

# Are Animals Necessary in 2002? Reply to Dr Michael Festing's Book Review of *Sacred Cows and Golden Geese: The Human Cost of Experiments on Animals*

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**Summary** — We appreciate this opportunity to defend the concepts we expressed in 2000, in *Sacred Cows and Golden Geese: The Human Cost of Experiments on Animals*. 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 essay will shed light on the debate.

**Key words:** fallacious reasoning, insulin, medical history, penicillin, rabies, vested interests.

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## Introduction

Dr Michael Festing's review (1) 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 criticise: modern-day research using animals to model humans. Of the four examples from *Sacred Cows and Golden Geese* (2) that Dr Festing chose to critique, three involved history, and one, an opinion on the power of money, in society in general, and in 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. In this essay, we will focus on the three areas Dr Festing critiqued that do not involve money: rabies, insulin and penicillin.

## 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 criticised Pasteur's vaccine if he did not, in fact, produce one? This is an example of a scientist, Pasteur, trying to use animals as causal analogical models (CAMs), or at least claiming he used them that way, when in fact he did not, as we shall see, and it exemplifies why animal models fail when used in this way.

The research Pasteur did on the vaccine has been recently re-examined, 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" (3). This had not occurred in the animals on which it was tested. Pasteur claimed he had established the efficacy of the vaccine in dogs (having 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 (4). 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 weakness of 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* (5) 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 (6):

*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 immunisation 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 central nerv-

ous system (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, fewer than 50 deaths occurred in any given year (7). 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 (8). It is fallacious to count those as *vaccine successes*.

On the other hand, some people who received the vaccine may have otherwise gone on to die from rabies (9). 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 (10). 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 what would, today, be referred to as CAMs, but he 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" (11).

## Insulin

Dr Festing states:

*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 1990s, 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" (12).

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 glyco-gen. 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' (13).

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 instruments 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 do 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 states:

*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 are people who have written them. The how's and why's of the discovery and development of penicillin are hotly debated. 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 metabolised 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 four humans suffering from ophthalmic neonatorium, and three of them responded well (13).
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, and all responded 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 to give the definitive historical account of penicillin. 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 direction. 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 support 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. 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" (14). They also ignore the statements of Macfarlane, another early penicillin researcher, who emphasised species differences when he stated (see 15):

*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.*

With regard to the role of cats and rabbits: V.D. Allison (a student, laboratory worker, and protégé of Fleming), wrote in *The Ulster Medical Journal* in 1974 (16):

*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.

Allen B. Weisse, Professor of Medicine at the University of Medicine and Dentistry of New Jersey, and author of *Medical Odysseys: The Different and Sometimes Unexpected Pathways to Twentieth-Century Medical Discoveries* (Rutgers University Press, 1991), wrote in *Hospital Practice*, 15 August 1991 (17):

*[Fleming was discouraged about penicillin's possible use because . . .] 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?

Craig H. Steffee, of Bowman Gray School of Medicine, writing in the *North Carolina Medical Journal*, stated (18):

*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 (17) 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 (17) 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 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 [19].)

Human observation also encouraged Florey to continue the penicillin purification process. As John Warren Henderson wrote in the *Mayo Clinic Proceedings* (20), "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 purer 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 selective serotonin reuptake inhibitors (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.

A related criticism that has been levelled 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 criticised 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.

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