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Evidence-Based  
Science



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Excerpt from [\*FAOS about the Use of Animals in Science\*](#); Shanks PhD and Greek MD  
University Press of America, 2009.

### Chapter 5 Animals, Specific Drugs and Diseases, page 70:

What was the role of animals in the discovery of penicillin?

The how's and why's of the discovery and development of penicillin are hotly debated among scientists and medical historians; numerous versions have been circulated for many years. (This is true of most medical and scientific discoveries of the past.) However, there are some details of the penicillin story that seem to be factual and more or less universally agreed upon, beginning with the rediscovery of penicillin by Alexander Fleming in 1928. (It had actually been discovered in the late 1800s.)

Fleming then tested it *in vitro* and *in vivo* on rabbits and mice; he mentions the rabbits specifically 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.

Some have criticized Fleming for not trying penicillin on humans. His reluctance was based on the rabbit study. Allen B. Weisse:

[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? [74]

Steffee of Bowman Gray School of Medicine 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*. [75]

Steffee defends Fleming's setting 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. [74]

Fleming continued to grow penicillin and even routinely gave it to humans as a topical treatment for infections prior to the 1940s [76-79]. Through a student of his, GG Paine, Fleming gave it to four humans suffering from ophthalmic neonatorum, an eye disease of infants. Three of them responded well [80, 81].

Human observation also encouraged British scientist Florey to continue the penicillin purification process. As 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 neonatorum with a crude broth of penicillin. All these factors gave Florey and Chain hope that systematically administered penicillin might have therapeutic potential in humans. [80]

Florey and his colleague Chain conducted research with penicillin and, using basic chemistry, developed a method of extracting and purifying small amounts of penicillin. The purified product was tested on mice, resulting in cures of otherwise fatal infections.

The penicillin story is actually a good example of one of the many follies of using animals to model humans, which is: "Which animal do we believe?" Florey himself 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. [82]

Prior to Florey and Chain testing penicillin on humans, Fleming administered it systemically to a friend of his who was dying in the hospital. It was a desperate measure done out of necessity and the reason why many such advances are initially applied to humans. (World War II, for example, provided an opportune field trial for penicillin.) 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. Publicity surrounding Fleming's friend led to funding to develop the drug and Fleming went down in history, rightly or wrongly, as the person responsible for penicillin [74].

Interestingly 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 friend. Florey's cat died.

Under certain circumstances, penicillin kills guinea pigs and Syrian hamsters [83, 84]. In addition, penicillin is teratogenic in rats, causing limb malformations in offspring. This is one of the problems with using animals to predict human response. If you had been Fleming, Florey, or one of the other scientists, which species would you have believed? The dead cat? The rabbit that metabolized penicillin so rapidly? The guinea pigs and hamsters it would have killed had it been tested on them? Or the mice on which it worked?

Regardless of the role played by animals in the discovery of penicillin, animals could not then, nor can they now, predict human response to drugs and disease.

## References

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