently to certain drugs and certain diseases. Cardiovascular disease and myocardial infarction being top of the list. We also know that there are ethnic differences. This is a report from the New

England journal of medicine in 2006. And it says, "Among cigarette smokers, African Americans and native Hawaiians are more susceptible to lung cancer than whites, Japanese Americans, and Latinos." Same number of packs smoked, et cetera, et cetera. Ethnic differences.

And today we also know that there is a large body of literature showing that identical twins do not always get the same disease and do not always react the same way to drugs. Okay. If a man cannot be used to predict what a drug is going to do in a woman, if there are differences between races, if there are differences even between identical twins, what do you think the probability is that an entirely different species is going to be able to predict what smoking does to a human or what a drug does to a human and so on and so on?

So we usually hear four things from the animal model community. We hear that we must use animals to predict human response. And the old adage is very familiar, "Would you take a drug that had not been tested on an animal?" Well, yes, I would. I would also take a drug that had not been tested on my car engine because it's a non sequitur, okay? Regardless of what the drug does in 15 different animals, we still don't have any idea what it's going to do in humans.

Okay, then you'll hear the animal model community say, well, we must use animals to study human disease. We want to see how HIV infects the white blood cells and so on and so on. But a lot of studies on animals, for example, smoking, heart disease, environmental poisons, and so forth, again, prove that animal models are actually misleading, and they're certainly not predictive.

So the question then becomes, should we use animals in basic science? This is not a basic science debate tonight. This is a debate about predictability. But maybe we should use animals in basic science. Now, before we make that decision, there are some very legitimate questions that we can ask. What has been the track record when using animals? What has been the track record when not using animals? Is there a difference between using vertebrates and invertebrates and so on and so on and so on. Again, that's a debate for another time and another place.

And finally, you'll hear people say, well, we don't have any other options. Well, yeah, we do. That's like saying what will we do if we don't eat apples? Well, we'll eat the other 99 percent of food. I mean there are myriad options that are scientifically viable.

So in closing, I would challenge Eric tonight to provide published unbiased studies, not anecdotes, proving that animal models per se are predictive, not that they're useful, not that the FDA requires them, not that they're heuristic. That they are predictive.

And there must be enough studies to offset the ones that I have already presented. And remember, it takes far less to prove a hypothesis wrong than it does to prove a hypothesis right. And he would need to explain why the studies that I quoted are actually the exception.

He would also need to explain why the theory of evolution, complexity theory, evo-devo, gene relation and expression explain species differences while simultaneously allowing for one species to predict the response for another. That's almost a contradiction.

And finally, he would need to explain why many in the pharmaceutical industry, the FDA, and the NIH agree without discussion that animal testing is not predictive for human drug response.

And again, thank you very much.

(Applause.)

ZWEIFEL: Thank you, Dr. Greek.

Just as a reminder, if you do have any questions at this point just jot them down on those pieces of paper you have and pass them to the center aisle, and Susan will collect them.

Now next we have Dr. Sandgren and his response to Dr. Greek. He has 35 minutes.

SANDGREN: So I would like to start out with some of the same thank-yous. I very much appreciate the Capitol Times and Dave Zweifel for sponsoring and hosting this. It's an important issue, not just to all of us here, but to a lot of other people. I would like to thank Rick Vogel and his colleagues for initiating this.

And I also would like to thank Dr. Greek for two things: one, for attending, and two, for so nicely outlining for me in his final slide what it is I'm supposed to talk about tonight. And I'm sure I would have done that if he'd let me know a little bit earlier.

But instead I'm going to -- going to take a slightly different approach. And there are two ways of addressing issues. Actually there are many ways of addressing issues, but I want to contrast two of them. And this -- this contrast is, I think, illustrated very nicely by something called Zeno's paradox.

And there are a number of ways to put it. The one that I think is the most straightforward and the quickest to tell is that when you are approaching a subject from the outside, when you really don't know how it works but rather you're just looking at it, reading about it, perhaps applying logic to it, you can sometimes trap yourself.

So Zeno's paradox is this. The conclusion is it's impossible to walk from one side of the room to another. And the reason for that is first you have to walk halfway. And then you walk half of the remaining distance, then half of the remaining distance, then half of the remaining distance. And you will never be able to go all the way because those halves are infinite.

Don't worry, I'm not going to actually walk across the room. I don't need to do that. I just tend to wander, and I know I will trip if that's there.

And to a certain extent, the presentation I've heard tonight reminds me of that. It's a look from the outside, not a look from those who actually do animal research and understand how the data is used.

So there's a very simple way of solving that paradox. And the story is that when this is brought up among some ancient Greek philosophers, one of them finally got disgusted, stood up, and walked across the room. And in a sense that's what biomedical scientists do.

So I'm going to actually have a slightly different presentation. What I want to do is -- is really formulate this as a story. And from my perspective this is a nonfiction story. I'm sure Ray will not agree with that.

So that's me, and what story I want to tell is how scientists precisely match the questions they ask to the tools, and sometimes those tools are animal models that will give appropriate answers that in some cases will be predictive. And there is -- there are some ways in which I agree with Ray on his definition of predictive, but there are others in which I do not.

I do not think an animal model has to be identical to a human or the same 19 times out of 20 or the same 9 times out of 10 in order to be predictive. An animal model may be very different from humans, but in one aspect of its biology it can be predictive for humans.

So I'm going to tell some stories about how scientists have used animal models to be predictive and do this from a historical perspective, starting in an area where Ray would agree that the use of animals was appropriate and then carrying it up to some studies that have been done today and along the way making a few other observations.

So I'd like to talk a little bit about some of the things that I've learned from Dr. Greek over the last few days in person and well examining his Web site, which is listed up there. And notice I'm giving you the free publicity there. I think it's definitely worth looking at that.

So he commented on this earlier, that there are a number of acceptable ways to use animals in medical research. And by and large I would agree with that.

He also commented that there are several scientifically unacceptable ways to use animals, animals as models for disease, animals as test subjects, for example, drug testing. And that's really where we get into the issue of prediction, how well and how do or do not the animals predict what can happen in humans.

Here are some other comments that I've taken from the presentation that he has on his Web site and, again, I think he's reinforced tonight. The animal model must be predictive to be useful. And I would agree with that, although I don't necessarily hold the same definition or apply the same definition that he applies. And basically the animal model has outlived its usefulness. It was useful in the present -- in the past, but -- but now we have gone beyond it in our knowledge, the stage where we can use information from animals. The

differences between species outweigh their similarities, in other words. And that was one of the issues he got to in his last slide. Certainly evolution has created animals that are separate from each other.

The -- there -- he also claims there is not an alternative to animal models to study human disease. And I hope he does come back to that a little bit later on, perhaps in his rejoinder, because I'm not quite clear on what he means. But he says because animal models are a nonviable way to study human disease, there's no alternative to them. That's not the way I use "alternative."

But he then even further states we cannot consistently rely on members of our own species as being models or as being predictive. And again, he mentioned that as well. He talked about how identical twins in fact could be very different.

We'll come back to these. But those issues pose some problems in terms of how science can be conducted.

And finally, Eric Sandgren says animals and humans are not identical. And I think that's something that everybody recognizes. And that includes scientists. Animals and humans do have much in common, though, also something that everyone recognizes.

Animal models have in the past been predictive. And I think up to this point Ray and I perhaps agree. But we break at the point where I say animal models continue to be predictive. I'm going to show you an example, an example may be counted as an anecdote by Dr. Greek, but examples give you a sense for how science is actually performed. And again, that's the story that I'm trying to tell you, how it is that a scientist uses animals in such a way, given the differences and given the similarities, so that they can be predictive.

And -- and I also think the ideal approach to the study of human disease generally is to combine animal and human studies. So there is clearly a place for studies involving humans in the understanding of human disease. Whether or not identical twins are different, I still think it's important to use humans in that study.

So remember, as Ray said, we are talking about prediction here. We're talking about predictability. We're not talking about a number of other uses of animals. We're really not talking about ethics either. Although ethics, I think, is as important an issue as efficacy when we're talking about using animals or using humans, for that matter, in research.

All right. So my outline. History, current events, and the future. Can there possibly be a more generic outline? But I wanted to just let you know what I'll be talking about. This actually came with the PowerPoint program.

William Harvey and the circulation of what? This is an example that he brings up on his Web site and talked about early -- earlier. And I want to reiterate that and show how it gave an example where perhaps we both agree that animal studies can be predictive.

So earlier Galenic views, centuries old, were that venous blood originated in the liver and provided nourishment and growth. Arterial blood originated in the heart and provided vitality -- I'm not sure what vitality means in this context, but it sounds good -- and that each type of blood flowed then from those organs to all parts of the body. And this is something that had been believed for thousands of years.

Harvey discovered, based on controlled studies, using a number of different species -- and he spoke about this in 1616 and published in 1628 -- he determined that blood was pumped around the body by the heart in two closed loops, the pulmonary loop and the systemic loop. Now today we consider this obvious, but of course after the fact, after something's been discovered, we always consider something obvious. Things that were only discovered a year ago to the scientists actually now are obvious. Scientists move forward basing their work on what has come before.

And that was really the dramatic part of this. It was a tremendous step forward relative to what had been known before. He was followed by Marcello Malpighi, who was considered the first microscopic anatomist. That doesn't mean he was tiny; it means he used the microscope. And he identified the capillaries which were the connections between the veins and arterial systems that Harvey had not been able to identify but could only speculate about using frog skin, another animal model.

So for understanding of organ structure, physiology, and function, animals have been predictive. This is one example. And this is something that Ray also stated, that for understanding these basic processes animals can be predictive.

And I would point out that today our understanding of brain function, our understanding of what is the source of rage, what is the source of depression or anxiety is still at an incredibly rudimentary level. And studies being performed on this campus now and elsewhere, in this case studies that use both invasive and noninvasive procedures in both humans and nonhuman primates, are being used to try to identify what is the function of the brain, how does it function.

And interestingly enough, the Rhesus and the human tend to show exceptionally similar responses in this area. So here is one organ where we're still at the very basic level. And according to the criteria that Ray provides, this then also is an appropriate subject for animal modeling.

Here's a trickier case, Harry Harlow. Trickier because of all of the ethical aspects associated with the work that he performed. I suspect there will be rather broad agreement in this audience that the studies that he performed should not be performed now. And perhaps not just because that would needlessly repeat something that's already been done but because all of us perhaps might feel that those studies are inappropriate as ways to treat animals.

And I think there will be a number of people that consider that those studies never should have been done at all. But they were performed. So let's look at them. Let's look at this difficult case and see whether or not that large series of studies was predictive.

So the general question he was asking was, what is the connection between human development, affection, and love? And the paradigm that existed at the time in the '50s and '60s was that affection created needy and demanding offspring and had the likelihood of spreading infectious disease if touch was included as part of it.

And using Rhesus monkeys he performed a large series of experiments with cloth mother, wire mother, abusive mother. So these were study, where, for example, an electric current was put through this substitute mother, this surrogate mother to shock a child that was clinging to it. And that's where the ethical issues come in. But again, we're talking about prediction today. He also used methods of social isolation, also filled with some ethical implications.

And his findings were that touch, facial expressions, particularly of the mother, that affectionate interactions, expressions of love, these were all fundamental to healthy mental and emotional and physical development. Again, a dramatic break from what was the dominant paradigm at that time.

Deborah Blum, who is on campus here, wrote a book called Love at Goon Park, which describes Harry Harlow and his work. And I would like to read how she finished her book. "So let us remember the best of Harry's contributions as well as the worst. Let us not slip backwards ever into believing that we are not necessary to each other's health and happiness."

Now, she's talking about humans here, us, each other. You don't have to like the way Harry found his answers. Almost no one could admire every choice he made. But neither should we pretend that he did anything less than arrive at some fundamental truth. Our challenge is not to squander it. So there's a lot in there. There's a lot about how we as humans should deal with each other and treat each other, about how we need each other.

And all of this was based on Harry Harlow's work with nonhuman primates, with the Rhesus. This series of studies was exceptionally predictive for this aspect of human biology, human psychology. And it dramatically changed our understanding of human relationships.

So now I'll move to something a bit more like what you were probably expecting me to talk about. Michael Gould and breast cancer susceptibility. Michael is a faculty member on this campus and has done for a long time a large series of studies using the rat as a model to study mammary cancer. Listed at the top is the title of the article that I'm referring to. I'm not going to read it. You can read it yourselves. As I said, he's using rat models of chemically induced mammary cancer.

And by using two strains of rats, Michael and his colleagues identified four regions on different chromosomes in those rats that influence rat mammary cancer susceptibility.

Furthermore -- and I think this is the most important thing -- they then examined the human equivalent of the first chromosomal region. They still have three more to look at. They've looked at this first using human population-based studies. And the type of study is mentioned there. So looking in people. And they found the same susceptibility modifier.

So I'm going to give you a couple of slides that any scientist is required to present in any presentation, and that involves some jargon. It was one of the things that I had to sign that I would do when I got tenure.

So everybody has their own particular kind of nomenclature, their own particular kind of record keeping. Bookkeepers use spread sheets. Electricians use wiring diagrams. Frustrated parents on Christmas Eve use poorly written assemblist instructions. And this is one of the ways that geneticists present the information that they've learned. And it's actually relatively straightforward.

And I don't have a pointer, so I'm going to step away and try to talk loudly enough so that you can hear me. And if you can't in the back, please let me know.

So on the bottom is just a diagram of a portion of the rat chromosome 5, which has been generated via the genome mapping studies that have been done, that include multiple species, including humans. These various lines represent the genetic composition of the some of the rats that Dr. Gould and his colleagues used in their studies.

And up at the stop Mcs5a1, Mcs5a2, those are two regions that are part of the Mcs5a locus that they identified. And Mcs stands for mammary carcinogen sensitivity. Okay, so this is in the rat.

What about in the human? I'm going to show you a very similar kind of a map now. Along the bottom is the corresponding region of human DNA that happens to be on the human chromosome 9 and at the top show the same two regions of susceptibility. But I think the most important thing that this slide illustrates is that -- and now remember this was identified in the rat. On the left for the Mcs5a1, the first, the dark portion on the left, six percent of women in this large study -- and the study was a series from Wisconsin and from the United Kingdom -- six percent of women carried genetic makeup at that Mcs5a1 that gave them a 19 percent increased breast cancer risk.

Looking at the other half, 22 percent of women in this population had a genetic composition at that area that gave them a 14 percent reduced breast cancer risk. So what does this really tell us? In this example what is the rat telling us about humans?

So in summary, the genetic studies by Dr. Gould and his colleagues identified cancer susceptibility DNA that predicted the same areas of DNA with the same effects in humans.

And interestingly, human studies themselves had not been able to identify these areas. The reason for that is the human population is very diverse. The background noise is very high; whereas rat strains are inbred. So that gives us an advantage. It's one more way that these animals are different than humans but a scientist can use that fact, can use his or her understanding of that difference and turn it into something, if it's used appropriately, that is predictive of a biological phenomenon in humans, in this case predictive of human susceptibility to breast cancer.

And they still have these four other loci to look at, these three others to look at. So stay tuned.

So what do we know? Scientists recognize both the similarities and the differences between species and between individuals. That's kind of a duh. We don't think that there's a one-to-one correspondence between a mouse and a human. We don't think that there's a one-to-one correspondence between a nonhuman primate and the human primate. And I would agree with Ray that there's not even a one-to-one correspondence between any of us in the audience.

But using the information, using this information about similarities and differences that we've accumulated over a lot of years, we can use animals in the appropriate ways to make accurate predictions about humans.

And animal models have contributed immensely to our understanding of human biology and to our understanding of human disease. And the reason is because rather than emphasizing the differences and giving up, scientists identify and take advantage of the similarities and use those as ways of learning, of taking information from one species into another species.

What's the future? Biomedical scientists will continue to develop and employ advanced methods to answer questions. So science is an incredibly rapidly evolving field in terms of the methodologies that are available. Ray talks about some of these on his Web site, ways of performing tests in humans. And in fact, many of those same things are being adapted to use in animals. So scientists don't simply perform the same studies over and over again, not good scientists. Rather they change their approaches and change their methods as the information that we do understand changes.

And as we develop a greater understanding of animal and human biology and disease, we become better at choosing the right animal model. And by right animal model I mean the animal model that is most predictive for a certain type of study.

And finally, more studies will address translational medicine. And that is the application of information from animals to humans, trying to take what we've learned in animals and specifically use that as and transform that into a pattern that has meaning in the human population.

Sorry, I got distracted by that phone call, and I was just thinking that thank god mine is turned off. My daughter taped a song for my ring. And I don't know how to change it. And it's very embarrassing.

Anyway, and then also more studies will employ human subjects. And many studies right now are doing that in fact. Here is an example. So this is -- these are some data from UW Madison as reported to the United States Department of Agriculture. There are certain covered species. There are certain species that the USDA regulates that whose numbers we have to report each year. Rats and mice and birds aren't included. You have to add 60,000 rats and mice to these numbers.

But you can see the numbers of dogs, cats, guinea pigs. And boy, I don't know why experimental subjects are called guinea pigs anymore, because certainly there's not very many experimental subjects that are guinea pigs. Hamsters, rabbits, nonhuman primates, those all add up to about 4,000. And in fact during that time about 4,000 humans were enrolled in clinical trials here. So we on this campus are not ignoring humans as a subject for human medicine. Rather, we're combining animal data with human data, sometimes in the same laboratories, and using that information as a way to gain an understanding, to gain predictability about human disease and animal disease.

And finally, I want to make a point that could get lost in this argument. And here is where I kind of want to take a step and just cross the room and not so much worry about dividing everything by half, by half, by half. Let's take a look at clinical medicine. So if animals are to be predictive for humans, you'd expect humans to be predictive for animals. And in fact it does go both ways.

And on this campus we have a chance to see this. I work in a veterinary school. There's a large medical school on this campus. And this slide is the result of a five-minute conversation I had with one of my veterinary colleagues where I asked, what are common clinical treatments for conditions? Let's pick dogs, one of the -- probably the most common companion animal species. Dogs or cats, can't remember which is most common. I'm sure most of you know.

Anyway, so in a number of areas, cancer, for instance, cytoxine, prednisone, adriamycin, are used in humans. All of those are used in the dog. And if you haven't already scanned all the way to the bottom, you'll see that the human and dog columns are identical. So the drugs that we actually use, the drugs that work, the drugs that have gone through testing -- and in in fact in some cases these studies were first tested in dogs, found to be safe, then used in humans, and the prediction was good -- they worked in humans.

And then the veterinary clinicians take that information on human dosing together with the original toxicity studies and use that as a way to determine the appropriate dose for the dog. And they use it on the dog. And in general the same dose fits, the same kind of side effects are seen, and the same methods of controlling those side effects are used.

So cancer, asthma, heart disease, kidney disease, liver disease, seizures, vomiting. I did not want to go beyond one slide, and I also didn't want to make the font too small. But the list could have been much longer. When you look at the medicines that are actually used on humans, the medicines that are actually used on animals and this is true for the dog and it's true for many species -- they're very often the same.

Another point I'd like to make is that in some cases they're very different. Don't give Tylenol to your cat. The cat metabolizes that in a very different way than the human does, and you can kill a cat. But there's an example of information that we've gathered that we use when we try to predict from one species to another species. So it's just as important to understand the differences as it is the similarities to be accurate in your predictions.

Final thoughts, we have many safe drugs that have passed through a stage of animal testing. Different complex systems can have the same output. By that I mean species, different species, even though at the biochemical level, the level of regulation of (inaudible) expression, even though they may be very different, can still end up looking very much the same and responding very much the same, having the same output to (inaudible) disease or toxic chemical. Mechanistic identity, in other words, one-to-one correspondence between dogs and the human, for example, is not always required for us to be able to use animals in a way that's predictive.

And finally -- and here is where I would like to give my assignment to Ray for what he should talk about in his rebuttal -- if animal models are abandoned, what will the study of disease look like? This is a critical question. And there are two ways in which I'd like the answer to that. And if he does not choose to address that now, I hope it comes up as a question. Because this is an honest question. And it's a question that all of us have, regardless of whether we believe animals should be used or we believe they should not be used. How are we going to understand disease, particularly early stages of disease?

One of the diseases I work with is pancreatic cancer. It's almost always identified in late stages. We really don't even understand the cell type of origin of pancreatic cancer. We're using animal models, we hope very effectively, to address that issue. But if we can't use those animal models, how are we going to find in a human population people with early stage disease? It's probably impossible. So how are we going to learn anything about the genesis of that disease?

And finally, Dr. Greek focused a lot on how drugs would be screened and tested for effectiveness. And certainly that's a critically important issue because that is one of the larger uses of animals. What are the options if we don't use animals, not just for testing metabolism, not just for giving very small quantities and examining how they're metabolized in the human body, but for determining whether something actually has an effect, is efficacious, is therapeutic against a particular disease?

And in particular, if humans are so different from each other that even identical twins respond differently and if that means, according to the logic that Ray is using, that no human is predictive for another human, what will drug testing look like? I understand his

notion about individualized medicine. And I expect that's where he will go. We can look at an individual and examine the metabolic pathways in that individual and target our therapies for that.

But we're not at a stage where our basic understanding is good enough for that yet, but ultimately that is an objective that I think all of us would favor. It's also a rather elitist objective because that's not something that we're going to be able to accomplish worldwide at this stage. I think in fact even in this country it's not something that we can afford. So that's something I'd very much like to hear, and I think all of us would, what will be the face of research? How do we understand human disease and what will be the face of pharmacology and toxicology? How will we find broadly active drugs that we can use across species safely and reproducibly?

With that I'd like to close, thanking you all again very much for attending. I think this is a very important issue. We've approached it in different ways. And I don't know about you, but I'm dying to stick around to see what happens next.

(Applause.)

ZWEIFEL: Thank you, Dr. Sandgren.
And again, before Dr. Greek gets up here for his five minutes of rebuttal, if you have any questions, please pass them to the center aisle. And Susan I think is walking up the aisle now to collect them.

Okay, Dr. Greek, your turn.

DR. GREEK: Well, number one, let me thank Eric again for the excellent presentation. I do have some did agreements, as should be expected. But it was an excellent presentation. And again I thank you for being here this evening.

I came here this evening to debate the predictive value of animal models. And I don't think that Eric came here to do that. I really don't think that this has been a debate as a debate is usually defined. In order to have a debate both parties must address the same issue. Now, I've never said that using animals is useless or that animals cannot be used successfully in various scientific endeavors or that animals and humans don't have a lot of things in common.

What I have said and what I still maintain is that the animal model, defined in just about any way you want to define it, is not predictive for drug testing and mechanisms of disease research.

Now, I went to great lengths to define how the word "prediction" is used in science. And I will leave it up to you to judge who has presented data consistent with that definition.

Now, what I would call the tactic that Eric used tonight is one that I'm somewhat familiar with. And there are people in the world who do a lot of debates. We have a lot of controversies going around: creation-evolution, global warming. There are people who don't think that HIV causes AIDS. And a lot of these people, when they get into a debate and they're faced with absolute facts that contradict their position, they use a form of bait and switch, okay. They change the conversation around so that instead of studying prediction, as it is defined by science, for example, we can talk about how animals and humans did in fact react the same way to the same stimuli. We can cherry-pick the data.

Or we can talk about how examples from the past showed that animals and humans, again, did have things in common. We can discuss these topics at length. And they're worth talking about. But I think tonight we should have talked about prediction. Just saying that something predicted something carries no weight in science. You remember those slides that I showed about the drugs, the six drugs and these many times the animal model matched, this many times it didn't. That's evidence. That's not anecdote.

So the technique that I'm talking about was illustrated very nicely in the movie Thank You for Smoking. And it goes something like this. Yes, one can discuss instead of the topic at hand, one can discuss something else and do a very nice job with it and present very impressive data and very interesting data. But it's not about the topic.

And so at the end of the lecture, you can leave your opponent, in this case me, shaking his head going the audience really loved that talk and they, you know, thought it was fascinating and they really liked you. But you didn't talk about the things that we were supposed to talk about.

So I think that's a problem.

To give a couple of examples where certain animal species reacted similarly to humans and from those limited examples to conclude that an animal model as a paradigm is predictive is the fallacy of bloated conclusions. It would be like profiling several lottery winners and concluding that playing the lottery is the best way to save for retirement. It is simply misleading.

I'll very briefly talk about Harry Harlow. Nobody in their right mind in the 1950s and '60s thought that ignoring babies was the proper way to raise them. Now, yes, there were a handful of scientists who were writing articles and books saying, yes, don't -- ignore the baby. Don't hold the baby. Don't go to the baby when the baby cries.

Any mother of two who was above a third grade education ignored that, okay. So there was not some vast scientific question hanging in the air that Harry Harlow addressed. That's just nonsense.

So what will we do if we don't experiment on animals? There's two points to this. This is trephination. This is what we did in the old, old days, back when I was an intern. In order to expel the spirits from the person's head and thus curing them of schizophrenia, measles,

the mumps, or whatever. We don't do trephination today, not because we don't have anything else to do, but because it just didn't work, okay.

So before I talk about the proven methods that we should be using, if a modality is not predictive, then don't claim that it's predictive. Now, if you want to do other stuff with it, that's fine. But don't claim something that you cannot prove, especially in science.

And what should we be doing today? Well, I'll tell you what we are doing today. In about one percent of the cases we are using DNA chips. If somebody has breast cancer, they're going to get genotyped, their cancer's going to get genotyped, and their treatment is going to be determined by that DNA chip, okay. There are drugs today that we will give to certain people and will not give to certain people based on their genotype.

And the only predictive ADMET testing, the only predictive modalities that we're going to have in the future are going to be your DNA. And that is where science is going. And if NIH funded personalized medicine, pharmacogenomics, and so forth, instead of funding animal models of Parkinson's, animal models of this, animal models of that, you would get to personalized medicine a lot sooner.

And Eric, again, thank you very much for doing this. Appreciate it.

Thank you ladies and gentlemen.

(Applause.)

ZWEIFEL: Susan, do you have --

This has been extremely interesting. I second the thanks.

Eric, we're going to start with you here. Here's a question. Harry Harlow's studies may have been predictive, but were they necessary? Could we not have learned the same thing by studying, say, human orphans or babies who had been abused?

SANDGREN: So the issue of looking back and determining whether or not a different method could have been used to identify certain pieces of information really I don't think is a very useful exercise. I can imagine that there could have been many different ways to identify that. But most of the scientific outcomes that we look back at could have been identified in many other ways. But they weren't. They were identified in a single way.

So to answer the question, I suspect there would have been other ways to address those questions. But those were not the ones that were used. Those were not the ones that had the influence that they did.

And in fact the government was sending out pamphlets to people around the country telling them not to show affection, telling them not to touch their children. So it actually

was a situation that existed in the society. It wasn't something that was so outlandish that no one believed it at all.

So yes, other modalities could have been used but in this case weren't.

ZWEIFEL: Dr. Greek?
DR. GREEK: Thank you. I agree with Eric in part about not dwelling too much on the past and looking at how things could have been done but how they were done and so on and so forth. And I think that's largely an exercise in futility. Except for the fact that if the animal model community is going to draw from the past to justify the present, then it is very legitimate to say, okay, this is how Harry Harlow did it, but did he have to do it this way?

If you're going to maintain that the animal model is vital, then you have to go back in history and say we could not have done it this way here, we could not have done it this way here and so on and so on. Otherwise, you're saying that the animal model is sufficient. It's not necessary, but it's sufficient.

And finally, my grandmother was raising children during the time that these memos from the government went out. She had a third-grade education. She lived in the middle of Michigan. And she thought that was just the stupidest thing she ever heard. Now, maybe that's because she's from the Midwest and, you know, had a little more common sense than other people. But if this was some great scientific mystery during that time frame, gosh I don't know any of the people who were being hoodwinked by that.

ZWEIFEL: Dr. Greek, question for you. Regarding Dr. Sandgren's example of breast cancer gene, the probability of finding that gene in humans by coincidence is astronomically small. In this case would you agree that the rat model was predictive? And if so, are there some areas of research where animal models could be predictive, or would you say they are universally inappropriate?

DR. GREEK: I would say they are universally nonpredictive. Because again, if you're going to say that the rabbit is predictive for birth defects, for example with thalidomide, you have to at least show 19 out of 20 times where the rabbit got it right. All right? In science and in drug testing in particular even 19 out of 20 is inadequate.

Vioxx was pulled off the market because a very, very small number of people were harmed by it. Millions and perhaps even as high as a billion people were actually helped. All right. So in science, again, prediction has a very specific meaning.

And with regard to the breast cancer example, yes, that's a very good question. Most of the gene association studies that we do today are not done in animals for reasons that I think should be obvious. They are done in humans. And they're called genomewide association studies. And if you pick up the New England Journal just about any given week, you'll find on

the cover a genomewide association study that has identified in humans what genes are associated with cancer, heart disease, and so on and so on.

So you have to study humans. There was a study done about ten years ago that identified nine genes, I believe it was, that caused seizures in mice. And everybody went looking for those genes in humans. And they found them in people who had no seizure disorders whatsoever. So occasionally getting it right -- and I'll just grant you that animal models occasionally get it right -- that's not prediction.

ZWEIFEL: Okay. Eric?

SANDGREN: I think my response to that highlights the principal difference in the way we approached this presentation. I believe that I am using and continue to use prediction in precisely appropriate way. Looking back historically, probably that's something that Ray and I should have talked about before, coming up with a definition.

But in some ways I think it's better this way because you can see two approaches. And again, as I liken that to the -- to the Zeno's paradox. The approach that scientists use is to make predictions that turn out to be accurate using animals. They do that based on their understanding of the animals, similarities and the differences from humans. And that mammary cancer, that breast cancer example of I gave, I picked very deliberately. Because according to my understanding of the word "prediction," that data from the rat predicted something in humans that had not been identified by a human genomewide study.

And that is how scientists work, over and over and over again. Every finding doesn't translate to humans. But that's part of the scientist's job, to identify those that do. Every seizure gene in a mouse may not cause seizures in humans, but there are some other cases. There are some storage diseases, for instance, where there are defective enzymes, and you get accumulation of byproducts in cells in the nervous system. And there the animals happen to be exceptionally predictive for humans. The diseases that develop are identical, at least to all of the tests that we can provide.

So there are examples like that. The nine times out of ten or the 19 out of 20, that's sort of a straw dog or -- in veterinary medicine we say a straw dog argument, a straw man argument. That's really irrelevant to the way scientists perform their work. We instead, as shown by this particular example, identify those cases where we can get information and then take advantage of that.

ZWEIFEL: Okay, thank you.

Dr. Sandgren, we'll continue with you here in the next question. The thalidomide tragedy of the 1960s demonstrated quite well the necessity of animal testing. If more animals had been tested, wouldn't a thalidomide tragedy have been prevented?

SANDGREN: If in fact the study had been done on the particular type of rabbit that showed the same response, then that would have been identified. I don't think, though, the direction that we want to take is to test every drug on every animal. Just as the direction we don't want to take is to test every drug on every human being.

The direction that we want to take is to identify those areas where humans and animals have similarities so that we can provide more information, so that we can gather more information, so that we know which are the appropriate animals to use. At the time we did not have a way to do that.

Now our ability is improving as we learn more about animals and as we learn more about humans.

ZWEIFEL: Dr. Greek, do you have a response?

DR. GREEK: Thalidomide is actually a very good example. If I can get my computer to work, I'll even show you a slide. This is from a book on teratogens 1976. It says, "In approximately 10 strains of rats, 15 strains of mice, 11 breeds of rabbits, 2 breeds of dog, 3 strains of hamsters, 8 species of primates and other varied species, such as cats, armadillos, guinea pigs, swine, ferrets, in which thalidomide has been tested, teratogenic effects have been induced only occasionally."

If, as Eric suggests, we're going to pull every drug out of development that causes birth defects in one animal species, you're not going to have any drugs. Every drug on the market today will cause birth defects in some animal, if given at the right time and in the right dose. That's called Karnofsky's Law.

And this is from, again, a textbook in 1985. And it says, "The actual results of teratogenicity testing in primates, which have been the most disappointing in consideration that these animals -- of these animals used as a possible predictive model. And it goes on to say of 15 listed putative human teratogens tested in nonhuman primates, only 8 were teratogenic in one or more species."

And it's actually pretty much universally agreed upon, if you read the textbooks of teratology. "The example of the thalidomide disaster illustrates this problem particularly clearly. Such a medicine-caused disaster could no more be prevented with adequate certainty through animal experimentation today than it could have at the time."

Look. You test on ten different species, you get ten different answers. Yeah, one of them is probably going to be what humans do. How do you know prospectively which species? Every drug we have on the market today will kill something. I'll guarantee you. If it kills one species or one strain of mouse, are you going to pull it -- are you not going to allow it through development? That's ridiculous.

But that's what the animal model community would have you believe. They would say, well, see, the rabbit actually did predict this. No, I'm sorry. But the word "prediction" has

a very definite meaning. And if you wonder what it is, ask your bookie, okay. If the bookie will allow you to bet -- put a $10 bet on six different horses, okay, for only $10, I'd go with that bookie. But most likely he'll charge you $60, 10 for each horse.

ZWEIFEL: Okay. Thank you.

Dr. Greek, if the NIH believes that animal models aren't predictive why are they funding animal-based experiments?
DR. GREEK: The NIH at the meeting I attended was very specific in saying that the animal model for ADMET, or ADMET, testing was not predictive, okay.

And in fairness to the NIH, the NIH by and large does not fund studies because they think they're predictive. The NIH is pretty outspoken for funding basic science research. All right. So if you would ask the NIH, do you expect this study to be a predictive model for humans? They'd probably look at you funny. Because that's not the business that they're in.

The reason NIH was at that meeting was because there was this very nice lady who got up at the very first of the meeting and said, "I have a $100 million budget. And I want to give it to you." Because NIH is concerned that there is no predictive modality for drug testing, okay, and we are so concerned about this we're going to give money to Pfizer, right -- like they really need it -- because we are so concerned about it.

So I hope that makes sense.

ZWEIFEL: Eric?

SANDGREN: The NIH funds a large variety of research. And part of the funding is -- a large part of the funding is -- in fact there have been several recent initiatives in this area -- go specifically to animal models of human disease. That's how they classify it. So the NIH very clearly does believe that animals can serve as appropriate models for human disease. The data coming out from the laboratories that are supported shows that animals can serve as good models for human disease. And by that I mean predicting aspects of those disease.

So that's why NIH continues to fund it, particularly now when funding of all federal agencies but one is very strapped. That funding continues for animals because they can see the benefits that have come from it.

ZWEIFEL: Eric, here's another question for you. What are the sources of funding for animal research here at the UW? And what is the range of costs for animal studies undertaken here?

SANDGREN: The sources of funding for animal research are varied. Most of it comes from National Institutes of Health. Some of it comes from the United States Department

of Agriculture. Some of it comes from the National Science Institute. Much of it comes from private foundations.

And what was the second part of that question? The -- not just the source but --

ZWEIFEL: What is the range of costs for animal studies?

SANDGREN: It's really impossible to give a single number for the costs. That depends on the species that are involved and obviously the number of animals that are involved. The typical grant to an investigator from the National Institutes of Health is the RO 1 grant. And generally that's for approximately $200,000 a year and lasts for four or five years. That would be a typical budget for a laboratory that used animals but also a lot of other supporting materials. It's not just the animals, but it's the types of analyses that are done. Some laboratories have more than RO 1 -- more than one RO 1.

I don't know what the average figure is for research dollars per laboratory on this campus. But I would guess it's somewhere in the 300 to $400,000 a year with a very broad range going from zero up to several million dollars a year.

I hope that addresses the question. It's the best I can do.

ZWEIFEL: Dr. Greek, do you have any response to that?

DR. GREEK: I can add a little bit to that. This is from 1999. These are some of the costs associated with using animals. As you can see, it's a wide range. Mouse sales -- again, this is from 1999 -- mouse sales amounted to over 200 million in 1999. These are industry figures, by the way. Mice with a specific gene missing costs from $100 to $1500. So we're talking about a lot of money that's being spent here.

SANDGREN: I wish all that was coming to this University, but it's not.

DR. GREEK: It's going to some university.

So it's a lot of money. Exactly how much money is it? The very few studies that have been done show that about 50 percent of the budget from NIH goes to animal-based research, okay. And that's from a GAO study in roughly 1985. I have the reference if anybody wants it.

ZWEIFEL: Okay, thank you.

Dr. Greek, TB, malaria, and HIV cause the death of millions of people every year. Without animal models, how do you expect to create vaccines to protect people against these diseases?

DR. GREEK: Well, that's a very interesting question because just this week another HIV vaccine failed. It worked really well on monkeys. It's I think the third or fourth or fifth. And there's another 20 that are in clinical trials. The choice of infectious diseases in that question is also very interesting because chimpanzees and monkeys do not suffer from HIV. Monkeys suffer from SIV, which is a completely different virus.

Chimpanzees and monkeys I believe do suffer from tuberculosis, and malaria I'm not sure about. I don't remember. But this illustrates the problem. Here is three different viruses that cause at least two different reactions, completely opposite reactions, in humans versus humanity's closest evolutionary cousin the chimpanzee.

And in terms of how are we going to make vaccines in the future, pretty much the way we've made them in the past. If you want to know how the polio vaccine came about, there are some outstanding books on that written circa 1970 by people who were actually involved in the polio vaccine.

And somehow society has got this impression that the polio vaccine was dependent upon monkeys. And monkeys were used as incubators during that time. They absolutely literally grew polio virus in the monkeys.

But in terms of a model for polio, they were very misleading. And Al Sabin even said that the monkey model probably set the polio vaccine back about, I think he said, 20 or 30 years.

So how are we going to make vaccines? Pretty much the same way we've always made vaccines. It wasn't until polio was grown in culture that we finally got the vaccine, because then they could work with it and so on and so forth.

ZWEIFEL: Eric?

SANDGREN: I guess I didn't really hear an answer to that question. Pretty much how we've always made vaccines. I remember the first vaccination, some of the first ones were that scabs from cow pox were rubbed into a cut in a human to immunize against smallpox. I don't expect that's what he means.

There have been a lot of vaccines that have been developed in animals and then applied to humans.

There's also another issue, and that's accuracy. And I think it's very important to be cautious about what you say. So it turns out that there was a vaccine study that was reported as failing this week for HIV, AIDS. The results in monkeys using this same vaccine, though, were not a success, as Ray said. There were two vaccines tried on monkeys. One, the monkeys were infected twice with a virus that contained some of the molecules from HIV. In another case the monkeys were infected once with that virus. The second time were administered naked DNA that is incorporated into the monkey cells and produces the antigen that serves as a vaccine.

And as it turned out, the monkey trials showed failure with the two adenovirus infections, the two viral infections, and showed success with the adenovirus plus DNA. But the drug company, because it was so difficult to prepare the DNA, went ahead and performed the adeno-adeno, the two-virus trial.

So here is an example of where the monkey was predictive for humans. It failed in the monkey. It failed in the humans. And I think it's very important to get the facts straight. And I think this is an important fact.

ZWEIFEL: This is a follow-up to that question. Dr. Sandgren, do you believe we have lost drugs that would have cured diseases because they tested poorly in animals?

SANDGREN: So whenever -- and I -- and Ray and I agree on this, although certainly I think the extent of our agreement overlaps only very slightly.

If you are relying on animals to give you information about humans, there are going to be times when you're not going to know whether that information is accurate or not. So I would say absolutely there have been cures that we have lost because we've tried them on animals and that they have not been efficacious or because they've hurt the animals.

But then I would say what's the alternative? Do you do large-scale toxicity testing on humans? There was a slide that Dr. Greek showed about toxicity in liver. And I can't remember whether it was mice and humans or a different species and humans. And he commented that the humans weren't really given large doses, just small doses. And yet the word "toxicity" was there.

Well, that's a misuse of that term. Toxicity means damage. And I don't know of any institutional review board that reviews human studies that's going to allow testing to the levels where toxicity can be determined or damage can be identified in humans.

So yes, we do lose some promising therapeutics. But the alternative is testing specifically on humans and having a lot of humans die. And even according to Dr. Greek that would not be enough because humans are so different. So we're doing what I would say is the best we can.

DR. GREEK: So Dr. Sandgren and I do agree on the fact that we have lost cures for diseases, just like the National Cancer Institute and other people have said. There are numerous quotes throughout the literature that I won't bore you with since Eric and I actually agree on this point.

But I think your comments about the HIV vaccine are very telling. Now, I still maintain that I'm right on that, surprisingly enough.

However, let's assume for the sake of argument that you're right. What does that say about the pharmaceutical company's confidence in the monkey tests? If they're going to ignore

the monkey tests and the data and they're going to go ahead with this vaccine, even though it failed miserably in monkeys, boy, that sure looks like somebody at the pharmaceutical company doesn't believe in animal models either.

ZWEIFEL: Okay. Thank you.

Dr. Greek, do you recognize the use of chimpanzees for HIV and AIDS as a failure?
DR. GREEK: Not only do I, but the current head of the National Institute of Allergy and Infectious Disease -- or I may have that slightly wrong -- he has recognized it as a failure. The chimpanzee researchers have recognized it as a failure. There is a very nice essay on the use of chimpanzees in HIV research in The Scientist, I don't know, probably six, seven years ago. And the NIH recognizes it as a failure.

To the best of my knowledge -- and I'm pretty sure I'm right on this -- there no chimpanzee HIV studies that are currently being funded by NIH. Now, if it was a great model and it brought us a lot of interesting data and so on and so on, I think we'd be pursuing that.

SANDGREN: And I'd say Ray illustrates very nicely the way science adapts to information. When scientists discover that something is not a good model, they abandon it, as they should.

ZWEIFEL: Dr. Sandgren, isn't it true that many laboratories keep using animals because the companies that provide lower costs rather than moving towards nonhuman techniques -- not sure I quite understand that question -- thus the breeding and selling of animals is big business so changes just don't happen?

SANDGREN: I'm not sure I understand that either. Would you read that one more time?

ZWEIFEL: Isn't it true that many laboratories keep using animals because of companies that provide -- I guess the animals are lower cost than, I guess, using other techniques that could be employed. Thus the breeding and selling of animals is the big business -- is big business, so changes just don't happen?

SANDGREN: So breeding and selling of animals is a -- I don't know if you'd call it a big business compared to a lot of other businesses, but it is a business. I do know as a scientist that a critical aspect of performing science is matching the model that you use to the question that you're asking. And if you can answer a question without using an animal, that's the approach you're going to take because it's far less costly.

So there is a bigger expense to using animals in research than most other types of methodologies. That's why it's important for there to be strong justification for the use of animals in research.

ZWEIFEL: Okay. Do you have a response?
DR. GREEK: This will give me the opportunity to very briefly say why I think the animal model continues to be used. And you won't find science on any of the bullet points.

The reason that animals continue to be used in science, yeah, there's a lot of money involved, that's true. But you really can't say that money is the only reason. I wouldn't even say it's necessarily the biggest reason.

I think the biggest reason is tradition. Okay. The system is based on it. Okay, we've always done it that way. And I don't care if you're society or the FDA or the pharmaceutical company, there's a lot of resistance to change. Okay, and these are two very innocent reasons why the animal model persists despite its many failures.

Now, there's some more nefarious reasons, okay. But the only point that I'm trying to make is that there are a lot of reasons why bad habits are not immediately dropped. Perhaps we could think of a war that we could use as an example.

So there's a lot of reasons why it persists. It's not a very, you know, straightforward simple linear problem. Yes, money's involved, but there's a lot of other reasons.

ZWEIFEL: Okay, Dr. Greek, question for you. If not animal research, you say there are several other options. Name three and give some statistics demonstrating their utility over animal testing.

DR. GREEK: I think that's a very good question. I don't have that data on the tip of my tongue. But if we would like to pursue that at another time, I think that's a very excellent question.

So since I don't have data and I'm not going to try to make it up, let me just say that the so-called alternatives -- and I don't like that word, and I'll tell you why.

With the so-called alternatives to using animals to study human disease is to use humans. Okay. Not as guinea pigs, not in a human experiment like in Nazi Germany, but to study human beings in an ethical fashion. And I don't care -- there's a lot of different ways to do that. Epidemiology is a way to do that. In vitro reach is a way to do that. And we do that every time we take a surgical biopsy. We look at that tissue. If the tissue's interesting, we look at it a little further, and so on, and so on, and so on. So human tissues from autopsy, from pathology, human genetics like these genomewide association studies, plain old clinical research and clinical observation.

Clinical observation has been sold very short in the importance that it has played in the development of medicine.

And Eric asked me earlier, and I didn't have time to address it, why I said there's no alternatives to using animals. And a lot of the things that he said were taken very much out of context from my Web site. And I do encourage you to go there and look at what was on that slide versus what I actually say.

I say there's no alternatives to using animals to studying human disease just like there's no alternatives to using a used car to travel to the moon. You can't use a used car to travel to the moon, despite what the used car salesman will tell you. Okay? And he will tell you that you can jump in that puppy and go to the moon tomorrow. But you can't.

Alternative implies viability. And if we'd like to get the dictionary out, I think you'll find that I'm correct on that. So no, there's not an alternative to something that doesn't work. Okay? There's a lot of things that do work, and that's what we should fund.

But I hope that answers your question.
ZWEIFEL: Do you have a response?

SANDGREN: Yes. So all of these methods that are listed up there are very important. And scientists are aware of them. Scientists have been developing them. In fact, many of them have been developed through animal research. In fact furthermore, consider how much of the information that Ray presented tonight is based on animal research. Almost all of it. He's coming up with one conclusion; I'm coming up with another.

With respect to the alternatives, I and all scientists that I know favor moving toward human studies when that's possible. That's why the slide about ego and guilt and greed is -- may explain why some people use animals. But not any scientist that I know. To a scientist, the issue is answering a question, testing an hypothesis. And if there is no other way to do that than use an animal, that scientist will use an animal. If another way comes along, that scientist will shift. I've seen it many times.

I've seen people shift from cell culture work into animal work. I've seen people shift from animal work into cell culture work. I think that is a reflection of Ray's not knowing science from the inside. Because science -- scientists simply do not function that way.

ZWEIFEL: Okay. Thank you.

Dr. Sandgren, a question for you. How can you claim accurate predictive information when it was obtained from experiments on animals in which you introduce the disease to that animal?

SANDGREN: So if I understand the question, it is how do we interpret research -- how do we interpret the outcome of disease when that disease has been introduced into an animal? And how do we use that to give us any indication of a similar disease process in humans?

Well, humans aren't constantly affected by disease. All of us are given diseases, maybe when we're in the airport, maybe when you're, oh, goodness, in the day care center. And so when you design an experiment and you give an animal a disease, that's really simply controlling the timing of a process that occurs naturally in the human population.

So I really don't see any reason at all why that is a problem. In fact it's a strength because it allows you to control the situation better and therefore gather more information.

DR. GREEK: Could you repeat the question?
ZWEIFEL: If I can find it.

How can you claim accurate predictive information when it was obtained from experiments on animals in which you have introduced the disease to that animal?

DR. GREEK: Well, that's actually an easy question to answer. If you're going to claim predictability, you have to explain slides like this. Okay. And you have to explain slides like the one that I showed with the six drugs in the head-to-head comparisons. And you have to use the word "prediction" in the way that scientists and even bookies use the word "prediction."

And I just ignored it when Eric said it the first time, but he's now said two or three times that I don't know science from the inside.

Actually, I have done research on animals. I did a year of neuroscience research on animals. We drilled little holes in their skull. We lesioned parts of their brains. And the study that we were doing was we were looking for obesity centers. I never got anything published out of that, but I did work on it for a year.

I've also had, I think, 11 papers published in the peer review scientific literature. I've had numerous abstracts presented based on human research. And so on and on on. So I'm curious as to why Eric says I don't know science from the inside. I think my CV would dispute that.

Now clearly I don't have an NIH grant, and given what I say about NIH, I'm not likely to get an NIH grant. But I don't think that we can say, you know, the definition of a scientist is someone who has a grant from NIH. Einstein never had one. Okay. I'm no Einstein, let me assure you, but we do have that in common. So I would like to keep this discussion more on a scientific level.

And the slide that I showed about why animal experimentation persists, guilt is one reason. I've done numerous debates in this country and abroad, and frequently a woman will come down to the podium at the end of the debate with tears in her eyes, and she'll say, "Dr. Greek, if what you say is true, why have I killed all those rabbits?" That's guilt, okay? And the psyche doesn't like guilt, and it doesn't like to deal with guilt. So guilt is absolutely one of those reasons. I didn't dwell on it because, again, I think tradition and resistance to change are much bigger and more important reasons.

ZWEIFEL: Okay, thank you.

A question for you, Dr. Greek. Can you talk about the use of primates and Parkinson's research in general and specifically in deep brain stimulation?

DR. GREEK: Matter of fact, I can. I've been working on that subject for about the past year, and I just wrote my little 50- to 100-page summary of that topic.

Parkinson's disease was discovered in humans. It was worked out in humans, and so on and so on. The big breakthrough that the animal model community claims about Parkinson's disease came when physicians noticed that some people who had used illicit drugs came in demonstrating Parkinson's-like syndrome. The drug was called MPTP, and some of the animal model community said, wow, let's give this drug to monkeys and let's see what it does.

And it does reproduce the symptoms of Parkinson's disease. It does not reproduce the disease in its entirety. And it certainly doesn't reproduce the disease in its etiology.

The other claim to fame for nonhuman primates in Parkinson's research is in the area of deep brain stimulation. This is a very long story. And again, when I did my little summary, it was like 50 to a hundred pages. To make a long story short, we drilled a lot of holes in a lot of monkey's heads and put electrodes down there to see what would happen, okay.

But what the animal model community fails to also explain is that before we were doing any of that in monkeys, we had done a lot of that in humans. And the real claim that the animal model community says is that the reason we do deep brain stimulation on a very specific area of the locus ceruleus, okay, the subthalamic nuclei, they claim that we had never thought of doing that lesion in humans before they did it in monkeys.

And again, if you really read the literature -- and trust me, there's hundreds and hundreds of articles in the literature that you have to read -- that simply is not true. The subthalamic nuclei was isolated as a potential target in the 1920s, okay, long before -- now, it was ignored. I mean I'll grant you that. And the monkey studies kind of woke the scientific community back up to using the STN and deep brain stimulation. But no, there was no discovery there.

SANDGREN: So I haven't just finished writing a 100-page monograph on Parkinson's and animal models. I do know a little about it. Some of that work is being done here.

And I would comment that in many cases reproducing symptoms, whether or not by the same route, can be a very useful -- can be a very useful function of animal modeling, particularly if you can then use that animal as a way to identify a means to treat those symptoms. And that is the basis of very many studies. I made that point in one of my slides, that complex systems can be different yet still have the same output.

Since we're getting within two minutes of close, I want to just make a couple of comments. One, I think that both of us have commented that it's important for you to go out and check facts. So go to Dr. Greek's Web site and take a look at the information there. Check some of these papers that we've been referring to. Think yourselves about prediction.

Scientists use prediction in the way I've used prediction. And I apologize if Ray thinks that we had a discussion on a different topic. But the way prediction is used among scientists, I think I covered it very appropriately.

The final comment I want to make is that I think despite the differences that we have, it -- this forum provides an outstanding means for you and for anybody else looking in to hear how two individual people who come at an issue from a different perspective view that issue. And hopefully that will provide you with a couple of models at least that you can test.

Think about what I've said. Think about what Ray has said. Do some reading. And try to determine then which of us you agree with or maybe neither of us or maybe both of us.

And that's what I do when I haven't prepared hundred-page monographs on questions. But I think those are important things to say. I'm really pleased that this event happened and that Ray took part in this.

ZWEIFEL: Okay it is 9:00 o'clock and we promised everyone that they'd be out of here in two hours. Let's give a big hand to these two gentlemen for their excellent presentations.

(Applause.)