Response to Dr. Michael Festing’s Review
of Sacred Cows and Golden Geese:
The Human Cost of Experiments on Animals

AND

Material for the 4th World Congress Point Counter-
Point: Is Animal Research Necessary in 2002?

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“Muddy water is not necessarily deep.”
Nietzsche
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Part 1

Introduction

We appreciate this opportunity to expand on the concepts we expressed in *Sacred Cows and Golden Geese: The Human Cost of Experiments on Animals* (Continuum International Publishing 2000). Enthusiastic critiques such as Dr. Michael Festing’s are extremely valuable if those within and without the field of “science” are finally to understand, choose among, and embrace viable research modalities that are meant to result in cures and treatments for human disease. Criticisms also help to clarify misunderstandings. We hope this (unfortunately long) essay will shed light on the debate. We encourage the widest distribution of our mutual critiques and here give our permission to post our response in any forum.

It is our position that, today, animal models of human disease give data that is not reliable and that can indeed be harmful for humans; consequently, we believe they should be abandoned. The crux of our argument is that today we are studying disease and drug response on the genetic or molecular level and that small variations on this level not only define a species but also confound the ability of one species to model another in a meaningful, reliable, predictive way. Dr. Festing’s review of *Sacred Cows and Golden Geese* ignores the main thrust of our argument, which attempts to answer the question: Are animal models useful in modern-day research? *Sacred Cows* does comment on the history of medical discoveries but concerns itself primarily with answering this question. We stand by our reading of historical texts, but note for the record that it is not unusual for historians to hold differing interpretations of historical documents and accounts. We acknowledge that many discoveries of the 1600s to early 1900s involved animals. Harvey could have conducted autopsies to prove the heart circulates blood, but he dissected a horse, as well as performed autopsies. In the past, one could argue that the similarities between species outweighed the differences (because we knew so little about anatomy, physiology, biochemistry and so forth), and hence, animal models were useful for medical research. Times have changed. We are beyond the level of superficial similarities and are now studying disease at the molecular level. It is at the molecular level that a rat becomes a rat and a human, human. We can argue the past benefits of animal models, but the argument is largely of academic interest and ignores the more pressing question of, “Does the practice of using animals as models, today, do more harm than good?”

Dr. Festing’s review is representative of the criticisms we have received from people associated with the animal experimentation industry. It relies on fallacious reasoning, takes examples out of context, is historically inaccurate, and ignores the heart of our argument. It is also noteworthy for what it did not explicitly criticize: modern-day research using animals to model humans.

The four examples from *Sacred Cows* Dr. Festing chose to critique involved history (3) and an opinion on the power of money, in society in general, and biomedical research in particular. Dr. Festing’s review assumes that the book, which was written for the lay reader, should adhere to the standards of *Nature* and *Science*. This stance implies that the public should not be informed in language they can understand, about research they are paying for and which affects their health and safety.

Simplifying things is a normal part of every science teacher’s and physician’s life. We do not accuse a physics teacher of fraud because she explains Newton’s ideas to a high school physics class without including the details of relativity theory. *Simplifying* is not a sin. It is essential if the general public is to understand and be involved in discussions and decisions regarding current scientific issues. Atmospheric scientist Stephen Schneider, of the National Center for Atmospheric Research was honored with the AAAS (American Association for the Advancement of Science) Award for the Public Understanding of Science in 1991. He stated the following about the methods he uses to communicate science to the general public: “To
do that [reduce the risk of potentially disastrous climatic change] we have to get some broad-based support, to capture the public's imagination. That, of course, entails getting loads of media coverage. So we have to offer up scary scenarios, make simplified, dramatic statements, and make little mention of any doubts we might have. This ‘double ethical bind’ that we frequently find ourselves in cannot be solved by any formula. Each of us has to decide what the right balance is between being effective and being honest.” While we would not go quite that far (although the AAAS thought it acceptable), we do agree that simplification is a part of communicating with the public.

The essence of simplification is taking complex concepts and making them understandable to the less educated. Those who simplify in order to communicate effectively win Pulitzers and AAAS awards. Physicians, scientists, and writers do this successfully every day. Thomas Jefferson said, “I know of no safe depository of the ultimate power of the society but the people themselves; and if we think them not enlightened enough to exercise their control with a wholesome discretion, the remedy is not to take it from them, but to inform their discretion.”

Simplifying something to the point of changing the meaning is dishonest. So there are essentially two questions: 1. Did we simply certain concepts? Yes we did, and we did so intentionally. And, 2. Did we do so without the changing the meaning? We will defend our answer of yes to the second question in this essay. In this response, we will expand on the three specific areas of historical interest Dr. Festing criticized, evaluate Dr. Festing’s response to our position on the role of money in animal experimentation, [and suggest] explain why Dr. Festing’s critique ignores the heart of our argument. We present further documentation for our position in the August 2002 Point-Counter Point.

We ask the reader to keep in mind that animal experimentation is not a single entity and that animals can be used in science in the following ways:

1. Spare parts (e.g., heart valves).
2. Factories (e.g., production of insulin and monoclonal antibodies).
4. Test subjects (e.g., drug testing, carcinogen testing).
5. Tissue donors (e.g. for the study of basic physiological principles).
6. Educational tools (e.g. dissection, psychology).
7. Modalities for ideas (for the purpose of heuristic procedure).
8. Systems of interest unto themselves (knowledge for knowledge sake).
9. Models for animal disease (e.g. using an animal to study a disease or condition for the benefit of the same species but not the benefit of the individual animal being studied).

In this essay and in our books we focus on numbers 3 and 4. We do not suggest that the arguments we present against the use of animals, vis-à-vis numbers 3 and 4, have any relevance to the other uses.
Rabies

Dr. Festing states:

On page 33 of this book, the authors state that Pasteur used animals as pseudo-humans as he attempted to craft a rabies vaccine. “He took spinal column tissue of infected dogs and made what he thought was a vaccine. Unfortunately, the vaccine did not work seamlessly and actually resulted in deaths. Yet, this gross failure somehow did not detract from the reverence for the animal-lab process.” This account is simply not true. The vaccine did not cause any deaths, it failed to cure one person out of the first 350, for a very good reason, and it was highly successful. The book does not even acknowledge that Pasteur did in fact produce a rabies vaccine.

How could we have criticized Pasteur’s vaccine if he did not, in fact produce one?

This is an example of a scientist trying to use animals as causal analogical models or CAMs (or at least claiming he used them that way when in fact he did not, as we shall see) and exemplifies why animal models fail when used in this way. We will discuss this more fully in a later section.

The research Pasteur did on the vaccine has been re-examined of late and some interesting things have come to light. Today, all agree that there were problems with the vaccine. Pasteur’s initial vaccine had contaminants that led to “paralytic disturbances with central nervous system inflammation and demyelination, presumably on an allergic basis.” This had not occurred in the animals on which it was tested. Pasteur claimed he had established the efficacy of the vaccine in dogs (used dogs as CAMs) but this has also been proven false. He had vaccinated dogs prophylactically, but not after exposure to rabies as he was doing with humans. Pasteur’s vaccine administration was human experimentation justified by a low mortality rate, with the mortality rate serving as a control (which was based on nothing more than pure conjecture). This is not science.

Relying on a single case of unproved rabies (the boy who was bitten repeatedly and was Pasteur’s first patient) to support his argument that Pasteur’s rabies vaccine was effective is representative of our problem with Dr. Festing’s critique. Citing questionable, undocumented examples of historical events to justify modern-day animal models is the problem with our critics’ arguments. Maybe the first person Pasteur administered the vaccine to, the boy, would have come down with rabies, maybe not; we have no way of knowing. A conclusion based on the assumption that the boy would have come down with rabies, is fallacious.

There are myriad publications that support our observation that the original rabies vaccine killed people and may have been ineffective. Princeton University historian, Gerald L. Geison writing in the Hastings Center Report stated:

…it remains certain he had not yet established the safety and efficacy of his method in the case of animals previously infected with rabies by the method in which he and his collaborators placed the greatest confidence. At least in that sense, it seems to me, Pasteur violated his own public standards of ethicality when he undertook to treat Meister. That conclusion is powerfully reinforced by the otherwise inexplicable (if temporary) defection of such disciples as Emile Roux. In a very few cases, moreover, it seems probable that Pasteur’s subjects died because of rather than in spite of, his “intensive” treatment. Such, at any rate was the conclusion of the English Commission on Rabies, which conducted the most dispassionate of contemporary inquiries into Pasteur’s work.
Physician, medical historian, and medical writer for the New York Times, Dr. Lawrence Altman wrote:

Word about the success of Pasteur’s vaccine began to spread. But it turned out that his original fears about its safety were well founded. The immunization therapy involved a series of injections lasting for as long as twenty-one days. During this time the patient received up to two and a half grams—a very large amount—of animal brain tissue, as well as weakened rabies virus, in the vaccine. Just a few molecules of brain tissue were enough to incite fatal allergic reaction in some people. Over the next two years, 350 people were treated with Pasteur’s vaccine. In 1886 Pasteur reported that of the 350 treated cases, only one person had developed rabies—a child whose therapy had been delayed. But a few of the patients treated with the Pasteur rabies vaccine developed permanent damage to the brain and central nervous system. Some died because of the vaccine.°

Pasteur’s rabies vaccine killed some humans and induced permanent brain damage and CNS changes in others. Our account of the history of the vaccine is as accurate as a fair reading of history can produce.

Rabies was and is a difficult disease to diagnose prior to the onset of symptoms. It has a long incubation period (weeks to months) and gives little hint of its presence before full-blown manifestation. After manifesting, it is almost always lethal. Further, most cases of bites from a rabies-infected animal never lead to the disease in humans. It is estimated that during the years preceding Pasteur’s vaccine, less than 50 deaths occurred in any given year.° Pasteur vaccinated hundreds in about a year’s time. In light of these statistics, most people who received the vaccine probably did not have the virus in their systems. When Pasteur began using his vaccine he administered it to people who in all likelihood did not have rabies.° It is fallacious to count those as vaccine successes.

On the other hand, some people who received the vaccine probably would have otherwise gone on to die from rabies.° The question is the same as in any vaccine trial: Did the vaccine do more good than harm? To say that the vaccine allegedly saved people is far from the whole story. Pasteur himself estimated that only 16% of those who came to him would have gone on to die had it not been for the vaccine.° The problem is that Pasteur never allowed controlled trials of the vaccine, so we will never really know how effective the first vaccine was. Festing’s statement, “The vaccine did not cause any deaths, it failed to cure one person out of the first 350, for a very good reason, and it was highly successful” is a gross misrepresentation of history and does a disservice to the philosophy of science.

Pasteur initially said he used the dogs as CAMs but retracted the assertion when questioned more closely. The animal model community should acknowledge that the vaccine’s arrival was due, in part, to Pasteur’s genius, but certainly not because of the tests on dogs. Since this essay is largely about the lack of reliability of trans-species extrapolation it is appropriate to quote Pasteur on the probability of his vaccine’s success in humans being based on his dog research: “what is possible in the dog may not be so in man.”°
Insulin

Dr. Festing states,

2) On page 51 of their book, the Greeks state that "Banting and Best experimented on some dogs and by sheer happenstance persuaded people who had knowledge of in vitro research to look for insulin and purify it." They go on to say "The real credit for purifying insulin should have gone to Collip who used chemistry to purify the insulin," It is perfectly true that the purification of insulin posed some severe problems particularly in scaling up for volume production. What the book fails to mention is that Collip had to have an assay method to determine whether his isolation methods produced active, injectable, insulin. "It was Collip who found that pancreatic extracts were effective in rabbits. And not necessarily diabetic rabbits, perfectly normal ones. Extract lowered their blood sugar from normal to below normal." Collip tried many ways of extracting insulin from the pancreas of farm animals, and used the rabbits to assay the results. The problems in scaling up the methods meant that Ely Lilly, the commercial company chosen for this task, used over 100,000 rabbits in the first six months in order to try to get a consistent product. Insulin has saved many millions of lives, but its discovery and isolation depended on the use of laboratory animals, which continued to be needed to assay the potency and safety of each batch of commercial insulin until the 1990's, when an in vitro method was finally developed.

We do not dispute the fact that the sample of tissue from which insulin was purified came from a dog. What we dispute is that the dog was the vital part of the experiment and that experiments on animals played the vital role in linking insulin production to the pancreas and the pancreas to diabetes. Chemists and chemistry alone, not dogs, gave us insulin. The claim that insulin could not have been discovered without a dog is baseless. Neither do we deny that Collip used rabbits to measure purity. What we said was that the linking of diabetes to the pancreas and the discovery of insulin was not dependent upon animals. This is in response to the constant litany of the pro-animal experimentation community that “insulin was discovered in dogs and animal models led us to the pancreas as the cause of diabetes.” It wasn’t and they didn’t. It was discovered in humans and purified with tissue from dogs. There is a big difference. What we said was: Certainly, animals have figured largely in the history of diabetic research and therapy. Again, however, there are profound holes in the assumption that animal experimentation was necessary.

To accuse us of saying something we did not and then refuting it is a straw man fallacy. The point we are arguing in Sacred Cows is that animal models were never great, and that today they are even less viable. We have never stated that animals always gave the wrong results or that animals were not associated with great breakthroughs. We do believe that animal models were a very mixed blessing even in Banting’s day. Currently, they are either harmful or unnecessary. Examples like the one below (from Sacred Cows) are why animal models were, even in the late 19th century, a mixed blessing:

In 1895, Hansemann reviewed the literature and found seventy-two cases of diabetes accompanied by lesions of the pancreas. However, based on dog experiments he concluded that diabetes had nothing to do with the pancreas…. Claude Bernard conducted experiments on dogs that produced sugar in the urine. Remember, this had already been observed in humans. However, the condition in quadrupeds led Bernard to conjecture that diabetes was a liver disease, linking sugar transport to the liver and glycogen. He also conducted many experiments on animals’ central nervous system in an attempt to establish a link there. Granted the liver is involved in carbohydrate metabolism and injuries to the brain can result in hyperglycemia (elevated blood sugar levels), but this is not insulin resistance at the cellular level or a lack of insulin production from the pancreas. These
animal studies threw diabetes research off the track for many years. Because of animal studies, many scientists did not believe the pancreas to be involved in diabetes nor that a hormone such as insulin existed. One scientist, Pflüger stated that the pancreas does not “play any part at all in the origin of diabetes, whether, in fact, there is such a thing as pancreatic diabetes.” J. B. Collip, a biochemist in MacLeod's team, said that the administration of the dog insulin was “absolutely useless.” Note what scientists said about the dog experiments in 1922: “The production of insulin originated in a wrongly conceived, wrongly conducted, and wrongly interpreted series of experiments.” Even Banting and Best's supporters said they were “unqualified to do good work.”

Neither do we dispute that animal-based assays have allowed measurements of purity. But the question is, why do people see this as a justification for the current day use of animals to model human disease? Furthermore, does anyone really believe that with the advent of high-tech devices like HPLC we still need to test a drug’s purity in an animal? If we continue to use animal assays we must admit that we so for convenience, not out of necessity. In the above case, Dr. Festing’s criticism of Sacred Cows is based on something we did not say. Dr. Festing’s argument is, again, a straw man.
Penicillin

Dr. Festing:

On page 73 of their book, the Greeks claim that animal testing delayed the introduction of penicillin, because Fleming used it on a rabbit and it did not work. Given that he was unable to purify the penicillin; that the use of a rabbit is not mentioned by Hare; that had Fleming had some pure penicillin, there were patients he could have tried it on; that mice would have been the natural choice of test animal, because of their small body size; and that the only references to the use of a rabbit are from anti-vivisectionist literature, I doubt whether this is true. The Greeks go on to claim that "He later had a very sick patient, and since he had nothing else to try, administered penicillin. The rest is history." In fact, Florey gave Fleming the purified penicillin. The vital part played by Chain and Florey in isolating it, proving it by using mice, and developing it, is largely ignored in their book.

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

1. Fleming re-discovered penicillin.
2. He then tested it in vitro and in vivo on rabbits and mice (he mentions the rabbits in his original paper). The in vitro results showed promise, as did topical application on rabbits. But when given systemically, the rabbits metabolized it too rapidly and led Fleming to believe it would be useless for humans when administered systemically.
3. Fleming continued to grow penicillin and even administered it to humans prior to the 1940s. Through a student of his, G. G. Paine, Fleming gave it to 4 humans suffering from ophthalmic neonatorium, 3 of whom responded well.11
4. Florey and Chain conducted research with penicillin and produced a purified product using basic chemistry.
5. The purified product was tested on mice and on more humans, all of whom did well.
6. Publicity surrounding Fleming's patient led to funding to develop the drug. Fleming went down in history, rightly or wrongly, as the person responsible for penicillin.

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

Under certain circumstances, penicillin kills guinea pigs and Syrian hamsters. In addition, penicillin is teratogenic in rats, causing limb malformations in offspring. Dr. Festing has derided us for ignoring certain facts. We have explained why we didn’t mention them: they were not relevant to our point about species differences.

The questions we want answered are: Why do Dr. Festing and others, who give unqualified support to animal experimentation, ignore the facts above? And why do these same people ignore the fact that H. W. Florey, co-winner of the Nobel Prize for penicillin, administered penicillin to a sick cat at the same time Fleming was giving it to his sick human? Florey's cat died. Who should Florey have believed, the dead cat, the rabbit, or the mice on which it worked? Neither do these individuals address the quote attributed to Fleming by his student, “How fortunate we didn't have these animal tests in the 1940s, for penicillin would probably never have been granted a license, and possibly the whole field of antibiotics might never have been realized."12 They also ignore the statements of Macfarlane, another early penicillin researcher, who emphasized species differences when he stated: "Mice were used in the initial toxicity tests because of their
small size, but what a lucky chance it was, for in this respect man is like the mouse and not the guinea-pig. If we had used guinea-pigs exclusively we should have said that penicillin was toxic, and we probably should not have proceeded to try and overcome the difficulties of producing the substance for trial in man.\textsuperscript{13}

With regard to the role of cats and rabbits: V. D. Allison (a student, lab worker, and protégé of Fleming’s), wrote in \textit{The Ulster Medical Journal} in 1974:

Subsequent events are well known—the short life of the mold extract, its lack of damage to blood cells and tissues, its ability to cure certain infections in rabbits, and topically in the human eye and skin infections….

He [Florey] asked Fleming not to use it (the penicillin) until he (Florey) had injected some into the spinal canal of a cat to see if it was innocuous. However the patient was moribund with all hope given up, so Fleming decided to inject the crude penicillin into the patient’s spinal canal on the evening he received it. Fleming slept at the hospital that night and early next morning, Florey phoned Fleming and told him the cat had died. [Fleming’s patient made a complete recovery because of the penicillin.]

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

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

Hello, nice to hear from you! Yes, he tested the crude broth extract on rabbits and mice. These were described in his original paper, sent to the British Journal of Exp. Path. on 10 May, 1929 and published in June 1929.

Ref: Fleming A, Brit J Exp Path., 10 : 226, 1929. I have not got a copy of it (although I have almost every book published on the discovery, many of them with rubbish in them!) but you will find quotes from it in the book by Ronald Hare, "The Birth of Penicillin", George Allen & Unwin, 1970, p 90. "Twenty cc. injected intravenously into a rabbit were not more toxic than the same quantity of broth". Also "Half a cc. injected intraperitoneally into a mouse weighing about 20 gm. induced no toxic symptoms".\textsuperscript{15}

Allen B. Weisse, Professor of Medicine at the University of Medicine and Dentistry of New Jersey, and author of \textit{Medical Odysseys: The Different and Sometimes Unexpected Pathways to Twentieth-Century Medical Discoveries}, (Rutgers University Press, 1991), wrote in \textit{Hospital Practice} August 15, 1991:

[Fleming was discouraged about penicillin’s possible use because first…] Third, after injection into an ear vein of a rabbit and with blood samples taken periodically thereafter for testing, it was found that penicillin was rapidly removed from the bloodstream. Samples taken at 30 minutes were found almost completely devoid of activity.

Of what use might be an antibacterial agent that took several hours to act but was removed from the body within 30 minutes and inhibited by the blood with which it would obviously be mixing?\textsuperscript{16}

Craig H Steffee of Bowman Gray School of Medicine, writing in the \textit{North Carolina Medical Journal} states:

Fleming considered penicillin a potential chemotherapeutic agent, but his early in-vivo investigations were discouraging. In rabbits, serum levels of penicillin dropped rapidly after parenteral administration, too fast to allow the several hours of contact with bacteria required for an effect in vitro.
Steffee defends Fleming’s laying penicillin aside based on the rabbit work stating:

…how many therapeutic modalities with the poor in vivo results of Fleming’s early penicillin trials would be offered continued funding today?  

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

One might well wonder why, given the uncontrolled devastation of bacterial diseases, no further experiments on animals or humans were undertaken. The rapid disappearance from the blood has already been mentioned…. Even the choice not to use animal experiments more extensively, a routine practice of investigators on the continent, could be defended by Fleming and his group. After all, there might be differences between humans and other animals in resistance or susceptibility to different infections.

While researching Sacred Cows, we easily discovered that Fleming used a rabbit and concluded from it that penicillin would not be effective in humans. The general public does not understand the differences between $t_{1/2\alpha}$ and $t_{1/2\beta}$ and $t_{1/2\pi}$ (and perhaps neither do some of the readers) but they do understand what is meant when someone says, “it doesn’t work.” We stand by our statement.

Weisse continues:

In August 1942, a close personal friend of Fleming had contracted streptococcal meningitis. When conventional therapy failed and death seemed imminent, Fleming turned to Florey for help. The latter personally delivered his remaining supply of penicillin to Fleming and instructed him in the initial use of it. A dramatic cure was obtained, even the more so since penicillin was administered into the spinal canal for the first time to enhance its effectiveness. This “miracle” at St. Mary’s was reported in the London Times and the following day a letter from Almroth Wright identified Fleming as the one on whose brow the laurel wreath should sit.

Because of the prestige of Wright, Fleming was largely credited in the press with the miracle of penicillin. (That Florey avoided the press like the plague did not help clarify the situation. Then, as now, once the press has awarded credit to a single individual, that eclipses the important contributions of his colleagues.) Regardless of the truth of the press’s claim that Fleming was the brains behind the drug, the reason money was then poured into penicillin was Fleming’s successful administration to his friend and the publicity surrounding it. (Others confirm that Fleming routinely gave penicillin to humans with infections for years after 1929.)

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

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

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

The true story of how penicillin came to be is probably known only to God. The point of our passage is that Fleming received data from rabbits, which led him to abandon penicillin as a systemic antibacterial agent. Many references support this. We do not deny that penicillin can be used in many species. We do deny that animals can be used as predictors for humans because, as the penicillin story illustrates, animals vary in
their reactions and a reaction in animals does not mean the same will occur in humans. Thalidomide, cyclosporin, the statins, the SSRIs, and scores of more recent drugs attest to this. The penicillin saga is, again, an example of using animals as CAMs. The practice proved ineffective in the 1920s and is even less effective today. (We will shortly explore why this is so.) A related criticism that has been leveled against us is that because clinical trials did not uncover adverse side effects, we cannot blame animal tests for not doing so either. Again, this is fallacious. The medical community has long criticized the drug industry for its abbreviated clinical trials. Clinical trials assume approximately 60% of the cost of bringing a drug to market. Because studies on animals are cheaper and still offer liability protection in the USA and Europe, Big Pharma is reluctant to extend costly clinical trials to the numbers that are needed to ensure safety upon release. Dr. Festing cannot justify the failure of animal models by citing the failures of the drug industry. (In light of current research in pharmacogenomics, Big Pharma should be, and in some cases is, developing multiple drugs to treat the same disease rather than focusing on the blockbuster.)
The Role of Money in Animal Experiments

Dr. Festing:

A book like this always has to have a villain. And, true to form, chapter 5 is a polemic about how vested interests are making money out of animal research. It is true that the supply of animals, cages, diet and sundries for animals is a valuable business. However money for medical research comes largely from government (for example, the Medical Research Council in the UK, and the National Institutes of Health in the USA), the pharmaceutical industry, research charities such as the Wellcome Foundation, and universities. All these organisations already spend many millions on clinical science and on non-animal alternatives, such as research with insects (for example, Drosophila) and the nematode Caenorhabditis elegans, and with cell cultures. All of them would be only too pleased to save money by not using animals if they thought real alternatives were available.

This is a very naïve view of the world. Indeed it is so naïve as not to be believable. (Not to mention the fact that insects and roundworms are animals.)

Has it been Dr. Festing’s experience that all government and non-government programs are funded based on merit? Perhaps in the UK, the government never awards funds based on special interest lobbying or to curry favor with a subset of constituents back home, but we doubt it. To state that governments and charities do fund some nonanimal-based research is hardly relevant. Of course they do. They also provide funds for hungry children.

What we are referring to is the ratio of funds allocated to animal-based models compared to non-animal research modalities, and how decisions are made concerning the research that is funded. In a cost-benefit analysis, animal experimentation comes up wanting in regard to benefit, yet significant in regard to economic cost. The fact that governments and charities fund research other than animal-based research is immaterial to the question of whether they fund animal experimentation for reasons other than altruistic ones. This is again an example of fallacious reasoning. The US government funds programs to benefit the poor and mentally ill but that does not justify the “pork” that is present in every budget. Funding housing, welfare, and food for indigent infants and children does not justify building an unnecessary road in a congressional district just because doing so will help re-elect the congressman.

To state that: “All of them would be only too pleased to save money by not using animals if they thought real alternatives were available” is unfounded, unproved, inconsistent with reality and assumes the answer to the question we are posing, namely: “does animal experimentation work in 2002?” We will expand on this presently. (It also contradicts what other FRAME officials say about why animal experimentation persists.)

In Doing Science, Ivan Valiela states:

Scientists respond to a variety of motivations: excitement about learning new things, self-promotion (thirst for prestige and success, envy, careerism), altruism and sense of service, and, surely enough, profit. Surprisingly, out of this chaotic melange arises a remarkable series of upward steps to understanding the world around us. The scientists who do science are human beings, as flawed or admirable as those in any other endeavor. There is no guarantee that at times even clever, honest scientists will not ask misdirected questions, and no warranty that perhaps clever, but less honest, scientists will provide authentic answers.
To state that the government is beyond the influences of everyday politics is laughable, but to assert that pharmaceutical companies are, if not altruistic, at least trying to "do the right thing" is shameless. Big Pharma will do whatever necessary to make a buck. Consider the following from Trust Us, We're Experts! (We apologize for the long quotes but think they are necessary to show that we are not merely expressing an unusual opinion but are in fact well within the mainstream. By placing the very long quotes in a box, we hope the reader will find them easier to follow across the pages.)

The tobacco industry is hardly alone in attempting to influence the scientific publishing process. A similar example of industry influence came to light in 1999 regarding the diet-drug combo fen-phen (a combination of fenfluramine, dexfenfluramine, and phentermine), developed by Wyeth-Ayerst Laboratories. Wyeth-Ayerst had commissioned ghostwriters to write ten articles promoting fen-phen as a treatment for obesity. Two of the ten articles were actually published in peer-reviewed medical journals before studies linked fen-phen to heart valve damage and an often-fatal lung disease, forcing the company to pull the drugs from the market in September 1997. In lawsuits filed by injured fen-phen users, internal company documents were subpoenaed showing that Wyeth-Ayerst had also edited the draft articles to play down and occasionally delete descriptions of side effects associated with the drugs. The final articles were published under the names of prominent researchers, one of whom claimed later that he had no idea that Wyeth had commissioned the article on which his name appeared. "It's really deceptive," said Dr. Albert J. Stunkard of the University of Pennsylvania, whose article was published in the American Journal of Medicine in February 1996. "It sort of makes you uneasy."

How did Stunkard's name end up on an article without his knowing who sponsored it? The process involved an intermediary hired by WyethAyerst called Excerpta Medica, Inc., which received $20,000 for each article. Excerpta's ghostwriters produced first-draft versions of the articles and then lined up well-known university researchers like Stunkard and paid them honoraria of $1,000 to $1,500 to edit the drafts and lend their names to the final work. Stunkard says Excerpta did not tell him that the honorarium originally came from Wyeth. One of the name-brand researchers even sent a letter back praising Excerpta's ghostwriting skills. "Let me congratulate you and your writer on an excellent and thorough review of the literature, clearly written," wrote Dr. Richard L. Atkinson, professor of medicine and nutritional science at the University of Wisconsin Medical School. "Perhaps I can get you to write all my papers for me! My only general comment is that this piece may make dexfenfluramine sound better than it really is."

"The whole process strikes me as egregious," said Jerome P. Kassirer then-editor of the New England Journal of Medicine. "the fact that Wyeth commissioned someone to write pieces that are favorable to them, the fact that they paid people to put their names on these things, the fact that people were willing to put their names on it, the fact that the journals published them without asking questions." Yet it would be a mistake to imagine that these failures of the scientific publishing system reflect greed or laziness on the part of the individuals involved. Naiveté might be a better word to describe the mind-set of the researchers who participate in this sort of arrangement. In any case, the Wyeth-Ayerst practice is not an isolated incident. "This is a common practice in the industry. It's not particular to us," said Wyeth spokesman Doug Petkus.

Medical editor Jenny Speicher agrees that the Wyeth-Ayerst case is not an aberration. "I used to work at Medical Tribune, a news publication for physicians," she said. "We had all these pharmaceutical and PR companies calling, asking what are the writing guidelines for articles, because they wanted to have their flack doctors write articles, or assign a freelance writer to write under a doctor's name. I've even been offered these writing jobs myself. We always told them that all of our articles had to have comments from independent researchers, so of course they weren't interested. But they kept on trying."

"Pharmaceutical companies hire PR firms to promote drugs," agrees science writer Norman Bauman. "Those promotions include hiring freelance writers to write articles for peer-reviewed journals, under the byline of doctors whom they also hire. This has been discussed extensively in
the medical journals and also in the Wall Street Journal, and I personally know people who write these journal articles. The pay is OK—about $3,000 for a six- to ten page journal article."

Even the New England Journal of Medicine—often described as the world's most prestigious medical journal—has been involved in controversies regarding hidden economic interests that shape its content and conclusions. In 1986, for example, NEJM published one study and rejected another that reached opposite conclusions about the antibiotic amoxicillin, even though both studies were based on the same data. Scientists involved with the first, favorable study had received $1.6 million in grants from the drug manufacturer, while the author of the critical study had refused corporate funding. NEJM proclaimed the pro-amoxicillin study the "authorized" version, and the author of the critical study underwent years of discipline and demotions from the academic bureaucracy at his university, which also took the side of the industry-funded scientist. Five years later, the dissenting scientist's critical study finally found publication in the Journal of the American Medical Association, and other large-scale testing of children showed that those who took amoxicillin actually experienced lower recovery rates than children who took no medicine at all. In 1989, NEJM came under fire again when it published an article downplaying the dangers of exposure to asbestos while failing to disclose that the author had ties to the asbestos industry. In 1996, a similar controversy emerged when the journal ran an editorial touting the benefits of diet drugs, again failing to note that the editorial's authors were paid consultants for companies that sell the drugs.

…Corporate-sponsored scientific symposiums provide another means for manipulating the content of medical journals. In 1992, the New England Journal of Medicine itself published a survey of 625 such symposiums, which found that 42 percent of them were sponsored by a single pharmaceutical sponsor. There was a correlation, moreover, between single-company sponsorship and practices that commercialize or corrupt the scientific review process, including symposiums with misleading titles designed to promote a specific brand-name product. "Industry sponsored symposia are promotional in nature and . . . journals often abandon the peer-review process when they publish symposiums," the survey concluded. Drummond Rennie, a deputy editor of the Journal of the American Medical Association, describes how the process works in plainer language: "I'm the advertising guy for the drug. I tell a journal I will give them $100,000 to have a special issue on that drug. Plus I'll give the journal so much per reprint, and I'll order a lot of reprints. I'll select the editor and all the authors. I phone everyone who has written good things about that drug. I say, 'I'll fly you and your wife first class to New Orleans for a symposium. I'll put your paper in the special issue of the journal, and you'll have an extra publication for your c.v.' Then I'll put a reprint of that symposium on some doctor's desk and say, 'Look at this marvelous drug.'"

…In 1999, JAMA editor Drummond Rennie complained that the influence of private funding on medical research has created "a race to the ethical bottom." Known cases of suppression may be only the tip of the iceberg. "The behavior of universities and scientists is sad, shocking, and frightening," Rennie said. "They are seduced by industry funding, and frightened that if they don't go along with these gag orders, the money will go to less rigorous institutions."

The consistency of research support for the sponsor's desired outcome intrigued Richard Davidson, a general internist and associate professor of medicine at the University of Florida. "It struck me that every time I read an article about a drug company study, it never found the company's drug inferior to what it was being compared to," Davidson says. He decided to test that impression by reviewing 107 published studies comparing a new drug against a traditional therapy. Davidson confirmed what he had suspected—studies of new drugs sponsored by drug companies were more likely to favor those drugs than studies supported by noncommercial entities. In not a single case was a drug or treatment manufactured by the sponsoring company found inferior to another company's product.

When other researchers have examined the link between funding sources and research outcomes, they have reached conclusions similar to Davidson's:
• In 1994, researchers in Boston studied the relationship between funding and reported drug performance in published trials of antiinflammatory drugs used in the treatment of arthritis. They reviewed 56 drug trials and found that in every single case, the manufacturer-associated drug was reported as being equal or superior in efficacy and toxicity to the comparison drug. "These claims of superiority, especially in regard to side effects, are often not supported by the trial data," they added. "These data raise concerns about selective publication or biased interpretation of results in manufacturer-associated trials."

• In 1996, researchers Mildred K. Cho and Lisa A. Bero compared studies of new drug therapies and found that 98 percent of the studies funded by a drug's maker reached favorable conclusions about its safety and efficacy, compared to 76 percent of studies funded by independent sources.

• In 1998, the New England Journal of Medicine published a study that examined the relationship between drug-industry funding and research conclusions about calcium-channel blockers, a class of drugs used to treat high blood pressure. There are safety concerns about the use of calcium-channel blockers because of research showing that they present a higher risk of heart attacks than other older and cheaper forms of blood pressure medication such as diuretics and beta-blockers. The NEJM study examined 70 articles on channel blockers and classified them into three categories: favorable, neutral, and critical. It found that 96 percent of the authors of favorable articles had financial ties to manufacturers of calcium channel blockers, compared with 60 percent of the neutral authors and 37 percent of the critical authors. Only two of the 70 articles disclosed the authors' corporate ties.

• In October 1999, researchers at Northwestern University in Chicago studied the relationship between funding sources and conclusions reached by studies of new cancer drugs and found that studies sponsored by drug companies were nearly eight times less likely to report unfavorable conclusions than studies paid for by nonprofit organizations.

Again, to assert that pharmaceutical companies are interested in doing the right thing is shameless. Even they deny it in meetings of their peers. The only ones in the pharmaceutical companies who don’t deny it are the marketing and advertising divisions. Physicians have been caught allowing pharmaceutical sales representatives into their examining rooms. In exchange for money, the physicians allowed the representatives to see the patients with them and recommend what medicines to prescribe. This type of thing has become standard practice for many pharmaceutical companies. Warner-Lambert (now owned by Pfizer) rewarded physicians who prescribed their drugs in high volumes by paying them to do so. They did the same as they tried to influence physicians who wrote medical journal articles.

According to Melody Petersen of the New York Times, Dr. Franklin, the whistle-blower in the Warner-Lambert case, said in an interview she conducted:

…he was most troubled by the company's insistence that he press doctors to prescribe Neurontin in much higher doses than had been approved. ‘It was untried ground,’ Dr. Franklin said. ‘We were not sure what would happen at these high doses. I recognized that my actions may be putting people in harm’s way.’ Dr. Franklin said several Warner-Lambert marketing executives had told him that because Neurontin appeared to be safe in high doses it was reasonable to encourage doctors to try it for almost any neurological condition ‘just to see what happens.’ Dr. Franklin's lawsuit also accuses the company of paying dozens of doctors to speak about Neurontin to their peers — some earning tens of thousands of dollars a year. One internal memo listed doctors the company considered to be 'movers and shakers,' including some at prestigious medical schools such as Harvard, Cornell and Columbia.

Warner-Lambert also hired two marketing firms to write articles about the unapproved uses of Neurontin and find doctors willing to sign their names to them as authors. According to an invoice from one of the marketing firms, Warner-Lambert agreed to pay the firm $12,000 to write each article and $1,000 to each doctor willing to serve as author.
It is well known that prominent trusted figures such as the former Surgeon General, C. Everett Koop M.D., have been shown to be pawns of industry and that groups are formed that sound like they advocate one thing but in fact exist only to oppose it. Again, from Trust Us We’re Experts!

...Even scientists are human beings. They may be brilliant in a particular field of research but naive or uninformed about fields outside their specialty, and they are not immune from political ideologies or the lure of money. The conservative political views of Koop and Seitz are well-known. Although Koop certainly deserves credit for his principled stand regarding tobacco, since leaving public office he has participated in several ventures that call into question his objectivity and ability to avoid ethical conflicts of interest. In April 1999, for example, he circulated a letter in Congress urging legislators to allow the Schering-Plough Corporation to extend the patent on its allergy drug Claritin. By keeping the drug under patent, the company would be able to prevent other companies from offering cheaper generic versions, thereby garnering an estimated $1 billion in additional profits. The following month, he met with members of Congress to defend the company’s position on legislation involving another drug used to treat hepatitis C. Koop did not disclose that Schering-Plough [the company that manufactured the drug] had given a $1 million grant earlier that year to his nonprofit organization, the Koop Foundation.

On another occasion, Koop testified in defense of latex gloves, which have been linked to life-threatening allergies. Latex allergies affect roughly 3 percent of the general population and upward of 10 percent of health care workers who are regularly exposed through the use of latex gloves and other medical supplies. An estimated 200,000 nurses have developed latex allergies, which can be disabling and even deadly. Alternatives to latex exist and are gradually being adopted by the health care industry, but Koop told Congress that latex glove concerns are "borderline hysteria." He also claimed—falsely, as he later discovered—that a study undercutting concerns about latex gloves had been conducted by the U.S. Centers for Disease Control and Prevention. In fact, the study he cited had been sponsored by a company that makes the gloves. And Koop had failed to disclose the fact that two years previously another maker of latex gloves had paid him a reported $656,250 in consulting fees to serve as a “spokesman” for the company.

"What this long admired and respected man has done in taking money from a glove manufacturer and then speaking out on its behalf is wrong," said Susan Wilburn, senior specialist in occupational safety and health for the American Nurses Association. Another ANA representative, Michelle Nawar, noted that latex allergy "is a very serious disease" that "can be a debilitating, career-ending illness." In fact, five deaths have been reported from using latex gloves, four involving nurses.

In light of the above, why should any reasonable person believe that Big Pharma tests on animals because it works? Industry knows that any lie, told often enough and by influential enough people, will be believed. The vested interest groups are known to organize and support supposed disinterested third party organizations that act as a mouthpiece for their views. The Philip Morris tobacco company created the front group called the National Smokers Alliance, which, posing as a grassroots organization, advocated the right of people to smoke. The magazines Playboy and Penthouse created Americans for Constitutional Freedom to counter proposals by Attorney General Ed Meese limiting pornography by calling supporters of such proposals pro-pornography. The Global Climate Coalition and the British Columbia Forest Alliance were created to fight environmental groups. The Council for Tobacco Research (TCTR) was formed by the tobacco industry to be a supposed disinterested third party that studied the effects of smoking; not surprisingly, it was unable to prove that smoking was dangerous. The PR industry is talented, and the concepts they use are well known and implemented by many in the so-called alternatives (to animal models) or 3R’s community.

In its early days TCTR hired Dr. Clarence Little, a former director of what would become the American Cancer Society, to “head its investigations into smoking.” Nothing beats hiring a person who appears to be an opponent and then getting them to endorse your idea or product. Public relations firms have relied on moderates in the environmental and other social movements to come over to their side to legitimize their
positions. The way Monsanto promoted their rBGH (bovine growth hormone) is another example. Monsanto hired nutritionists, scientists, physicians and animal welfarists to promote the safety of their product. But probably the best example is the fact that the founder of MADD (Mothers Against Drunk Driving) was hired by the alcohol industry to help defeat legislation to strengthen blood-alcohol tests.

Some in FRAME (Fund for the Replacement of Animals in Medical Experiments) exemplify the game playing described above. They are just another example of the incestuous relationship between big business and those claiming to look for replacements for animal models. In *Toxic Sludge Is Good For You*, John Stauber and Sheldon Rampton explain why groups that oppose change fund front groups that appear to want it. They write, “Some of the biggest and best-known green organizations—the Izaak Walton League, the National Wildlife Federation, and the National Audubon Society among them—are receiving support, recognition and large cash contributions from corporate polluters. In exchange, the corporate beneficiaries have been able to buy a green image worth literally millions in the consumer marketplace.” David Callahan, a writer, echoes Stauber and Rampton when he states, “It is naïve to imagine that conservative think tanks are not extremely beholden to their funders in the business world or to the corporate leaders on their boards. This is simply the way the power of the purse works. Just as politicians can’t ignore the demands of their major donors if they want to survive, neither can institutions ignore their benefactors.”

John Ingham of the Great Britain-based Express newspapers wrote:

> “The public is tired of being given patronising reassurances about safety by experts, only to be later told that they were wrong... The public may have good reason to be generally suspicious. The scientists’ union, the IPMS, has found that big business is buying up science. In a survey, one in three of its members had been pressured to change their conclusions, either to suit the customer or to win further research contracts... Doctors were largely to blame for the thalidomide disaster of the early Sixties because they collectively ignored overwhelming evidence that the drug could harm babies in the womb. In 1995, it was revealed that government scientists had failed to issue warnings about the risks to babies in the womb from listeria in soft cheeses, cook-chill foods, chicken and pate. At least 26 babies died. Edwina Currie lost her job as agriculture minister after revealing the risks and the extent of salmonella infection in eggs, which had been played down for many years. Before 1996, government advisers repeatedly told the public that there was no evidence that eating beefburgers caused the human variant of mad cow disease. Cigarettes - once billed as good for your health - are now branded as killers.”

Just as the TCTR’s support came from the very industry it was supposedly seeking to study, look where FRAME’s support comes from (see table 1). This is a *Who’s Who* of corporations that obtain money or liability protection from animal studies. Is it really feasible to believe that this type of sponsorship comes with no strings attached?

Clinical studies are where most adverse drug effects are found. They are also far more expensive than animal tests. If FRAME’s sponsors really wanted to put safe products on the market, they would expand clinical trials as physicians have been requesting for decades. When Catherine the Great of Russia wished to impress foreign dignitaries, she had Field Marshal Grigori Potemkin arrange to have fake villages built to create an illusion of prosperity. Since that time, the public relations industry has used the term Potemkin village to refer to things that look legitimate but are lacking in substance. Such as the groups we have described above. While we acknowledge there are people within FRAME trying to do the right thing, many, especially in the hierarchy, are following the lead of the Field Marshall.

FRAME has done, and is doing, some good work, but in light of the above, one must question what FRAME is -- especially given the fact that different members of the board give very different views on animal models and that the same members give different views depending on whether the audience is public or private.
Table 1

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<th>Corporate Benefactors</th>
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<td>Asda Stores Ltd</td>
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<td>Avon Products Inc</td>
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<td>GlaxoWellcome Research &amp; Development Ltd</td>
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<th>Corporate Sponsors</th>
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<td>British Association for Chemicals</td>
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In *Trust Us, We’re Experts!*, Rampton and Stauber and write 30:

An organization called "Consumer Alert" frequently pops up in news stories about product safety issues. What the reporters almost never mention is that Consumer Alert is funded by corporations and that its positions are usually diametrically opposed to the positions taken by independent consumer groups such as Consumers Union. For example, Consumer Alert opposes flame-resistance standards for clothing fabrics issued by the Consumer Product Safety Commission, and defends products such as the diet drug dexfenfluramine (Redux), which was taken off the market because of its association with heart valve damage. In contrast with Consumers Union, which is funded primarily by member subscriptions, Consumer Alert is funded by the industries whose products it defends—companies including Anheuser-Busch, Pfizer Pharmaceuticals, Philip Morris, Allstate Insurance Fund, American Cyanamid, Elanco, Eli Lilly Exxon, Monsanto, Upjohn, Chemical Manufacturers Association, Ciba-Geigy, the Beer Institute, Coors, and Chevron USA."

Mae-Wan Ho stated in her review of the book *Captive State: The Corporate Takeover of Britain* by George Monbiot:

> Corporations have seized control of our hospitals, schools and universities. They have infiltrated the government and come to dominate government ministries, buying and selling planning permission, dispensing our tax money to research and development that benefit industry, taking over the food chain.” She cites as an example, her involvement in a situation with Huntington Life Science: “But the chief of HLS, Brian Cass, tried to intimidate me, in phone calls, and in an email, to get me to reveal the identity of the campaigning group. I refused to do so…George Monbiot gives many more examples of similar treatments university administrations mete out to academics daring to dissent from the corporate agenda or to criticise it.” She quotes Monbiot saying: “Today, there is scarcely a science faculty in the United Kingdom whose academic freedom has not been compromised by its funding arrangements. Contact between government-funded researchers and industry, having once been discouraged, is now, in many departments, effectively compulsory…. our universities have been offered for sale, with the result that objectivity and intellectual honesty are becoming surplus to requirements.”

Ho continues:

The sell-out began under the Conservative Government, and with science research funding which effectively controls what kinds of science would be done…. The Labour government extended those reforms enthusiastically…. Thus, it comes as no surprise that the Biotechnology and Biological Sciences Research council (BBSRC), the main funding body for Britain's academic biologists with an annual budget of £190m, is chaired by Peter Doyle, an executive director of the biotech corporation, Zeneca. Among the members of its council are the Chief Executive of the pharmaceutical firm Chiroscience, the former Director of Research and Development of the food company Nestle; the President of the Food and Drink Federation; the general manager of Britain's biggest farming business and a consultant to the biochemical industry. The BBSRC's strategy board contains executives from SmithKline Beecham, Merck Sharpe and Dohme and Agrevo UK (now subsidiary of Aventis, the company responsible for getting the Department of Environment, Transport and the Regions (DETR) to support the controversial 'farmscale' field trials with £3 million of taxpayer's money). The Council has seven specialist committees, each overseeing the funding of different branches of biology. Employees of Zeneca sit on all of them…. It has paid for researchers to work for Nestle, Unilever, Glaxo Wellcome, Smith-Kline Beecham, AgrEvo, Dupont, Rhone Poulenc and Zeneca… The same pattern of corporate takeover is repeated in the other research councils, the Natural Environment Research Council (NERC) and the Medical Research Council (MRC).” 31

We again emphasize that there are people in FRAME who are trying to do the right thing, but we would be remiss not to point out that there are others with less pure motives. If anyone seriously doubts the fact that industry seeks out groups like FRAME in order to appear to promote an agenda they in fact diametrically oppose we refer you to Stauber and Rampton’s books *Toxic Sludge Is Good For You* and *Trust Us, We’re
Experts! (there are others, but these are excellent) and you can judge for yourself whether our view is justified. We believe this is a serious problem for FRAME and it deserves discussion that should result in housecleaning within the organization.

This leads to the subject of FRAME’s sponsors’ concern for animals vis-à-vis the 3 R’s.

3 R’s

FRAME supports and funds researchers who employ the practice known as the 3 Rs (Reduce, Refine and Replace with Alternatives). The 3 R’s were described in the 1950s by Russell and Burch and stand for: REDUCE - meaning that when animals are used in biomedical research the lowest possible number should be used; REFINE - meaning refine the methods used in order to minimize suffering and the number of animals used; And REPLACE - meaning animals should be replaced as soon as viable alternatives are found.

Huntingdon Life Sciences has been in the spotlight lately so it is pertinent to see what they say about the 3 R’s. From their web site:

The 3 R's (Refinement, Reduction, Replacement)
It is the stated aim of all medical researchers to use as few animals and as responsibly as possible. Indeed, in the last 20 years, the annual number of animals used has halved and the search for validated alternatives continues.

Ultimately it would be ideal if the use of animals could be totally replaced by non-clinical methods. Unfortunately few of these currently exist and where they do they are often not yet fully accepted by the worlds (sic) regulatory authorities. This means that the use of animals will continue for some time to come.

However, the search for alternatives continues and is guided by the principle of the 3 R's. This stands for- Reduction, Refinement, Replacement.

Reduction - Quite simply this means that fewer animals are being used in many areas of medical research. Scientists are now able to be more confident in the results that they have achieved. This confidence means that fewer animals are required to be sure that the results are valid.

Refinement - This concerns the manner in which the animals are treated. This covers areas such as animal housing and veterinary care. The principle of Refinement ensures that if an animals (sic) is involved in scientific research, it is treated with care and respect.

Replacement - In recent years there have been advances in non-animal techniques. These include computer modelling, cell cultures and in vitro (literally in glass - test tube) techniques. In some cases these techniques, can replace some of the existing animal tests but it will be many years before all animals tests will be made redundant by non-animal techniques.

It is a common misconception that animals are used because they offer a 'cheap alternative' to non-animal techniques. The reverse is in fact true.

Just as HLS supports the 3 R’s, and many of the worst corporate polluters support Earth Day, many, if not most in the pro-animal experimentation community support the 3 R’s. The corporations sponsoring Earth Day use their sponsorship as proof that they are concerned about the environment just as the animal-model community uses its support of the 3 Rs as proof that they are concerned for animal welfare.
The 3 R’s philosophy is based on the assumption that experiments on animals are valid, that they lead to cures and treatments for human disease, and that all that needs to be done is reduce, refine and replace them with alternatives. All these assumptions are erroneous.

Another flaw in this reasoning is that the very animal tests that this community is supposedly seeking to replace have never been proven effective in the first place. The 3 R’s philosophy deflects attention and debate away from the very real issue of the invalidity of animal experimentation in medical research. The 3 R’s is mainly supported by those with a vested interest in animal experimentation. The 3 R’s allows those with a vested interest to avoid entering into any dialogue about the scientific validity of inter-species extrapolation. Anyone who endorses the 3 R’s acknowledges that animal experiments are useful and necessary and that they cannot be abolished until all such experiments, of which there are millions, are replaced by nonanimal methods. They claim that animal experiments can only be judged for scientific validity, necessity, and justification on a case-by-case basis. Note however, that they are not willing to justify animal experiments on a case-by-case basis.

There is really no end to what organizations will say as they strive to keep their financial supporters happy. According to an internal Environmental Protection Agency document, the Army Corps of Engineers’ dumping of toxic sludge into the Potomac River protects fish by forcing them to flee the polluted area and escape fishermen. The document says it is not a “ridiculous possibility” that a discharge “actually protects the fish in that they are not inclined to bite (and get eaten by humans) but they go ahead with their upstream movement and egg laying.”

The relationship between those funding animal experiments and those receiving the funds is complementary. The review panels that exist in order to determine whether the research projects are worth doing are composed of researchers and others who are sometimes directly tied to the applicants. These people are experts; but they also tend to scratch each other’s backs as well as the backs of junior scientists who perpetuate research that they themselves began. According to one U.S., Congressman, the peer review process is “an old boys' system where program managers rely on trusted friends in the academic community to review their proposals. These friends recommend their friends as reviewers…It is an incestuous ‘buddy system’.” In the U.S., Congress, via the NIH, appropriates grant money and calls the directors of NIH to testify as to how it is being used. These directors want to keep their jobs. Hence, they ask the recipients of grants to show up and impress a largely scientifically illiterate Congress with claims that their research is vital. This is the tail wagging the dog. We encourage all to read chapter 5 in Sacred Cows for a further explanation of the reality of biomedical research politics. Anyone who thinks politics and personal relations do not play a huge role in funding is too naïve to engage in meaningful discourse.
Specious Science: The Heart of Our Argument

In the old days, animal models appeared to be viable for two reasons: First, when so little was known about human physiology and disease, discovering something in a dog did in fact, at times, translate to humans. (Of course animal models were not adequate even back then when so little was known. In the first half of the twentieth century, animal models led to the notions that smoking was safe and cholesterol good for the heart. Probably no two mistakes have cost as many lives.) Secondly, some scientists believed doing something to combat disease, such as experimenting on animals, was preferable to doing nothing. Epidemiology, statistics, cell cultures, indeed all of science, was in its infancy. Clinical research was limited due to the lack of basic scientific knowledge about human disease. Artificial neural nets were not even thought of. Statistics was not what it is today. Technology was rudimentary. Mathematical modeling was unheard of, as was the human genome project, MRI and PET scanners, computer-aided drug design, and pharmacogenomics. The belief that using animals as models was better than doing nothing, proved to be untrue. History has revealed that time could have been better used by studying the basic sciences, by perfecting in vitro research, and by discovering and advancing the technology and methods that have proven so beneficial today. But hindsight is 20/20.

Our critics ignore the main thrust of our argument, which attempts to answer the question: Are animal models useful in modern-day research? We stand by our reading of historical texts, but note for the record that one can argue about most things of an historical nature. We acknowledge that many discoveries of the 1600s to early 1900s involved animals. As we mentioned earlier, Harvey could have conducted autopsies to prove the heart circulates blood, but he dissected a horse, as well as performing autopsies. Even in retrospect, there are doubts as to whether animal experimentation did more good than harm. However, times have changed. We are beyond the level of superficial similarities and are now studying disease at the molecular level. It is at the molecular level that a rat becomes a rat and a human, human. Does the practice of using animals as models, today, do more harm than good? Consider the following:

- Humans and chimpanzees differ in the way in which HIV enters the white blood cell. For this and other reasons, chimpanzees have been mostly abandoned as models of human AIDS.
- Saccharin triggers an enzyme that exists only in the bladder of male rats and leads to cancer in male rats but not humans.
- Asbestos causes cancer in humans but not in some animals.
- Fen-phen causes heart-valve abnormalities in humans but not in dogs.
- Rezulin and TRAIL kill liver cells in humans but not in commonly-used lab animals.
- Smoking was thought noncancerogenic due to animal models.
- A high fat/cholesterol diet was thought safe based on animal model studies.
- The National Cancer Institute (NCI) tested 12 anti-cancer drugs, currently used successfully in humans, on mice. The scientists took mice that were growing 48 different kinds of human cancers and treated them with the 12 drugs. They found that 30 out of 48 times the drugs were ineffective in the mice. In other words, 63% of the time the mouse models, even with human tumors were wrong.
- Starting in 1976, the FDA began to examine all the new medications it released for side effects. This was a ten-plus year study and has never been repeated. They found that out of 198 new medications, 102 (52%) were either recalled or relabeled secondary to side effects not predicted by animal tests. A similar study examined 6 drugs, the side effects of which were already known in humans. The study found that animals correctly predicted 22 side effects but incorrectly identified 48 side effects that did not in fact occur in humans and that the animals missed 20 side effects that
did occur in humans. This means that the animal models were incorrect 68 out of 90 or 76% of the time.36

- Mark Levin PhD and CEO of Millennium Pharmaceuticals presented data at the Drug Discovery Technology conference in Boston, MA August, 2001 about the inadequacy of current animal models in drug testing. 28 potential drugs were tested in rats for liver toxicity. 11 were shown to be toxic while 17 were shown to be safe. The drugs went to human testing anyway and the results were that of the 11 that were toxic in rats, only 2 were toxic in humans, while 6 were safe. And of the 17 that were safe in rats, 8 were safe in humans, but 6 were toxic to the human liver. Levin restated the frequent observation that this basically means that the animals were about as accurate as a coin toss.

- Of 20 compounds known not to cause cancer in humans, 19 did cause cancer in animals37 while of 19 compounds known to cause oral cancer in humans only 7 caused cancer in mice and rats using a standard NCI protocol.38 Of 22 drugs tested on animals and shown to be therapeutic in spinal cord injury, none were effective in humans.39

- An article by the AHA, the American College of Emergency Physicians, the American College of Cardiology, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, the Institute of Critical Care Medicine, the Safar Center for Resuscitation Research, and the Society for Academic Emergency Medicine in the journal Circulation stated that:
  1) in experiments into cardio-pulmonary resuscitation, “Unfortunately, the results of one lab may not be reproducible in another lab or in human trials”
  2) for cardiac arrest, “high doses of epinephrine therapy significantly improved survival in most animal models but does not improve survival in humans”
  3) “species differ in response to anaesthesia and drugs, and may require different doses to produce the same physiological response”
  4) “differences in metabolism, physiological function, response to ischemia, hypoxia, hypercarbia... return to spontaneous circulation... [are seen] in rats, dogs and pigs”
  5) rats, dogs and pigs show “anatomical differences [in] myocardial blood supply, pre-existing collateral circulation, sensitivation to arrhythmia...shape of chest”40

- Artificial heart valves, cyclosporin, beta-blockers, digitalis, the statins and other medications and treatments were kept off the market because animal models raised concerns that did not manifest in humans. Isoniazid and phenobarbital cause cancer in animals. Almost all currently used medications cause birth defects in some animal species.

Clearly the empirical data is not promising for animal models. (For further examples see Sacred Cows or Specious Science.)

Using animals to model humans should be abolished because this practice so frequently leads to human death or suffering and so rarely leads to cures or treatments. Society need not fear that by abolishing animal models for the study of human disease, they would be asked to give up medical progress. The effect would be precisely the opposite – it would lead to greater scientific excellence in medical research, greater safety, a greater expectation of sound results, and far higher probability of cures for human illness. A scientifically invalid practice cannot be replaced with an alternative.

Analogies or Disanalogies?

But science looks beyond empirical data. The scientific method does not allow any assumption to go unchallenged. It requires internal consistency and relies on axiomatic-deductive reasoning. The scientist sets forth principles or axioms that are true and self-evident and derives from them more “truths.” Testing on animals or studying diseases in animals can be done in a scientific manner. However, when the axiom is “animals and humans have so much in common that we can extrapolate the results from animals to humans”, the results may be disastrous.
Evolutionary biology lies at the core of our argument that animal models of human disease are scientifically untenable. Speciation is both the reason why it appears that we can use animal models as well as the reason why we cannot. Although animal models may appear feasible when first viewed, closer examination of the differences between animals and humans reveals the shortcomings in the concept. One way of speaking about the results of evolutionary biology is to categorize life forms into groups known as species. Homo sapiens will have characteristics that are unique to it, but it will also have characteristics that it shares with other species, like Drosophila melanogaster (fruit flies) or Pan troglodytes (chimpanzees). With the advent of molecular biology, we have learned that what each member of the species in question will have in common with the others is, in part, a collection of genes. However, while different species may have many of the same genes, the way the genes are regulated and interact will be different. All mammals are derived from a common ancestor, and so it is not surprising that we all share certain characteristics; neither is it surprising that each species is unique. The questions modern-day researchers must ask is ‘do the similarities outweigh the differences?’ ‘Can we extrapolate the results of an experiment on one species to a different species?’ There is evidence that we can. For instance, all mammals have hearts, lungs and immune systems. We all share the same cell types and tissues. But there is also evidence to the contrary. We have examined some of the empirical data that reveals that the results of animal models are not applicable to humans, so now we will examine the theory that predicts that such should be the case.

Living systems share biochemical systems and are subject to the same laws of physics, therefore it should not be surprising that they share common structures and biochemical reactions. However, out of all this commonality has evolved very different life forms: bacteria, humans, yeast and so forth. Peter W. Hochachka and George N Somero wrote in Biochemical Adaption, “Are all organisms relatively alike ‘under the skin’, that is to say, biochemically, despite their vast differences in habitat preference, body plan, and mode of life? As we will learn, the answer to this question represents a fascinating combination of ‘yes’ and ‘no.’”

One recent news item of interest was the discovery about the similarities between the genomes of mice and humans. According to New Scientist: “Mice and men share about 97.5 per cent of their working DNA, just one per cent less than chimps and humans. The new estimate is based on the comparison of mouse chromosome 16 with human DNA. Previous estimates had suggested mouse-human differences as high as 15 per cent.” This discovery has caused much speculation with regard to how well mice should function as models for human disease, especially genetically modified mice. We, and others, have said that the differences in regulatory genes would far outweigh the similarities in structural genes. Again, according to New Scientist: “Tim Hubbard, head of genome analysis at the Sanger Institute in Cambridge, UK, is sceptical about the significance of the 2.5 per cent difference. He thinks that the genes might in fact all be identical and that differences between species might arise solely through divergence in the ‘regulatory regions’ which switch other genes on and off.” While we will no doubt read many more stories about the similarities between the human genome and that of other animals, we should keep in mind that these similarities are meaningless without knowledge of how the structural genes are regulated. To conclude that a 98% or 99% similarity between genomes means that an animal will be a good model for studying human disease and drug reaction exposes an ignorance, willful or otherwise, of fundamental biology.

One reason for the differences between species, vis-à-vis the spatial organization of the cells, lies within the genes. Genes can be divided into structural and regulatory genes. The structural genes are responsible for the similarities. They are responsible for building the proteins of which the body is made. The regulatory genes turn the structural genes on and off thus affecting the development of the embryo and the physiology of the organism. They account for differences between species. Hugh LaFollette and Niall Shanks state that understanding the role of regulatory genes in evolution is “crucial to a proper understanding of biological phenomena. First, they focus our attention not merely on structural similarities and differences between organisms but also on the similarities and differences in regulatory mechanisms. Second, they illustrate an important fact about complex, evolved animal systems: very small differences between them can be of enormous biological significance. Profound differences between species need not indicate any large quantitative genetic differences between them. Instead, even very small differences, allowed to propagate in developmental time, can have dramatic morphological and physiological consequences.” (Emphasis added)
Lewis Wolpert continues this theme in *The Triumph of the Embryo*:

Compare one’s body to that of a chimpanzee—there are many similarities. Look, for example, at its arms or legs, which have rather different proportion to our own, but are basically the same. If we look at the internal organs, there is not much to distinguish a chimpanzee’s heart or liver from our own. Even if we examined the cells in these organs, we will again find that they are very similar to ours. Yet we are different, very different from chimpanzees. Perhaps you may wish to argue, the differences lie within the brain. Perhaps there are special brain cells which we possess that chimpanzees do not. This is not so. We possess no cell types that the chimpanzee does not, nor does the chimpanzee have any cells that we do not have. The difference between us and the chimpanzee lies in the spatial organization of the cells.

One reason for the difference between species, vis-à-vis the spatial organization of the cells, lies within the genes. Wolpert continues:

The face develops from a series of bulges in the head region and at early embryonic stages it is not easy to distinguish dog from cat, mouse from man. The differences in facial features are very dependent on just how much these bulges grow. One can begin to imagine how genes could control such changes in growth rates at different positional values. The key changes in the evolution of form are in those genes that control the developmental programme for the spatial disposition of cells. The difference between chimpanzees and humans lies much less in the changes in the particular cell types—muscle, cartilage, skin, and so on—than in their spatial organization. Direct confirmation of this comes from studies which compare the proteins of humans and apes. If we look at the genes that code for the average “housekeeping” proteins—proteins that function as enzymes or provide basis cell structure and movement—the similarity between chimpanzees and humans is greater than ninety-nine percent. The difference must reside not in the building blocks but in how they are arranged, and these are controlled by regulatory genes controlling pattern and growth.

A more concise way of explaining this would be to say that biological organisms are examples of a non-linear complex system and thus small differences between biological systems negate extrapolation. There are biochemical reasons for questioning the extrapolation of the results of experiments on animals to humans. Evolutionary biology supports and explains these reasons. Small differences between species lead to huge differences at the molecular level, which is where we focus when treating disease. This is the crux of our argument; that small variations on the genetic level not only define a species but also confound the ability of one species to ‘model’ another in aspects such as disease mechanisms and drug effects.

Epigenetics refers to a process whereby a change in gene expression frequency is noted but that change in frequency is not because of a gene mutation but instead because of some other inheritable trait (i.e., different regulatory gene control). While it is true that each cell contains all the DNA an organism possesses, only a portion of that DNA is expressed at any given time in the cell. The organism functions properly when all the cells are working in conjunction with each other. Considering the fact that humans have roughly the same number of genes as other seemingly less complex organisms, how did evolution accomplish this? Philip Cohen and Andy Coghlan wrote in *New Scientist*:

Another key finding from both public and private genome efforts is that many human “transcription factors” are unique and a cut above those of the fly and the worm. Transcription factors and other regulatory proteins dictate which genes are switched on at vital stages of development, as embryos form and organs take shape. It is they that orchestrate such amazing complexity from so few genes. Venter thinks all higher vertebrates have roughly the same genes. What's important is when they are switched on and off, he says. “We have the same number of genes as cats and dogs, but differently regulated.”

Same genes, but slightly different regulation. Humans are built from the pieces of older organisms. Evolution took advantage of pre-existing materials and constructed new organisms to fill a niche. Humans were not made *ex nihilo*, but rather evolution took a piece of an enzyme from a predecessor and combined
it with another piece to make the enzyme needed for the organisms that eventually became *Homo sapiens*. Evolution used pre-existing molecular devices much as a brick mason uses the same bricks to make different structures. If one examines bacteria, yeast, and humans one sees the same essential material used as one advances in evolutionary time. “Add-ons” account for the many other functions seen in the more complex organisms. In bacteria, simple processes turn on genes as needed. In yeast, the same processes are seen, but in addition, “add-ons” are seen that allow more complex regulation and hence a more complex organism. Tony Pawson of Samuel Lunenfeld Research Institute states in *Genes & Signals*:

For example, the principles they annunciate for gene expression apply equally well to signal transduction. This premise suggests that to evoke increasingly complex biological systems, it may not be necessary to invent many new kinds of gene products. Rather, more sophisticated functions can be achieved by, for example, increasing the number of interactions that any one protein can make, through the reiterated use of simple binding domains, thereby expanding the possibilities for combinatorial association.

All cells of the same species contain the same DNA, but clearly, all cells are not alike. Nerve cells function very differently from muscle cells which function very differently from liver cells. Likewise, all mammals are comprised of essentially the same genes. But a man is not a mouse. This is true because it is the products of the genes, not the genes themselves, that determine a cell’s architecture (e.g., a liver cell or a heart cell). Because the DNA in each cell or species is regulated differently, and thus expressed differently, a cell becomes a liver or heart cell and an organism, a mouse or a human. The genes that make the hands are basically the same ones that make the feet, but those genes are expressed at different times and places and in different combinations.

Genes and the proteins that signal the genes to express are reused by evolution to do different things. What genes a cell expresses depend in part on signals arriving from outside the cell. A protein called *Sonic Hedgehog*, when secreted at a particular time during embryogenesis, induces some cells to become nerve cells, but when secreted at another time, organizes limb formation. In an organism that evolved long before humans, a gene may be expressed by a signaling protein turning it on while in humans the same gene may require many signals in order to trigger mRNA to unravel DNA and make protein. Mark Ptashne and Alexander Gann write in *Genes & Signals*:

…it is generally believed that mammals—humans and mice, for example—contain to a large extent the same genes; it is the differences in how these genes are expressed that account for the distinctive features of the animals...changes in patterns of gene expression (rather than evolution of new genes) have had an important, perhaps even determinative, role in generating much of that diversity (that occurred during the Cambrian explosion)...a relatively small number of genes and signals have generated an astounding panoply of organisms. Thus, the regulatory machinery must be such that it readily throws up variations—new patterns of gene expression—for selection to work on.

Most of what we have learned about gene regulation has come from the study of bacteria such as *Escherichia coli* and yeast such as *Saccharomyces cerevisiae*. Most genes are expressed by initiation of RNA polymerase. The first studies to reveal that RNA polymerase regulate genes were done on bacteria in the 1950s. Even in the 1950s, scientists suspected not all 3000 genes in *E. coli* were expressed all the time. By studying *E. coli*, scientists determined that some genes were dormant until something turned them on. There are numerous ways of turning a gene on and the more recently evolved and more complex an organism is, the more ways there are. Bacteria evolved about three ways to control gene expression: regulated recruitment, polymerase activation, and promoter activation.

Yeast (with around 6000 genes) has evolved more than three ways to activate their genes. Yeast is more like humans than bacteria as we both have DNA wrapped around a protein and residing in a nucleus. Yeast and humans, and flies, worms, plants, and other organisms similarly organized, are thus categorized as eukaryotic. Yeast uses the same regulatory mechanisms as bacteria but has evolved add-ons that allow more complexity into the system. Nature did not throw away what worked in the bacteria; it merely made additions that allowed new functions and thus a more complex organism.
Humans have many more than three ways of regulating gene expression. There is far more signal integration than in yeast, more combinatorial control, and genes are often controlled by alternative sets of regulators. Thus, the typical gene in more recently evolved/more complex eukaryotes is subject to far more regulatory binding sites than less complex organisms. As a result, more complex products/functions can result. In discussing the conservation of ways genes are regulated through evolutionary time, Ptashne and Gann state: “The very simplicity of the underlying mechanism explains otherwise puzzling features. For example, there is no obvious ‘syntax’ to regulation. Thus, any given regulator can, evidently, be used to regulate any gene and, conversely, any given gene can be controlled by alternative combinations of regulators.” Further, the same signal can switch on (or off) different genes at different stages of development. They continue: “Analysis of the human genome sequence is just beginning as we write. Preliminary reports suggest that many of the ‘new’ enzymes found in humans (i.e., not found in flies and worms) are actually old enzymatic active sites attached to new or additional recruiting domains.”

John Maynard Keynes, said: “The difficulty lies, not in the new ideas, but in escaping the old ones; which ramify, for those brought up as most of us have been, into every corner of our minds.” Animal models were effective when gross observations of similarities and differences between species were still heralded as discovery. But because of the knowledge of evolutionary biology that we have today, vis-à-vis regulatory genes, it should come as no surprise that our level of knowledge has outstripped the animal models’ scope. Ptashne and Gann close Genes & Signals by stating: “…we realize that these systems evolved, stepwise. And so it should hardly be surprising that underlying all the complexities are certain rather simple mechanisms that, by being reiterated and constantly added to, can produce living systems.”

What all this means is that even though humans may share 100% of their structural genes with another organism, say mice, these two organisms can be as different as a mouse and a man. By studying mice it is obvious that we can see only a piece of the puzzle, a mouse piece not a human piece, and the rest of the pieces are usually ignored -- to the detriment of humans suffering from illness. By starting with humans, scientists could study human-relevant pieces from the outset, thus eliminating the risk of species differences.

Add-ons produce a system that is nonlinear. Nonlinearity means that the output of the system is not proportional to the input and that the system does not conform to the principle of additivity. The use of evolution has made of add-ons and the results thereof are similar to chaos and complexity. If an organism or machine has $X$ parts, part 1 can interact with no other parts, with part 2, with parts 2 and 3 and part 2 can interact with part 3 and so forth. But if you add on a part 4 to the system, the system does not increase in complexity linearly but exponentially.

This increasingly complex way genes are regulated is reminiscent of complexity or chaos theory. (Chaos theory is better known so we will look at it first, but complexity is really what we are interested in.) Chaos theory developed in the 1960s from the work of Edward Lorenz. Lorenz developed a simple model for predicting changes based on differential equations. When he ran his model on a computer, Lorenz discovered that a very small difference in the initial conditions led to large changes in the results over time. This discovery, sensitivity to initial conditions, is one of the fundamental characteristics of chaos theory. Simply formulated systems with few variables can display highly complex behavior that is unpredictable and unforeseeable.

Complexity theory is similar but different. Complex systems may display as much or even more profound changes when small changes are made. Lorenz showed that slight differences in one variable had profound effects on the outcome of the whole system; he was looking at systems less complex than the human body. Chaos is similar to complexity in that changes occur in a nonlinear fashion. Chaos can be defined as the qualitative study of unstable aperiodic behavior in deterministic nonlinear dynamical systems. In chaos theory: the system changes over time, the behavior of the system does not repeat itself, chaotic behavior is complex but it can have simple causes, the system is nonlinear, it is sensitive to initial conditions. Chaotic behavior is not random even though its aperiodicity and unpredictability may make it appear to be so.
Complexity theory explores systems in which many independent agents are interacting with each other in many ways. Pertinent to this discussion, Nicolas and Prigogine have stated: “Complexity is somehow related to the various manifestations of life.” We have the scientific understanding to travel to the moon and back, but are as yet unable to fully explain life on a cellular level. There is something fundamentally unique about the dynamics of living systems. Complex systems tend to give rise to new complex systems. The complex dynamical regime is believed to be favored under evolutionary adaptation because periodic dynamics are too simple for evolutionary innovation, and chaotic dynamics too unpredictable to support adaptation.

A complex system is one in which numerous independent elements continuously interact and spontaneously organize and reorganize themselves into more and more elaborate structures over time (as evolution has reorganized genes and gene regulation). Complexity is characterized by: a) a large number of similar but independent elements or agents; b) persistent movement and responses by these elements to other agents; c) adaptiveness so that the system adjusts to new situations to ensure survival; d) self-organization, in which order in the system forms spontaneously; [this is beginning to sound post modern] e) local rules that apply to each agent; and f) progression in complexity so that over time the system becomes larger and more sophisticated. As with chaos, the behavior of self-organizing complex systems cannot be predicted, and they do not observe the principle of additivity, i.e., dividing up and studying the parts in isolation will yield little understanding of the whole. The causes and effects of the events that a complex system experiences are not proportional to each other. The different parts of complex systems are linked to and affect one another in a synergistic manner. There is positive and negative feedback in a complex system. The level of complexity depends on the character of the system, its environment, and the nature of the interactions between them. Complexity can also be called the “edge of chaos.”

Complexity can be said to occur when the behaviour of a systems as a whole can be more than the sum of its parts. Complex systems are structures and processes that involve non-linearity. This includes both sets of many interacting objects as well as non-linear dynamical systems. Tamas Vicsek states in Nature:

…the world is indeed made of many highly interconnected parts on many scales, the interactions of which result in a complex behaviour that requires separate interpretations of each level. This realization forces us to appreciate the fact that new features emerge as one moves from one scale to another, so it follows that the science of complexity is about revealing the principles that govern the ways in which these new properties appear.

In the past, mankind has learned to understand reality through simplification and analysis. Some important simple systems are successful idealizations or primitive models of particular real situations — for example, a perfect sphere rolling down an absolutely smooth slope in a vacuum. This is the world of Newtonian mechanics, and it ignores a huge number of other, simultaneously acting factors. Although it might sometimes not matter that details such as the motions of the billions of atoms dancing inside the sphere's material are ignored, in other cases reductionism may lead to incorrect conclusions. In complex systems, we accept that processes that occur simultaneously on different scales or levels are important, and the intricate behaviour of the whole system depends on its units in a non-trivial way. Here, the description of the entire system's behaviour requires a qualitatively new theory, because the laws that describe its behaviour are qualitatively different from those that govern its individual units.

…Knowledge of the physics of elementary particles is therefore useless for interpreting behaviour on larger scales. Each new level or scale is characterized by new, emergent laws that govern it. When creating life, nature acknowledged the existence of these levels by spontaneously separating them into molecules, macromolecules, cells, organisms, species and societies. The big question is whether there is a unified theory for the ways in which elements of a system organize themselves to produce a behaviour that is typical of large classes of systems.

…What we are witnessing in this context is a change of paradigm in attempts to understand our world as we realize that the laws of the whole cannot be deduced by digging deeper into the details. In a way, this change has been wrought by the development of instruments. Traditionally,
improved microscopes or bigger telescopes are built to gain a better understanding of particular problems. But computers have allowed new ways of learning. By directly modelling a system made of many units, one can observe, manipulate and understand the behaviour of the whole system much better than before, as in the cases of networks of model neurons and virtual auctions by intelligent agents, for example. In this sense, a computer is a tool that improves not our sight (as does the microscope or telescope), but rather our insight into mechanisms within complex systems.\textsuperscript{53}

Hochachka and Somero write about complexity in living systems:

The difficulty a physiologist or biochemist faces in defining what a trait is arises from a common and fundamental challenge that every experimental biologist faces. One of the primary requirements for doing experimental biology is this: the investigator must ‘dissect out’ from nature a study system that is i) simple enough to be experimentally tractable, yet ii) is not so overly simplified that it fails to teach us about the properties of the ecosystem, organism, cell, or macromolecule as it actually appears in natural condition. Delineating the appropriate study system is a problem that faces all biologists, whatever the spatial or temporal scale of their investigations. As we show throughout this volume, making decisions about the right study system is a tall order for both technical and philosophical reasons...Similar concerns about the effects of studying systems in isolation arise at all levels of biological organization, not only in the context of biochemistry. For example, can we meaningfully study the adaptive importance of a single organ to the diving response of a seal—or must we adopt a more integrative perspective and determine how the function of the organ of interest is affected by, and integrated with, the activities of other organs? Just how do we draw boundaries around ‘traits’ so as to perform biologically realistic experiments and deduce how the characteristic of interest is adaptive to the organism?

...Category (v) genes are those specifying proteins that interface the inside functions of single cells with their environment, either the external world or the extracellular fluids. They are involved in sensing and signal transduction. Interestingly enough, these types of genes are more highly duplicated than most other families of genes, and, therefore, the number of protein isoforms encoded by category (v) genes are typically much higher than for other types of proteins. This condition can be well illustrated by protein kinases. Protein kinases, as we shall see in various places in this book, are critically involved in many signal transduction pathways. Instead of two to several isoforms, over 1,000 protein kinase isoforms may be present in eukaryotic cells. The number of isoforms of protein kinases varies among species: yeast (\textit{Saccharomyces cerevisiae}) has 114 protein kinase genes, \textit{C. elegans} has approximately 400, and the human genome is predicted to contain greater than 1,100 protein kinase genes. Of course, not all protein kinase isoforms are expressed under any given condition and the types of protein kinases encoded in the genome differ among eukaryotes. The differential expression and differential evolution of these kinds of genes-the category (v) group of genes above-supply raw material for evolutionary change and species specificity. That this is one key point of departure for physiological diversity in multicellular organisms is strongly supported by studies showing that genes involved in such functions are the most differentiated of all, that is, they are expressed in most numerous isoforms of all. We shall see later in this book (see the discussion of osmosensing in chapter 6, for example) that the complexity of physiological systems in multicellular organisms requires ever more complex sensing, signal transduction, and communication, as body plans attain higher levels of complexity. The control networks that have evolved are hugely complex by comparison with single-celled eukaryotes such as yeasts. We hypothesize that the need for these kinds of functions in metazoans explains in part why these species possess so many more genes than are found in unicellular eukaryotes. More formally, the hypothesis is that genes whose products are involved in such processes as inter-organism communication, in cell-cell communication, in development and differentiation, in general sensing and signal transduction, in immune defense systems, and in host defense against pathogens and parasites, are fundamental to the evolution of physiological diversity. We believe that this is a key element in resolving one major aspect of the unity--
diversity duality of biological systems. Several thousand or so genes in unicellular and multicellular organisms seem to be involved in so-called "core processes" central to cell level survival and representative of the "unity" of biochemical design. So-called "non-core" functions, such as those listed immediately above, are what a substantial fraction of the remainder of the protein-encoding regions of the large genomes of complex eukaryotes represents; these are the genes that account for physiological diversity.

Although the above analysis supplies us with some general guidelines as to the basis of unity and the origins of diversity in biological systems, it does not give a good indication of the size of the problem: How big are the differences between single cell function and function involving interactions among multiple cells? To get a feel for this issue, consider the physiology of wound healing. This physiological function in vivo is in part orchestrated by fibroblasts, which fortunately can be studied in cultured form. When fibroblasts in culture are deprived of nutrient for several hours and then are reintroduced to serum as a culture medium, they begin to divide and proliferate; at a cellular level, the fibroblasts are doing most (if not all) of the things they would do in normal wound healing physiology. Analyzing shifts in expression among approximately 8,600 genes using DNA microarrays, Iyer et al. (1999) showed that a huge (517-gene) transcription program is regulated in this complex physiology. On the order of 10 different time courses of expression were found for the hundreds of genes required to orchestrate the appropriate functional response. Of course, wound healing is just one kind of physiological system that is required in multicellular organisms, but it is not required in single-cell eukaryotes like yeast. Indeed, most physiologists would admit that, in the total scheme of things, wound healing represents a relatively simple physiological system. All the more informative, therefore, is the insight of how many new genes, compared to the total number of genes possessed by single cell eukaryotes, would have to be found to perform this function. If over 500 genes are required for evolving and regulating a simple physiological system, would 9,000, 35,000, or more be required for the complex, integrated physiologies of mammals, birds, or other metazoans? Until at least most of the genes in fully sequenced genomes are identified, the answer to this question remains unknown. However, the indications are that as the complexity of physiological systems increases, the recruitment of new genes will be mainly for those in category (v) above—not for those that are involved in "core" cell function and structure.

...To reiterate, the implications of these new studies are: i) that unity of biological systems derives mainly from the conservation of "core" genetic programs (involving perhaps several thousand genes) for "core" cellular level functions and structures; (ii) that the complexity and diversity of physiological systems arise in large part from genes that are involved in internal communication and in interfacing the organism with its environment; (iii) that going from single cell eukaryote function to complex physiological function in multicellular organisms requires huge numbers (probably tens of thousands) of genes; and, finally, (iv) that tissue and organ specific development and differentiation in multicellular organisms may require a large fraction of the genome of metazoans, even if tissue-specific physiology per se may not require an inordinate number of additional genes (268 in the case of the pancreas). The final question of biological diversity that arises concerns the species level: How much new or different genetic machinery is required to make a new species, the ultimate threshold indicator of biodiversity?

Interestingly, there is a huge database relating to this question, which we will not have the time or space to explore here in any detail. Suffice it to say that many molecular biologists have tried to evaluate this very question in many settings— in the rapid evolution of fishes in east African rift valley lakes, in the postglacial evolution of fishes in north temperature regions of the world, in nematodes, in insects, and in primates—to mention a few well-studied groups. The same general conclusion arises from all of these exceptional examples, and this result can be illustrated by well-known studies in primate evolution involving the separation of chimpanzees from the human lineage. The problem (and in some senses the paradox) is that protein and gene sequences in the common chimpanzee and in humans are remarkably similar. In fact, human and chimpanzee proteins appear to be nearly 99% identical at the amino acid level, and it is widely assumed that the same percentage similarity prevails at the DNA level. Yet no one could mistake the two
species as one. What these examples suggest is that only exceedingly minimal changes in genome sequences may be necessary to specify separate species, possibly with larger percentage changes in gene expression patterns. Of course, the longer any two such related lineages evolve separately from each other, the greater the genetic differences between them may become. However, in terms of the origins of unity and diversity, it is humbling as it is surprising to realize how very small the differences in the overall genome may be between two lineages as they separate from each other and thus extend our planet's biodiversity.

Living systems such as chimpanzees, mice, and humans are obviously examples of complex systems. It should be equally obvious, therefore, why extrapolation between species is problematic: small changes on the genetic level can lead to very large differences between species. Indeed, that is what evolution is all about. The claim that humans and rats are the same animal dressed up differently at the biochemical level just isn’t true. Moreover, it is irrelevant to point to observed similarities in genetic makeup between species, since the details of the differences are in the interactions between conserved genes, not in the genes themselves—it is as though humans and rats have a common genetic keyboard on which different phenotypic tunes are being played—what matters is not similarity with respect to the key board but differences with respect to the order and timing of the pressing of the keys (keys = structural genes, keys pressed on or off by regulator genes). Another analogy would be computers: Begin with two identical personal computers, then load one with MS-DOS and a late-1980’s text-based word processor, and load the other with the latest version of Microsoft Windows and an internet browser. Can you argue that, since the underlying hardware is identical, the behavior of the two systems must also be identical? In this case the behavior of the system is drastically altered by the software it is running.

**CAMs**

A theory, or in this case a model, is reliable or scientific if it has predictive value. Researchers maintain (at least in their public pronouncements) that animals are causal analogical models (CAMs) and thus can be used to study human disease. (Note that we are referring to animals as models of human disease and for use in drug testing, not for heuristic purposes or for obtaining knowledge for knowledge’s sake. To argue that animals are used in drug testing as anything others than CAMs is nonsense. The whole purpose is to predict human response.) Causal analogies are a subset of analogy arguments in which causal assumptions arise based on the model. LaFollette and Shanks explain that the first condition that must be met in order for a thing to be considered a CAM is this: “X (the model) is similar to Y (the object being modeled) in respects \{a…,e\}.” For instance, chimpanzees and humans have a) an immune system, b) have 99% of their DNA in common, c) contract viruses, etc. They continue, “X has additional property \(f\).” (For example, HIV reproduces very slowly in chimpanzees.) “While \(f\) has not been observed directly in Y, likely Y also has property \(f\).” (We therefore expect HIV to reproduce slowly in humans.) In fact in comparison it reproduces quickly in humans.

So if HIV replicates slowly in chimpanzees, animal experimenters reason by analogy that it will do the same in humans. Animals are used as causal analogical models and the reasoning process used is called causal analogical reasoning. LaFollette and Shanks state that, “CAMs must satisfy two further conditions: (1) the common properties \{a,...,e\} must be causal properties which (2) are causally connected with the property \{f\} we wish to project – specifically, \{f\} should stand as the cause(s) or effect(s) of the features \{a,...,e\} in the model.”

The causal/functional asymmetry theory implies that causal mechanisms may differ between species even when their functions are similar. Causal disanalogies compel caution in extrapolating data between species. The use of animal CAMs also suffers from the systemic disanalogy argument. Since systems (organs, tissues etc.) may differ in subtle and unknown ways, identical exposure to a given compound will often cause different reactions in different species. In other words, for a CAM to be predictive, “there should be no causally-relevant disanalogies between the model and the thing being modeled.” Considering our
knowledge of evolutionary biology, this is arguably impossible without total knowledge of both the model (animal) and thing being modeled (human). Only by comparing the results from testing each given substance or procedure in an animal species with human-based data can we determine whether the animal is sufficiently similar to humans to allow extrapolation. We can only know which animals mimic humans after we study the human data. (LaFollette and Shanks provide a more detailed explanation of CAMs and causal analogical reasoning in Brute Science. Interestingly, their work has also been publicly criticized by people who support the animal model but who, apparently, read only the first few chapters. Proving once again that there is no substitute for knowledge.)

There are areas of research that are scientifically tenable and do offer reliability and predictability. Such methodologies are: pharmacogenomics; human stem cells; epidemiology; in vitro research; clinical research; autopsies; mathematical modeling (e.g., artificial neural networks); computer modelling; computer-aided drug design; post-marketing drug surveillance; research with human tissue; basic science research in the fields of physics and chemistry and other human-based and technology-based research methods such as positron emission tomography; functional magnetic resonance imaging; magnetoencephalography; magnetic resonance imaging; transcranial magnetic stimulation and single photon emission computed tomography.

Animal experimenters will insist that animals, notwithstanding their lack of isomorphism and inability to be CAMs, are still necessary because without animals, researchers could not evaluate the drug or procedure in an intact system. We agree that life processes are interdependent, that the liver influences the heart, which in turn influences the brain, which in turn influences the kidneys, and so on. Thus, the response of an isolated heart cell to a medication does not confirm that the intact human heart will respond as predicted by the isolated heart cell. The liver may metabolize a drug to a new chemical that is toxic to the heart whereas the original chemical was not toxic. We also concede that cell cultures, computer modelling, in vitro research etc., cannot replace the living intact system of a human being. But the question is: does the intact animal model do better than the non-animal scientific methodologies mentioned above? The evidence suggests that it does not. Animal models may be intact but they fail, and this failure is predicted by the systemic disanalogy argument.

Most researchers deny that they use animal models as CAMs. If they are being used heuristically, then their grant proposals are disingenuous, so let us assume they are using animals as models in a different sense of the word; weak CAMs perhaps. Ivan Valiela writes about models:

Models have been important in most fields of science, for at least three reasons: (1) we can use them to make predictions, (2) models can tell us if we know enough, and (3) if we can be convinced that the models are good enough, we can use them to do simulation experiments that may be logistically prohibitive or impossible.

Deductive models, as we know, can be used to make predictions. In general, the predictive success of models is variable. The ability of models to make successful predictions depends on the extent that the model captures the important processes controlling the prediction. Where conditions are relatively simplified by removal of influences of multiple processes that act at local, small scales of time and space, models do better. Examples of such simplifications are space travel and world-scale predictions.

Engineers can make marvelously accurate predictions of the position, course, and speed of a space vehicle. They can do that because this problem involves a relatively simple set of well-established scientific principles about the relationships among mass, inertia, and acceleration of just a few bodies in a frictionless void. Such predictions are therefore relatively easy, although an awesome amount of technical know-how is necessary to make them.58

Predicting human response based on an animal model is not an example of applying a “relatively simple set of well-established scientific principles.” Living organisms are better examples of complexity theory than Newtonian physics. A model airplane (frequently cited by many defenders of the animal model) is a good example of this. Studying a model airplane, especially a paper glider, will allow the observer to demonstrate the basic physics of flight. But if anyone seriously believes this method can be or is used to build or repair a 747, they are deluded. Just as animal models can be and were used to demonstrate very
basic facts concerning anatomy and physiology, so too a model plane can be used. But today, when we want to know why a 747 crashed, we do not build paper airplanes and neither should we suggest to the public, who is paying for animal experiments, that a cure for AIDS, cancer or stroke will be derived from animal models.

The idea behind CAMs is not restricted to the animal experimentation community, but is in fact a broader claim about the nature of modeling in science. LaFollette and Shanks, in *Brute Science*, were careful to introduce other senses of “model” e.g., HAMs (heuristic analogical models) that have played an important role in discussions of basic research. To claim, as some in the animal experimentation community have, that the basic idea behind CAMs is absurd is surprising indeed. How do we get a reasonable expectation of safety based on animal tests -- if not from the fact that it is believed that these tests convey reliable causal information about likely outcomes in humans? If one does not expect to get substantially similar results in humans that one finds in animal tests there would be little point in testing a substance for safety in an nonhuman animal trial. LaFollette and Shanks also differentiated between strong and weak CAMs -- between ideally desirable models and the sorts of models one is apt to find in the real world. But a discussion of these concepts is beyond the scope of this already too long essay. Suffice it to say here that neither we nor LaFollette and Shanks criticize the animal model solely on the basis of it not being a strong CAM.

*Sacred Cows and Golden Geese* was written for the general public and we stand by the statements we made. When we explain diseases to our patients or clients, we simplify the explanations without changing the meaning. [To explain fully why a melanoma in human patients needs excising would require years. The patient would need a significant understanding of anatomy, physiology, pathology, surgery, pharmacology, oncology and so on.] Our book, *Specious Science: How Genetics and Evolution Reveal Why Medical Research on Animals Harm Humans* (Continuum International Publishing 2002) and *Brute Science* by LaFollette and Shanks (Routledge 1996) are aimed at an audience with greater science understanding and hence use some of the above arguments. It is unfair to criticize *Sacred Cows and Golden Geese* because of what it did not say. We did not say that the earth is round, but that does not mean we are members of the Flat Earth Society. Dr. Festing’s criticisms of *Sacred Cows and Golden Geese* are fallacious, unfounded, based on incorrect historical data, or else motivated by some yet to be explained desire to see the animal model endure.

**Conclusion**

To summarize our argument: The very small differences between non-human animals and humans at the genetic and molecular levels make extrapolation between species dangerous. Our theoretical explanation for this is that causally relevant disanalogies exist between species. Researchers who use animals are operating under a misleading paradigm that wrongly assumes that all animals are more similar than different. Modern evolutionary biology demonstrates that the differences are far more important than the similarities with regard to how organisms operate at the cellular level, the level where disease occurs and pharmaceuticals act. The animal model paradigm appeared viable in the 19th century when we knew so little. On the gross level all animals are similar: dogs have hearts, so do humans; cats have electrical activity in their brains, so do humans. But today we are studying things on the very level that explains the species’ differences – the molecular level.

It is disturbing when one hears (in fact quite frequently) from medical colleagues that they frequently look back on their clinical learning and practice history with critical regret. For example, the problems of iatrogenesis and the poor results from former and ongoing protocols can prove demoralizing for doctors and other health care professionals. We ask: How much does this potentially preventable situation result from the use of animals in biomedical research? Science is such a successful philosophy because new theories are formed and old ones abandoned, based on evidence. From our examination of the philosophy of science and the results of using animal models to study human disease, we conclude that the use of animal models in biomedical research is not beneficial to humans today.
Using animal as models for humans is a failed paradigm and should be, and fortunately, is being, replaced by gene-based medicine. In light of the knowledge we have obtained about interspecies differences, vis-à-vis the Human Genome Project and studies like the following, it should come as no surprise that trans-species extrapolation is unreliable. Among 10 medications withdrawn from the US market between 1998 and 2001, eight had more severe side effects in women than in men. The 10 drugs were Pondimin, which led to valvular heart disease; Redux, which also led to valvular heart disease; Rezulin, which led to liver failure; Lotronex, which led to ischemic colitis; Seldane, which led to a life-threatening heart condition known as Torsades de Pointes (TdP); Posicor, which lowered heart rate and caused drug interactions; Hismanal, also caused TdP; Propulsid, also caused TdP; Raxar, also caused TdP; and Duract which led to liver failure. All but Raxar and Duract were more toxic to women. A study in Science revealed that one strain of mice could have a gene removed without obvious adverse effects while a similar strain of mice would die without the gene. If men cannot predict the effects of a drug for women and one strain of mice cannot predict what will happen to another if a gene is removed, is it not likely that medicine has reached the level of organization that distinguishes one species from another and even individuals from each other?

Because of very small differences between individuals of the same species, extrapolating results even within the same species is problematic. If men cannot predict drug response in women how will monkeys do it? In the not so distant future, if a woman and her twin sister are diagnosed with the same type of breast cancer on the same day, because of sister A’s unique genetic profile, she may receive a very different chemotherapy regime from sister B. Even though the sisters have far more genes in common with each other than they do with a genetically modified mouse or even a chimpanzee, sister A may have a gene that would cause a severe adverse reaction to one of the medications sister B will receive, hence another will be substituted. Or, sister B may receive a larger and more frequent dose of the same medication than sister A receives, because she is a rapid metabolizer of that drug. Or, both may receive very different treatment regimes because, even though the cancer is of the same type, sister A has genes that will allow it to progress more rapidly than sister B’s and hence will need more aggressive therapy. If we are to expand and refine our current gene-based treatments, our medical research must be more narrowly focused, not broadly focused e.g., on entirely different species.

We conclude that the abandonment of animal models is absolutely vital for medicine to advance. Modern-day molecular biology has revealed differences between species and the presence of these differences is explained by evolutionary biology. Paradigm shifts, such as occurred in physics in the early 20th century do occur. It is important to remember that when a paradigm shift occurs it does not mean that everything that went before it was wrong. Modern physics did not refute nor negate Newton’s laws but only modified them. Newton’s laws are still used daily, but Newton’s physics cannot explain objects at speeds near that of light, nor can it explain the effect gravity has on light. Hence a paradigm shift occurred. Likewise, animal models were successfully used to explain areas of physiology or anatomy that were less sophisticated than those we are studying today. The new physics of Bohr and Einstein explained everything that Newton’s physics did, plus much more. Modern-day biomedical research methodologies, such as those listed earlier, could likewise have been used to discover everything that animal models were used for in the past, but they also give us data and discoveries that animal models never could and never will.

In the final analysis it is the empirical data that counts when one asks if animal models are valuable today -- and the data indicate that animal models fail to predict human response. All the brilliant theories in the world cannot stand up to that one nasty little fact. Defending animal experimentation is scientifically sound if one is using animals as HAMs or if one is experimenting for knowledge sake alone. (Of course many things can be used as HAMs so we doubt the animal model industry will use that argument to trumpet their cause.) But the vast majority of the general public believes the pharmaceutical industry, the government, and charities are testing on animals or funding animal experimentation in order to assure a safe drug supply or to find cures for cancer, AIDS and so forth. The public, even if they cannot express it, believes animals are used as CAMs. And for good reason; whenever the Research Defense Society, the Foundation for Biomedical Research, pharmaceutical companies, or others with a vested interest in animal models speak to the public they express that concept. If researchers wish to defend their use of animals they should be honest and say they are being used as HAMs or for knowledge’s sake alone, and not end every grant
request with “we hope this study will lead to a cure for…” There would be little difference were we to say that we hope our books will lead to an end to world hunger.

Animal models of human disease are the most funded and least productive area of animal use in science. Dissecting animals does demonstrate anatomical principles and using animal derivatives such as insulin can also be effective. But these play a very minor role and from an animal-welfare perspective, alternatives are available. Those with a vested interest in animal models (either because they use them or because they are looking for replacements for them and hence would be out of a job if the thing they were trying to replace was itself useless) should offer proof of the effectiveness of the modality. Society deserves this basic accountability. Fear mongering and scare tactics have no place in science.

We again ask the 3 R’s community and others who profit from the animal model to produce data from prospective, third party studies showing how animal models can be used to predict drug effects and predict human response to disease. In light of the many times and many places we have made this request it appears that the emperor has no clothes; he may have had them at one time, but he is an embarrassment today.
Part 2

Additional Material for the 4th World Congress Point-
Counter Point

One hears constantly from drug manufacturers and scientists that only a very small percent of lead
compounds make it to the market and that we are in need of better ADMET tests.\textsuperscript{61,62} (ADMET stands for absorption, distribution, metabolism, elimination and toxicity.) According to William Bains, chief scientific
officer of Amedis Pharmaceuticals (Royston, UK), deficiencies in ADMET properties are the cause of
approximately half of the failures of drugs in development to reach the market, and that half of the drugs
that do make it to market still exhibit ADMET problems.\textsuperscript{63} Further, Barry Selick, CEO of the ADMET
modeling company Camitro (Menlo Park, CA) estimates that for every drug that is pulled from the market
as a result of ADMET difficulties not revealed in clinical trials, there are ten more that remain on the
market with labeled restrictions because of the potential for drug-drug interactions.\textsuperscript{64} To say the least,
conducting ADMET studies is a complicated, time-consuming process with many twists and turns.

While human epidemiological data and chemical structure analysis are utilized in ADMET assessments,
ADMET studies have been traditionally performed on animals and animal-derived tissue, despite frequent
admissions by researchers that animal-based ADMET studies often fail to be predictive. As Jürgen Drews,
former president of Global Research at Hoffman La Roche said,

\begin{quote}
For a long time it was considered necessary to carry out ADME studies on rats and dogs, or even on
small primates such as marmosets. Yet these experiments were often disappointing in view of
their lack of carryover to human beings. Only in recent years have models been developed from
comparative analysis of a variety of animal species that allow more precise prediction about
effects in man. \textit{Despite any existing uncertainties, ADME studies on human subjects remains the
basis for establishing correct dosages for patients and for the development of appropriate dosage
schemes.}\textsuperscript{65} [Emphasis added.]
\end{quote}

There have been many problems associated with the practice of using animals in ADMET studies. To begin
with, most animals are exposed to very high doses of the chemical in question over a short period of time
while most humans are exposed to low doses over a very long period of time. Humans tend to be exposed
to medications in small doses and intermittently (e.g., every eight hours) or continuously in small doses
(e.g., air pollution), while animals are exposed in large doses intermittently or in large doses continuously.
The routes of exposure can also differ. Animals may be exposed via their blood vessels while humans are
exposed via their lungs. Humans may metabolize the chemical to a different chemical than animals will
metabolize it to, or to the same chemical but by a different pathway. Animals and humans may also differ
in the way their organs and genes respond to the chemical. Different humans may even respond differently
because of genetic differences.

Toxicity is determined mostly by how the chemical is metabolized by the body -- and many different genes
influence how the drug is metabolized. As James P. Kehrer, Ph.D., of the Division of Pharmacology and
Toxicology at the University of Texas at Austin stated, “Small differences in gene structure can make large
differences in function.”\textsuperscript{66} Because ADMET studies in animals are so unreliable, when a drug enters
clinical trials, the company has very little idea if it will damage humans. Tom Patterson, chief scientific
officer at Entelos, likens the current practice of drug testing in humans during clinical trials to making
airplanes, trying to fly them, and marketing the one that does not crash.\textsuperscript{67} Why is the way a chemical is
metabolized so important and why does it vary so much between individuals and even more so between species?

We believe one of the best examples of why animal testing should be abolished is ADMET testing. Few studies have evaluated the efficacy of using animals to predict human toxicity for many reasons. Much of the data is proprietary and consequently the drug companies are reluctant to release it. Further, if the data did not support the drug companies’ contention that animal models are useful, they would be more liable for the harm their drugs do. But some data does exist.

One of the first attempts to evaluate the correlation between human and animal data was in 1962 by J. T. Litchfield. He reported that the toxicities that occurred in rats rarely occurred in humans while toxicities reported in dogs also were rare in humans. But when the same toxicity occurred in both species it also occurred in humans about 70% of the same.

Anticancer agents are usually toxic by their very nature and this is known before any testing just by studying the chemical nature of the drug. Not surprisingly, therefore, these drugs affect many species in a similar fashion. (The fact that sulphuric acid burns all mammals does not mean mice can be used to study heart disease.) But even then the rare toxicities are usually not seen in animals prior to being given to humans. For most toxicities however, animals have been very poor predictors. C. Lumley, in 1990 showed that animals did not predict 67% of toxicities that occurred in humans. T. Igarashi similarly showed that animals failed to predict 43% of toxicities that occurred in humans. The Igarashi study evaluated 139 drugs released in Japan from 1987 to 1991.

Another study revealed that in only 4 of 24 cases did animals predict human toxicity, and in yet another, 6 out of 114 times. Many studies have been published outlining the many differences between species that impact on predicting toxicity. Table 2 illustrates other reasons to distrust animal-model results.

### TABLE 2

Some Differences between Animals and Humans Critical to Prediction of Toxicity

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Animals</th>
<th>Man</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>Large groups</td>
<td>Individuals</td>
</tr>
<tr>
<td>Age</td>
<td>Young adult</td>
<td>All ages</td>
</tr>
<tr>
<td>State of health</td>
<td>Healthy</td>
<td>Usually sick</td>
</tr>
<tr>
<td>Genetic background</td>
<td>Homogeneous</td>
<td>Heterogeneous</td>
</tr>
<tr>
<td>Doses</td>
<td>Therapeutic to toxic</td>
<td>Therapeutic optimum</td>
</tr>
<tr>
<td>Schedule</td>
<td>Usually once daily</td>
<td></td>
</tr>
<tr>
<td>Housing</td>
<td>Uniform, optimal</td>
<td>Variable</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Uniform, optimal</td>
<td>Variable</td>
</tr>
<tr>
<td>Concomitant therapy</td>
<td>Never</td>
<td>Frequent</td>
</tr>
<tr>
<td>Diagnostic procedures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal contact</td>
<td>None</td>
<td>Intensive</td>
</tr>
<tr>
<td>Physical exam</td>
<td>Limited</td>
<td>Extensive</td>
</tr>
<tr>
<td>Clinical lab</td>
<td>Limited, standardized</td>
<td>Individualized</td>
</tr>
<tr>
<td>Timing</td>
<td>Predetermined</td>
<td>Individualized</td>
</tr>
<tr>
<td>Autopsy</td>
<td>Always</td>
<td>Exceptional</td>
</tr>
<tr>
<td>Histopathology</td>
<td>Extensive</td>
<td>Exceptional</td>
</tr>
</tbody>
</table>
In a study conducted by four drug companies, the results revealed a 69% true positive prediction rate. Concordance of the Toxicity of Pharmaceuticals in Humans and in Animals by Olson et al. was an article that summarized the results of a survey of multinational pharmaceutical companies in addition to a workshop and concluded that animal data was correct in up to 70% of the cases. But note that the word predict is not the same as animal data was correct in up to 70% of the cases. The study found that if a side effect occurred in humans there was an animal that it also occurred in. This study did not cover false positives and true negatives. The problem of prediction here is obvious. In retrospect it is easy to find an animal that replicates the human condition. Knowing, in advance which animal or groups of animals predict the human condition is another matter. That is why we use animals to test new drugs—to predict human response—and it is here that animal models fail. To use this 70% figure to mean that animals are predictive 70% of the time is a farce.

In a study designed to determine if absolute bioavailability in humans could be predicted from animal data using interspecies scaling as well as indirect approaches, Iftekhar Mahmood concluded:

“Fifteen drugs were tested and the results of this study indicate that all five approaches predict absolute bioavailability with different degrees of accuracy, and are therefore unreliable for the accurate prediction of absolute bioavailability in humans from animal data. In conclusion, although the above mentioned approaches do not accurately predict absolute bioavailability, a rough estimate of absolute bioavailability is possible using these approaches.”

Considering how many of these studies were either conducted or sponsored by those with vested interest in the outcome, the positive results are suspect. Even giving these studies the benefit of the doubt, today drugs are recalled or relabeled if they harm even 0.01% of humans taking them. Clearly 70% accuracy would not be good enough.

One adverse side effect that derails many drugs and causes relabeling and withdrawal is hepatotoxicity (liver toxicity). We have previously mentioned the data by Mark Levin, Ph.D. and CEO of Millennium Pharmaceuticals presented at the Drug Discovery Technology Conference in Boston, Massachusetts August, 2001. He discussed a study conducted at an associated company, where twenty-eight potential drugs were tested in rats. Eleven showed liver toxicity in the rats, while seventeen did not. Normally all eleven would have been tossed aside because it would have been assumed that the drugs would do the same in humans. But because this belief has been shown to be unfounded, all the chemicals went on to be tested in humans. Of the eleven that were thought to be hepatotoxic, two were shown to be toxic in humans also, but six were shown to be safe for humans. Of the seventeen that tested safe in the rats, eight were also safe in humans but six went on to be toxic to the liver. Levin concluded that this means the rat data were basically as accurate as a coin toss. (I do not know why the bottom numbers add up to 22 instead of 28 as this is Levin’s data and I have not been able to ask him. However it is obvious that regardless of how one calculates the statistics the coin toss analogy is going to be accurate.) This is why many New Chemical Entities (NCEs) fail in humans and why new predictive methods for testing are needed. Clearly, the animal models aspect of the ADMET testing process is inadequate.

Animals are poor predictors for humans for many reasons. The most common side effects of drugs cannot be predicted from animal tests. Things like nausea, dizziness, headache, heartburn, fatigue, tinnitus, vertigo and others cannot be judged in animals. Likewise, animal tests have often derailed good drugs because adverse effects were seen in animals that did not occur in humans or because of the general ineffectiveness in the animal model. Examples include cyclosporin, FK-506, fluoride, and digitalis.

A recent example of the failure of animal models to predict human response with regards to ADMET is the Roche calcium channel blocker Posicor (mibebradil). Designed to lower high blood pressure and control angina, Posicor was prescribed for millions of people. It was found however, to inhibit the metabolism of other drugs that many people suffering from hypertension and angina were taking, e.g., cholesterol-
lowering drugs, thus leading to dangerously high blood levels of these drugs. Posicor was taken off the market one year after it was released.

If a technology or model does not work, or is counterproductive, it should be abandoned. Treating brain cancers with bullets fired from guns is not effective therefore it should be abandoned/not begun. It is not incumbent upon us to find a cure for brain cancer even though we suggest that bullets and guns are not the answer. Likewise if animal models are neither predictive nor effective they should be abandoned. We do not have to find technologies that are effective in order to justify abandoning the ones that are not. Animal models should be abandoned because they are not effective, period. There is no need to talk of alternatives when the original is not viable. We need viable methodologies, not alternatives to nonviable ones. We have no cure for brain cancer and arguably there have been case reports of a patient using a gun to shoot a bullet into his head, killing all the cancer and leading a life perhaps not that much worse than would have otherwise been. We do, however, offer here what we think researchers should be focusing on:

Advances in ADMET technologies—improved *in vitro*, molecular, and cellular assays as well as DNA microarrays, to name a few—are beginning to reshape the drug development process by enabling researchers to predict a lead compound’s ADMET characteristics during the discovery phase, well before the preclinical phase. There is a flood of data for new drug development. Many companies are focusing on human-based ADMET tests. Camitro of Menlo Park, CA is developing computer models and simulation of drug metabolism. LION Bioscience of San Diego and Heidelberg is developing computer models from *in vitro* data. Genmatics of San Francisco is developing *in silico* modeling. Amedis of the UK is developing software for ADMET studies. D-Pharm/Pharma Logic of Israel is developing computer models. Cyprotex of the UK is developing high-throughput ADMET testing facilities and methods. Pharmage of the UK, Cell Technologies of Houston and Gene Trace Systems of Alameda are using human tissue for ADMET studies. Amphioxus Quintiles of Durham, MDS Pharma Services of Canada, Quest Diagnostics Clinical Trials of New Jersey and many others are also developing these technologies.

LION Bioscience has introduced the Absorption Module for the iDEATM (In Vitro Determination for the Estimation of ADME) Simulation System. iDEATM is a computational model developed to predict human oral drug absorption from a compound's solubility and permeability. The iDEATM Predictive ADME Simulation System is a modular approach to predicting the ADME characteristics of a compound. Each module is designed to model a specific ADME process. The modules interface with each other to form a comprehensive and integrated predictive ADME simulation system. iDEATM is designed to be accessed through a company’s intranet network and provides pharmaceutical and biotechnology companies with an enterprise solution for predicting the ADME characteristics of their compounds.

Accelrys® offers Desktop solutions (TOPKAT) for Computational Toxicology and UNIX applications (C2.ADMET) for early ADME/Tox profiling of individual compounds or combinatorial libraries. Accelrys' ADME/Tox Consortium has been formed for linking informatics-based predictive modeling with biology and chemistry to evaluate ADME/Tox properties in the early stages drug discovery.

Camitro has designed technologies to evaluate ADME/Tox profiles. Camitro's metabolism models are based on a novel, combined empirical/quantum chemical approach to predict enzyme-substrate binding affinities, metabolic sites, and relative rates of metabolism at discrete sites within a molecule. The initial focus is on the three major cytochrome P450 (CYP) enzymes, CYP 3A4, CYP 2D6, and CYP 2C9, which together mediate over 90% of human drug metabolism. In addition, Camitro has developed models for human intestinal absorption and blood-brain barrier penetration. Camitro's models are completely automated and thus provide a high-throughput means of predicting the associated ADME/Tox properties directly from compound structures.

Tripos also has technology to calculate ADME properties and create predictive ADME Models. VolSurf predicts a variety of adsorption, distribution, metabolism, and excretion properties using pre-calculated models, computes unique ADME-relevant descriptors, and performs statistical analyses to generate predictive models of bioactivity or property.
Screening in silico is taking the place of many animal tests. ComGenex of South San Francisco and Hungary is developing computer technology based on in vitro tests using human tissue to predict important properties of a new chemical like $pK_a$, log $P$ and log $D$. Ferenc Darvas, ComGenex president and chairman, said in Nature Biotechnology: “that the most promising use of data is to ‘calculate structure-activity relationships, convert those into rules, and then reintroduce those rules in a rule-based system for the design and selection of compounds or libraries.’” Along the same lines, Amedis of the UK has developed a structure-activity-based predictive test for carcinogenesis. Bains states: “The prototype software can predict carcinogenicity far more accurately then the Ames test can do.”

DNA microarrays are also taking the place of animals in toxicology studies. DNA microarrays allow an intersection of computers and biology. Thousands of genes interact in order to create proteins and, indeed, life as we experience it. They do not act alone but in combination with each other. DNA microarrays allow scientists to monitor the entire genome, or at least a very large percentage of it on a single chip. Thus scientists are able to look at how a chemical will influence genes, the proteins they make, and how the gene-gene interactions are effected. Numerous DNA chips are available: Biochip, DNA chip, DNA microarray, GeneChip, and gene array. Microarrays require sophisticated robotics and imaging technology. Several thousand genes can be analyzed simultaneously. They can be used to identify gene sequences, gene mutations, determine how active a gene is, analyze gene expression patterns induced by environmental factors or medications, create a profile for an individual patient, and to discover new genes. Genes can be exposed to medications and analyzed to see if they are more or less active after exposure.

Highly automated cell-based assays can provide a realistic sense of how a chemical can perform in a cellular system. These systems enable scientists to culture living cells very closely related to the cell types found in specific organisms. For example, scientists have discovered that Caco-2 cells, which come from a human colonic carcinoma, have many of the same cellular properties as those in the small intestine. As a result, these cells provide an appropriate in vitro assay for the absorption and secretion of drugs. MDCK, a kidney cell line used to mimic the blood-brain barrier, is also used to predict absorption in cell-based assays. Caco-2 cells have become the standard for predicting drug absorption. A human liver cell line, ACTIVTOX has been shown to predict toxicity and metabolism of drugs that were approved based on animal studies, terfenadine (Seldane) and astemizole (Hismanal), but went on to harm humans.

Drug-metabolizing enzymes were studied in dog, monkey, and human small intestines, and in the human adenocarcinoma cell line Caco-2. Overall, the results demonstrated that both the preparations of small intestines and Caco-2 cells exhibited significant drug-metabolizing enzyme activities, although several differences were noted between the intestinal enzymes in the animals or in the Caco-2 cells and those found in humans.

As we know, a single family of isoenzymes known as CYP, are responsible for metabolizing, or breaking down in the body about 95 percent all current drugs. Using this information, researchers can use cloned CYP enzymes in cell-based assays to test lead compounds for metabolic vulnerability. Liver cells from dogs or rats, or immortalized human liver cell lines, such as HepG2 are currently being used. However, Bob Coleman, chief scientific officer of Pharmagene insists that data from the primary human cells are far more informative than that provided by dog or rat livers, explaining that: “There are significant differences in the way that dog or rat livers metabolize compounds and differences in hepatotoxicity [liver toxicity] too.”

In a study designed to compare enzyme activity across species, P450 isozymes were used as probes to study in vitro metabolism in horse, dog, cat, and human liver microsomes. The researchers found that there were “large interspecies differences in the way the selective P450 inhibitors affect the in vitro metabolism of the various substrates in horse, dog, and cat liver microsomes.... Overall, no one species behaved exactly like humans regarding the efficiency of the various inhibitors.”

Traditional pre-clinical animal toxicology studies are time consuming, expensive, require high amounts of each NME under study, and may not accurately predict human toxicity. Gene expression data may help meet these challenges by providing a method that quickly evaluates the toxicity potential of compounds. Gene Logic's ToxExpress™ Module is an extensive gene expression database containing results from
studies of *in vivo* rat and *in vitro* primary rat and primary human cell samples treated with known non-
proprietary compounds. Gene expression profiles from organs and sites affected by toxicity that are
predictive of classic toxicology responses provide the backbone of this reference database. Compounds can
be studied in a number of ways including ranking targets for their potential toxicity, profiling the
anticipated pathology, and matching this to the closest compound in the ToxExpress™ database. In
addition to its capacity to reveal liver toxicity, the ToxExpress™ Module is being expanded to include gene
expression profiles from kidney, heart, CNS and bone marrow samples treated with corresponding tissue
toxins. The ToxExpress™ Module is part of the GeneExpress® Suite

We know that people metabolize drugs differently—and thus have different pharmacological and
toxicological responses to drugs—because of variations in their genes. As Guenther Heinrich, Ph.D.,
founder of Epidauros Biotechnologies AG, a company that applies the principles of pharmacogenomics to
the drug development process, has concluded based on the analysis of human genes, “It was quite clear to
me why drugs don’t always work: It’s because two unrelated people differ in some three million letters of
the biochemical alphabet of the DNA.”

Very soon, pharmacogenomics will make today’s one-size-fits-all approach to drug selection and dosing as
outmoded as an 18th century apothecary’s cabinet. Pharmacogenomics will deliver a host of social and
economic benefits as described by Alan Roses, head of genetics research at GlaxoSmithKline:

> Selection of predicted responders offers a more efficient and economic solution to a growing
> problem that is leading governments and healthcare providers to deny effective medicines to the
> few because a proportion of patients do not respond to treatment. The economy of predictable
efficacy, limited adverse events, lower complications owing to targeted delivery and increased
cost-effectiveness of medicines will improve healthcare delivery and eliminate the need for
rationing.

As we have already pointed out (p12), the final test of any drug will be that of clinical trials. Since human
clinical trials consume 60% of the cost of taking a drug to market, it should not be surprising to find Big
Pharma trying to avoid larger, longer clinical trials with a more diverse population. But in the final
analysis, it will remain the role of the clinical trial to separate drugs into beneficial and not. If larger clinical
trials were being conducted today, we would have a much safer drug supply and any solution to the
problem will ultimately involve instituting this strategy. Regardless of how society progresses, animal tests
are not now and will not be the answer. They are doing more harm than good and hence should be
abandoned.
Appendix A Dr. Michael Festing’s Review

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SACRED COWS AND GOLDEN GEESE
A Review by Michael Festing

In this book (The Continuum International Publishing Group, New York, 2000, 242 pp., US$24.95, ISBN 0-632-05052-7), C. Ray Greek and Jean S. Greek claim that "Animal experimentation... is a gross betrayal of science, . . . [and] that reliance on laboratory animals is not necessary- It is expensive. It is inaccurate. And further it is detrimental to the very species it professes to help - humankind."

Unfortunately, the book "... is a feat of omission and distortion", to use the words that it uses to describe somebody else's work. It cannot be described as a serious attempt to show the limitations of animal research, because any facts that conflict with the beliefs of the authors have simply been ignored, or history has conveniently been rewritten. As a way of reducing the use of animals in medical research, I think this book will be counter-productive, because even if the authors do have a few good points to make, its numerous inaccuracies and distortions make it impossible to trust anything that they have written.

There have been enormous advances in medicine in the last 75 years. Most bacterial infections can now be cured by one of the many antibiotics discovered following the development of penicillin in the 1940s; a wide range of diseases caused by viruses, such as polio, mumps and measles, can be prevented by vaccination and many other diseases, such as type I diabetes, and some types of heart disease and mental disease, can be controlled, if not cured, by medicines or biological preparations. Surgical methods have also advanced with new and better anaesthetics, organ transplantation and keyhole surgery. As a result, human life expectancy has increased, with many people now enjoying a life relatively free of serious disease. However, there are still many diseases that we are not yet able to cure or treat effectively, such as most cancers, a range of genetic diseases, diseases of old age (for example, senile dementia), and several viral diseases, including AIDS.

While many improvements in human health can be attributed to better hygiene, diet and working conditions, medical research has also made a substantial contribution. Unfortunately, medical research uses large numbers of animals. Worldwide, the total amounts to tens of millions of animals per year. Although these numbers are large, they are only a small fraction (less than 2%) of the number of animals that are killed for food. However, if it could be shown that the use of animals in research was scientifically unjustified, their use could be banned without detriment to medical research. Unfortunately, this book totally fails to make such a case.

Three specific examples serve to show how the book has rewritten history.

The development of a rabies vaccine by Louis Pasteur, by using dogs and rabbits.

In 1880, the microbiologist, Louis Pasteur, began to study rabies, a terrible disease which is usually passed from animals to humans when they are bitten by a rabid dog, though many other species can become infected and pass on the disease. Once the symptoms appear, the disease is invariably fatal. Pasteur's strategy was to find a reliable way of causing rabies in dogs, and then try to cure them by vaccination. There are many biographies of Pasteur which describe exactly how he did this by using intra-cerebral inoculations of infected neural tissue to induce rabies in dogs and rabbits, with homogenates of dried spinal cords of rabbits as a vaccine. Rabies is a unique viral disease, because it has a long incubation period, and the exact time of exposure to the infection is usually known. It took Pasteur five years to develop the vaccine, at which point he had about 50 dogs that were immune to rabies. According to same accounts, he thought that it would take many years to develop a human vaccine. However, ... on Monday, 6th July 1885, an Alsatian woman brought her child, Joseph Meister to the Rue d'Ulm. He had been attacked, two days before, by a dog, thrown down, bitten in fourteen places... and found covered with the dog's saliva and
his own blood." The dog had been shot, and its body had shown evidence of rabies. Pasteur and his colleagues examined the child and decided that they dare not refuse to treat him. Meister did not develop the disease, and by 1 March 1886, of 350 patients treated, only one had developed rabies, and she had not been treated until 37 days after she had been bitten. It has been estimated that 40-80% of people bitten by rabid dogs developed rabies, so there is not the slightest doubt that Pasteur had in fact developed a highly effective vaccine, which has since saved many thousands of human lives. The vaccine continued to be used for many years, until replaced by a vaccine produced in cell cultures.

On page 33 of this book, the authors state that Pasteur used animals as pseudo-humans as he attempted to craft a rabies vaccine. He took spinal column tissue of infected dogs and made what he thought was a vaccine. Unfortunately, the vaccine did not work seamlessly and actually resulted in deaths. Yet, this gross failure somehow did not detract from the reverence for the animal-lab process." This account is simply not true. The vaccine did not cause any deaths, it failed to cure one person out of the first 350, for a very good reason, and it was highly successful. The book does not even acknowledge that Pasteur did in fact produce a rabies vaccine.

The development of Insulin as a treatment for type I diabetes

"The discovery of insulin at the University of Toronto in 1921-1922 was one of the most dramatic events in the history of the treatment of disease. Insulin's impact was so sensational because of the incredible effect it had on diabetic patients. Those who watched the first starved, sometimes comatose, diabetics receive insulin and return to life saw one of the genuine miracles of modern medicine. They were present at the closest approach to the resurrection of the body that our secular society can achieve, and at the discovery of what has become the elixir of life for millions of human beings around the world." The work that led to these dramatic results was done in dogs and rabbits, and was initiated by Frederick Ranting, a young Canadian surgeon who worked in the Physiology Department of the University of Toronto, headed by J.J.R. Maclead. Banting was assisted by Charles Best, and the techniques for isolating the insulin were largely developed by J.B. Collip. By modern standards, the work was done in a haphazard manner, and it was surrounded by considerable controversy. Exactly who "discovered" insulin is still open to debate (see reference 2 for an excellent and detailed account). However, the research was successful, insulin was developed in a sufficiently pure state to be used in humans, and it has since saved many millions of lives.

On page 51 of their book, the Greeks state that "Banting and Best experimented on some dogs and by sheer happenstance persuaded people who had knowledge of in vitro research to look for insulin and purify it." They go on to say "The real credit for purifying insulin should have gone to Collip who used chemistry to purify the insulin." It is perfectly true that the purification of insulin posed some severe problems particularly in scaling up for volume production. What the book fails to mention is that Collip had to have an assay method to determine whether his isolation methods produced active, injectable, insulin. "It was Collip who found that pancreatic extracts were effective in rabbits. And not necessarily diabetic rabbits, perfectly normal ones. Extract lowered their blood sugar from normal to below normal. Collip tried many ways of extracting insulin from the pancreas of farm animals, and used the rabbits to assay the results. The problems in scaling up the methods meant that Ely Lilly, the commercial company chosen for this task, used over 100,000 rabbits in the first six months in order to try to get a consistent product2 (p. 72), Insulin has saved many millions of lives, but its discovery and isolation depended on the use of laboratory animals, which continued to be needed to assay the potency and safety of each batch of commercial insulin until the 1990's, when an in vitro method was finally developed.

The discovery and development of penicillin

The development of penicillin has resulted in the saving of more human lives than any other medical advance. The story of the discovery of penicillin by Alexander Fleming in 1929, as a result of the chance contamination of a bacterial Petri dish by a fungus, is well known. An excellent account is given by Hare, who was a friend and colleague of Fleming, working in the same department of St Mary's Hospital.
Penicillin is secreted into the medium in which the mould is grown. Unfortunately, Fleming was unable to purify it, so the only material he could work with was "mould juice". According to Hare, "Fleming evidently did think that penicillin might be of value when used locally, even though his attempts to employ it can only be described as feeble." Others did use this crude material on humans, sometimes successfully. Exactly why Fleming was not successful in purifying and developing penicillin is a bit of a mystery. Hare makes several suggestions. There were already several compounds that had anti-bacterial activity in vitro, but which turned out to be useless in practice. It had also been shown that some bacteria could become resistant to penicillin after only a short exposure. Also, the methods for the partial purification of small quantities were too clumsy for large-scale production, and in any case the penicillin was extremely unstable. So penicillin remained impure and untested for 11 years until 1939, when Ernst Chain and Howard Florey developed a method for purifying and preserving it on a large scale.

The account of how they tested it by using mice is well known. As recorded by Medawar, 4 'At 11 a.m. on Saturday, 25th May 1940, eight white mice received approximately eight times the minimal lethal number of streptococci. Four of these were set aside as controls, but four others received injections of penicillin - either a single injection of ten milligrams or repeated injections of five milligrams. The mice were watched all night (but of course). All four mice unprotected by penicillin had died by 3.30 a.m ... Next morning, Sunday 26th May, Florey came into the department to discover that the results of his experiment were clear-cut indeed... They all recognised that this was a momentous occasion... Animal experiments on a much larger scale soon made it clear that penicillin was indeed of great potential importance."

On page 73 of their book, the Greeks claim that animal testing delayed the introduction of penicillin, because Fleming used it on a rabbit and it did not work. Given that; he was unable to purify the penicillin; that the use of a rabbit is not mentioned by Hare; that had Fleming had some pure penicillin, there were patients he could have tried it on; that mice would have been the natural choice of test animal, because of their small body size; and that the only references to the use of a rabbit are from anti-vivisectionist literature, I doubt whether this is true. The Greeks go on to claim that "He later had a very sick patient, and since he had nothing else to try, administered penicillin. The rest is history." In fact, Florey gave Fleming the purified penicillin. The vital part played by Chain and Florey in isolating it, proving it by using mice, and developing it, is largely ignored in their book.

There are numerous other comments that could be made about the Greeks' book. For example, Chapter 4 gives a long list of drugs withdrawn because of adverse reactions in humans that were not predicted by using animal tests. Although it is certainly true that animal tests cannot predict all adverse reactions, the book fails to point out that all drugs undergo extensive clinical trials, so that if they later have to be withdrawn, it is because the clinical trials also failed to detect these adverse effects.

A book like this always has to have a villain. And, true to form, chapter 5 is a polemic about how vested interests are making money out of animal research. It is true that the supply of animals, cages, diet and sundries for animals is a valuable business. However money for medical research comes largely from government (for example, the Medical Research Council in the UK, and the National Institutes of Health in the USA), the pharmaceutical industry, research charities such as the Wellcome Foundation, and universities. All these organisations already spend many millions on clinical science and on non-animal alternatives, such as research with insects (for example, Drosophila) and the nematode C. elegans, and with cell cultures. All of them would be only too pleased to save money by not using animals if they thought real alternatives were available.

FRAME, of course, believes that there is still considerable scope for finding more alternatives, and will continue to press the scientific community to invest more time, effort and money in the search for them. But this book is not going to be of much help, because scientists set great store by the truth.

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In Vitro Comparison of Cytochrome P450-Mediated Metabolic Activities in Human, Dog, Cat, and Horse

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