

The Discovery and Development of Penicillin

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The discovery and development of penicillin is often heralded by those who advocate using animals in research as an example of a breakthrough that was *dependent* upon animals. They triumphantly point to the mice that were used to test the drug in the early 1940s. On a web page from the Foundation for Biomedical Research, the awarding of the Nobel Prize in 1945 to Fleming, Florey and Chain for the discovery and development of penicillin is listed as being dependent upon research with mice [1]. What role did mice specifically, and animals in general, play in the discovery and development of penicillin? In this essay I will show that far from being necessary, animals models in general misled researchers and society would have had penicillin much earlier were it not for these misleading results.

MacFarlane, a scientist that conducted research on penicillin credited serendipity for the discovery:
. . . a series of chance events of almost unbelievable improbability. [2]

The importance of serendipity can be illustrated by the fact that other scientists who initially tried to grow Fleming's anti-bacterial chemical in their own labs failed. For a time, many suggested that Fleming had been mistaken about his results. [2]

Another unfamiliar fact about penicillin is that Fleming actually *rediscovered* it. Steffee:

Folklore of the mid-19th century encouraged the application of mold to a fresh wound as protection against subsequent infection. In 1871, Sir John Burden-Sanderson reported that liquid culture media exposed to air rapidly became turbid with bacteria, but if a *Penicillium* mold happened to grow on the surface of the broth less turbidity ensued [3]. . . Subsequently, William Roberts in 1874 [4] and John Tyndall in 1876 [5] described the tendency of *Penicillium glaucum* to inhibit bacterial growth in liquid media. [6]

To begin with we might question the role of mice based on statements by Fleming himself:

How fortunate we didn't have these animal tests in the 1940's, for penicillin would probably never been granted a license, and possibly the whole field of antibiotics might never have been realized. [7]

And from Florey:

Mice were used in the initial toxicity tests [by Florey and Chain] 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. [8] (Emphasis added)

His statement was reinforced by Koppanyi and Avery [9].

Fleming re-discovered penicillin and proceeded to test 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 ineffective for humans when administered systemically that is by

mouth or intravenously. Therefore he put the life saving antibiotic on the shelf and essentially forgot about it. He did occasionally use it on topical infections but never even tried it on humans with systemic infections.

Some have criticized Fleming for not trying penicillin systemically on humans. His reluctance was based on the rabbit study. 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? [10]

Steffee 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. [6]

The rabbits excreted penicillin in their urine so rapidly Fleming did not think the drug would be effective. A believer in animal models being predictive, he assumed that humans would react like rabbits. This mistake cost lives! Unfortunately, the same mindset is still costly lives. Steffee, for example, 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 [6]?" 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 [10].

Fleming continued to grow penicillin and even administered it to humans prior to the 1940s. Fleming routinely gave penicillin to humans with topical infections for years after 1929 [11-14]. Through a student of his, GG Paine, Fleming gave it to four humans suffering from ophthalmic neonatorum, an eye disease of infants, three of whom responded well [2, 3, 15] p.634]. Paine went on to treat more patients with penicillin [15-17]. Fleming also treated KB Rogers, an assistant in the lab [3]. Physicians at Columbia University also used penicillin to treat bacterial infections of the eye [3, 16, 18, 19]. Fletcher of Oxford was another physician that used penicillin to treat bacterial infections of the eye [3]. All these were topical uses, not systemic.

Such human observation also encouraged 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. [2]

Florey and Chain conducted research with penicillin and produced a *purified* product using basic chemistry. The purified product was tested on mice resulting in cures of otherwise fatal infections. Fleming obtained the more pure form of penicillin, which he gave to his friend in 1942, from Florey. 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 penicillin story is actually an example of one of the conundrums of using animals to model humans. The bottom line is: “Which animal do we believe?” Florey 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. [8]

The fact that Florey and Chain used mice to test penicillin is not an example of animals being *necessary* for a discovery. In fact, Florey and Chain almost made another animal-based mistake. If they had the guinea pig, society would have had to wait even longer for penicillin. The basis for the claim that mice were necessary for penicillin’s development emphasizes the fact that the animal model community, even in light of current knowledge of evolutionary biology, genomics, and complex systems continues to insist that results from animals can be directly extrapolated to humans. It is thinking of this nature that delays personalized medicine and cures. Animal models are not predictive for humans *vis-à-vis* drug testing and disease research. (See *Animal Models in Light of Evolution* and *FAQs About the Use of Animals in Science* for more on this.)

Prior to Florey and Chain testing penicillin on humans, Fleming eventually tried penicillin on a human because of necessity (the reason many such advances are initially applied to humans). Fleming gave it to a friend who was dying in the hospital. 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 as the person responsible for penicillin [10]. Florey and Chain’s use of mice so they could administer penicillin to humans was for naught as Fleming gave the drug to his friend out of necessity, not based on the tests in mice.

Florey, co-winner of the Nobel Prize for penicillin, administered penicillin to a cat at the same time Fleming was giving it to his sick friend. Florey’s cat died [20]. Under certain circumstances, penicillin kills guinea pigs and Syrian hamsters [21, 22]. 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?

Penicillin was not the result of basic research using animals. Animal use actually misled Fleming suggesting penicillin would be ineffective systemically.

References

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