HISTORY

Howard Florey, Alexander Fleming and the Fairy Tale of Penicillin

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The public myth of the discovery of penicillin is an archetypal "quest story" of the type common to every human culture. But the real story of the discovery, testing and refinement of penicillin is a complex tale of accident, serendipity, oversight, conflict, the pressure of war, idiosyncratic personalities and even — the invention of history. ***(MJA 2002; 176: 178-180)***

THE STORY OF PENICILLIN that we were taught as children was a simple story of how Alexander Fleming searched in vain for antibacterial agents until *Penicillium* mould spores drifted through his open laboratory window onto a plate of bacteria and killed them. Realising immediately the potential, he spent many years fighting against a resistant medical establishment and then guided Howard Florey and Ernst Chain to refine and test his great discovery.

This myth meets the specifications of the archetypal "quest story", as described by the Russian anthropologist Vladimir Propp.[1] The basic quest story seems to be a template in every human culture. It involves heroes who undergo trials or answer riddles, usually with the help of magical or divine intervention (in this case, mould spores drifting through windows). It has been argued[2] that the quest story's structure (along with other story structures) is "hardwired" into the human brain, and that such structures evolved, like poetry and music, in human brains as mnemonic aids to help preliterate people store and remember vast quantities of words.

Of course, we also have a tendency to rewrite history in a manner that renders it more momentous or more pleasing to the reader or listener. For example, Captain Robert Lewis, copilot of the plane that carried the first atomic bomb, records in his published account of the flight that his words immediately following the explosion were "My God, what have we done?". His exact words, as recalled by the rest of the crew, were "My God, look at that son-of-a-bitch go!".[3]

Among numerous inconvenient details missing from the penicillin myth is exactly how long the son-of-a-bitch took to get going, who was responsible, and why.[4,5] The fact that Florey eschewed publicity while Fleming actively sought it did not help reveal the true story. A BBC film about Fleming, made as late as 1970, still perpetuated the myth, at least in popular culture.

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Alexander Fleming (1881–1955) in Edinburgh, where he had just been appointed Vice-Chancellor of the University, was received with just cause as a benefactor of humanity.
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The search for non-toxic antimicrobial chemical agents

"We can see further because we stand on the shoulders of giants", Albert Einstein said of Isaac Newton. The "giant" Louis Pasteur allowed the world to see the power of microbes in disease and the ability of the body's antibodies to combat these microbes. The search was then on for antimicrobial chemical agents — but antiseptics were too toxic for anything but surface use on wounds. In Frankfurt, Paul Ehrlich[6] (who later won a Nobel Prize for his work on the theory of immunity) began to systematically test substances, searching for the "magic bullet" that could be taken internally, but ended up with little more than a high-risk arsenic-based treatment for syphilis. The resulting mindset was fixed — chemical agents were too toxic for internal use in the human body.

Fleming, working in London, had been looking for antibacterial agents in human secretions. His discovery of the enzyme lysozyme (which he regarded as much more important than penicillin) came from an accidental sneeze onto a Petri dish (another divine intervention). He noticed that the area on which he had sneezed subsequently did not

grow bacteria. "Noticed" is a key word — Fleming had a genius for taking notice of small, superficially inconsequential effects.

Contrary to the myth, *Penicillium* spores did not fly in through an open window, as the windows of his laboratory were fixed shut. Luckily, Fleming's laboratory work practices were substandard. After stacking uncleaned plates in a corner while he was on holidays, he noticed (that word again) on his return that *Penicillium* mould had inhibited the growth of staphylococcal cultures.

Fleming had little idea what to do with his mould apart from dabbing it on infected wounds. It seems astonishing now that he went so far as to inject his early "mould-broth" into a healthy rabbit, discovering it to be non-toxic, yet failed to take the further step of injecting it into infected rabbits to investigate its therapeutic effect. He then effectively forgot about it for 13 years. What was he thinking? And why, in this instance, did he not take notice? It's easy to see his mistake in retrospect, easy (in the words of author Julian Barnes) "to make the past suck up to the present".[7] Fleming was of his time, a victim of the pessimistic mindset against toxic chemical antimicrobials.

Ernst Chain at work in his laboratory at Oxford. Keystone (London)

The contribution of Howard Florey

Howard Florey, the abrasive Australian who, Robert Menzies said, had more effect upon the welfare of the world than any other Australian, had also been working on lysozyme with his team at Oxford.[8] He was a more methodical scientist than Fleming — methodical to the point of obsession — but the psychological imperatives behind this (the "madness in his method") had various origins.

Florey suffered from a range of gastrointestinal symptoms, on which he blamed his irritable personality.[8] He investigated his own condition by — among other tests — regularly swallowing a rubber tube to extract his stomach contents. The diagnosis was achlorhydria. His famous pinched smile was to hide the erosion of his teeth that resulted from drinking hydrochloric acid. The tests also sparked his interest in saliva and mucus and the antibacterial qualities of lysozyme.

An important driving force in the quest for penicillin was Florey's idiosyncratic temperament, with its elements of idealism and obsession. His absorption with his work, and his rather unusual relationship with his wife Ethel, illustrate the power of an idea, or ideal, to sustain passion in the absence of reward. His relationship with Ethel began in his final year of medicine and was continued, in idealised form, by correspondence for five years of separation after he left for England. Even when she later joined him, the couple sometimes preferred to communicate via notes left on the hallway table. Florey worked seven days a week in his laboratory, seldom eating at home, and family holidays were generally spent visiting overseas laboratories. Ethel's involvement in his research was perhaps the one facet of the relationship that worked. She administered and recorded the clinical progress of the first large-scale trial of 187 cases of sepsis.

Florey continued to work on lysozyme long after Fleming had abandoned it. Florey had the advantage of the services of a great biochemist, Ernst Chain (a refugee of the Hitler regime), on his team. Chain had purified lysozyme and understood its antibacterial function. Florey and Chain searched the medical literature for other antibacterial substances, and in so doing they rediscovered Fleming's finding of many years before.

This was around the time of the discovery of sulfonamides and their minimal toxicity. To Florey, as to many others, this meant the end of the earlier mindset against toxic "magic bullets". He was interested in the fact that staphylococci, while resistant to sulfonamides and lysozyme, were apparently sensitive to the *Penicillium* mould. Chain was intrigued by the failure of Fleming and others to identify the active ingredient in the penicillin "mould-broth".

The background of war in 1939 was a crucial spur to research on antimicrobial agents. Delayed infection (especially staphylococcal infection and gas gangrene) was killing more men than the immediate organ damage caused by shell and bullet wounds. Florey's awareness of this was not without an emotional resonance, as he felt some guilt about not having enlisted in the First World War.

World War II provided an impetuous and risk-taking research environment. Resources normally denied could be commandeered, money was freed up, and Florey was able to persuade breweries to ferment mould for the conduct of trials on the battlefields of North Africa. Florey did many things that a modern researcher would be admonished for. He did not patent his work, despite being implored to do so by Chain. The United Kingdom was forced to buy back the technology from the United States for the mass production of penicillin.

Florey shunned the media for fear of creating false expectations and had nothing but contempt for their intrusions into his life. He believed that sensational stories about penicillin would create a demand that could not

possibly be met. He always stressed the team effort involved (teamwork was an unusual feature of medical research in those days), and claimed that he got more credit than he deserved. As a consequence, he almost left Fleming — seldom out of the limelight by then — to receive the Nobel Prize alone.

Howard Florey. Photograph courtesy Dr Joan Gardner, AO.

The moral of the story

The philosopher Richard Rorty has written that "inquiry is never pure … It is always a matter of getting us something we want".[9] The story of the quest for penicillin contains too many complicated semi-heroes to allow itself to be twisted into a myth of the usual impoverished Hollywood dimensions. If there are mythical heroes in scientific research they work in teams — sometimes in teams that are not even aware they are teams, being disconnected in time and place. If a relay team is the closest analogy, the baton is more often tossed into the air in the hope that someone — anyone — will grab it than passed on directly.

But, like most archetypal stories, the story of penicillin doesn't lack simple moral lessons. Perhaps the most lasting is the recurring theme of human creativity: how to see what has been hidden in full view all along.

The great clinician Sir William Osler wrote of an earlier mindset in 1905:

> "We may have become more plastic and receptive, but I doubt it; even our generation . . . had a practical demonstration of the slowness of the acceptance of an obvious truth in the long fight for the aseptic treatment of wounds. . . . [It was] a long and grievous battle, as many of us well know who had to contend in hospitals with the opposition of men who could not — not who would not — see the truth . . .
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> "In making knowledge effective we have succeeded where our masters failed. But this last and final stage, always of slow and painful consummation, is evolved directly from truths which cannot be translated into terms intelligible to ordinary minds."[10]

As the philosopher John Locke wrote, "Truth scarce ever yet carried by vote anywhere at its first appearance. . . . The final struggle for acceptance is the real challenge in achieving knowledge".[10] The narrative impulse always seeks to personify that struggle, to dramatise it as a battle between individuals, in black and white — but the truth is much more messy and complex.

References

1. Propp V. Morphology of the folktale. 2nd ed. Austin: University of Texas Press, 1968.
2. Goldsworthy P. Navel gazing: essays, half-truths and mystery flights. Ringwood, Victoria: Penguin, 1998.
3. Thomas G, Morgan-Witts M. Ruin from the air: the atomic mission to Hiroshima. London: Sphere Books, 1978.
4. Macfarlane G. Howard Florey: the making of a great scientist. New York: Oxford University Press, 1979.
5. Bickels L. Florey, the man who made penicillin. Melbourne: Melbourne University Press, 1995.
6. Mann J. The elusive magic bullet: the search for the perfect drug. New York: Oxford University Press, 1999.
7. Barnes J. Flaubert's parrot. New York: Vintage International, 1990.
8. Australian Broadcasting Corporation. Howard Florey. Part 1. The Health Report. ABC television, 14 September 1999.
9. Rorty R. Consequences of pragmatism. Minnesota: University of Minnesota Press, 1985.
10. Horton R. An autopsy of Dr Osler. *New York Review of Books* 2000; 47: 36-39. ❑