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When I use a word . . . Medicines regulation—penicillin

Penicillin has a history that antedates its discovery by Alexander Fleming in London and its isolation and purification by Howard Florey, Ernst Chain, and Norman Heatley in Oxford. Before that it had been used as a raw broth of *Penicillium* organisms in local treatment of infections such as furuncles and conjunctivitis. After its introduction for parenteral administration and its manufacture in the USA during the second world war, shortage led to its being misused in dilute solutions, as described in Graham Greene's film treatment for Carol Reed's film *The Third Man* (1949), later published as a novella. The use of penicillin in the UK during the war had been governed by the Control of Penicillin Order No. 731, established under the Defence Regulations, a set of wartime emergency regulations, promulgated under the Emergency Powers (Defence) Act 1939. The order made its sale a criminal offence, unless it had been prescribed by a doctor. In 1947, largely because of concern about the emergence of resistant organisms through the use of low doses and the marketing of many types of non-parenteral formulations, the Penicillin Order was replaced by the Penicillin Act, which restricted the sale and supply of penicillin to duly qualified medical practitioners, registered dental practitioners, or registered veterinary surgeons, and to registered pharmacists or authorised sellers of poisons.

Jeffrey K Aronson

Penicillin before Fleming

If you ask anyone who it was that discovered penicillin, the chances are that they will say Alexander Fleming. However, penicillin has a striking prehistory, antedating Fleming.

According to Sydney Selwyn,[1] a species of *Penicillium* was first isolated in 1911 from its growth on hyssop, whose therapeutic efficacy is described in the Bible (Psalm 51:7). The Aztecs have also been said to have cultivated *Penicillium* mould on bread and taken it for medicinal purposes. In *The Boke of Children* (1545) Thomas Phayre (ca 1510–60) recommended "the musherom that groweth upon an elder [to treat] quinsy and swellyng under the eares." *Penicillium* perhaps?

In a 1949 review Florey gave several examples of the use of types of fungi as topical applications for superficial infections.[2] For example, he quoted Cranch, who in 1943 suggested that "The Mosse upon dead mens Sculles.., which cureth wounds," mentioned by John Parkinson in his *Theatrum Botanicum* (1640), was a *Penicillium*. Florey also quoted information from several correspondents that folkloric use of moulds for the treatment of wounds was common in places as far apart as Brazil and the Ukraine, San Jose and Yugoslavia.

In 1883 John Burdon Sanderson, medical officer of health for the London Borough of Paddington, later Waynflete professor of physiology and then regius professor of medicine in Oxford, observed that *Penicillium* inhibited the growth of bacteria in a solution and prevented the overgrowth and rapid putrefaction that would otherwise have occurred in a guinea pig's exposed thigh muscle.[3] Joseph Lister[4] confirmed Sanderson's findings and used *Penicillium* to treat a deep-seated gluteal abscess, although he never published the results of his clinical experiment. The inhibitory effect of *Penicillium* on bacterial growth was later confirmed in the 1870s by William Roberts,[5 6] professor of medicine in Manchester, by the English biologist Thomas Henry Huxley,[7] and by the Irish physicist John Tyndall.[8] Tyndall seems to have regarded the effect of the *Penicillium* mould as a struggle with bacteria for the fitness to survive, and he believed that the action of the *Penicillium* was brought about by covering bacteria completely, depriving them of oxygen,[9] a view that Huxley disputed.[3]

The inhibitory effect of *Penicillium* species on bacterial growth was subsequently rediscovered on several occasions by a variety of investigators, including Gosio in Italy in 1896, Duchesne in France in 1897, and Tartakovskii in 1904, and by Lieske in Germany in 1921 and Gratia and Dath in Belgium in 1924.[2 10]

Although most of these workers did not investigate the potential therapeutic value of *Penicillium* moulds, some seem to have used them locally in the treatment of infections before Fleming. In addition to Lister, a Dr K Jaumain was reported by Gratia as having treated a patient with furuncles "by a series of injections of the mycolysat" [Gratia's name for his extract of *Penicillium*],[1] although this presumably meant injection directly into the furuncles rather than parenteral administration.

In 1929 Fleming himself used a broth of *Penicillium* to treat a chronic infection of a colleague's nasal antrum, without success, but in 1932 he successfully treated pneumococcal conjunctivitis in a medical student at St Mary's Hospital. Meanwhile, in 1930, a Sheffield physician, Dr CG Paine, successfully used a crude filtrate from a *Penicillium* broth in four babies with gonococcal conjunctivitis.[11]

Post-war penicillin

Movie enthusiasts will remember that in the 1949 film *The Third Man*, racketeer Harry Lime peddled substandard penicillin in post-war Vienna. Graham

Greene wrote the script for the film, building on an idea by the producer Alexander Korda, who wanted to explore economic and social corruption in the devastated city, which at that time was divided into four zones, under the control of the British, Americans, French, and Russians. Greene developed the script from a story that he never intended to publish. It was, he later wrote, "never written to be read but only to be seen." Nevertheless, the following year he did publish a prose "film treatment," in tandem with a short story "The Basement Room," which had also been turned into a movie, *The Fallen Idol* (1948), by the same director, Carol Reed.[12]

In the book, Colonel Calloway, who narrates the story, played in the film by Trevor Howard as Major Calloway, tells Holley Martins (originally called Rollo Martins, a name to which Joseph Cotten, who played the part, objected) what Harry had been doing:

"But the penicillin racket was a different affair altogether [from the black market in food]. Penicillin in Austria was supplied only to the military hospitals; no civilian doctor, not even a civilian hospital, could obtain it by legal means. As the racket started, it was relatively harmless. Penicillin would be stolen by military orderlies and sold to Austrian doctors for very high sums—a phial would fetch anything up to seventy pounds. You might say that this was a form of distribution—unfair distribution because it benefited only the rich patient, but the original distribution could hardly have a claim to greater fairness." Calloway then explained that the racketeers started wanting more money. "They began to dilute the penicillin with coloured water, and, in the case of penicillin dust, with sand. … We wouldn't worry so much if that was all, but just consider. You can be immunised from the effects of penicillin. At the best you can say that the use of this stuff makes a penicillin treatment for the particular patient ineffective in the future. That isn't so funny, of course, if you are suffering from V.D. Then the use of sand on a wound that requires penicillin—well, it's not healthy. Men have lost their legs and arms that way—and their lives. But perhaps what horrified me most was visiting the children's hospital here. They had bought some of this penicillin for use against meningitis. A number of children simply died, and a number went off their heads. You can see them now in the mental ward."

In his preface to the book, Greene wrote that "Reality, in fact [the reality of life in post-war Vienna], was only a background to a fairy tale; nonetheless the story of the penicillin racket is based on a truth all the more grim because so many of the agents were more innocent than Joseph Harbin. The other day in London a surgeon took two friends to see the film. He was surprised to find them subdued and depressed by a picture he had enjoyed. They then told him that at the end of the war when they were with the Royal Air Force they had themselves sold penicillin in Vienna. The possible consequences of their act had never before occurred to them." In the film Harbin was a hospital orderly involved in the penicillin trade and also played an important part in the mystery of the third man.

Post-war regulation of penicillin in the UK

Because penicillin was isolated and purified in Oxford during the war, Florey took it to the USA to have it manufactured in industrial quantities, facilities for doing so not being available in the UK. Initially, it was in very short supply, and in 1946 the Control of Penicillin Order No. 731 made its sale a criminal offence, unless it had been prescribed by a doctor. The order had been established under the Defence Regulations, a set of wartime emergency regulations, promulgated under the Emergency Powers (Defence) Act 1939, which gave the British government the freedom to enact whatever powers it deemed to be necessary in prosecuting the war.

When, in 1947, the availability of penicillin increased, the government considered whether it was right to allow penicillin to be "bought and sold like most other articles in a chemist's shop quite freely and without restriction." However, expert advice was that it would be dangerous to allow unrestricted use of penicillin, especially because the use of inadequate doses increased the risk that resistant organisms would emerge.

On 25 February 1947, Sir John Mellor, at that time the Conservative MP for Sutton Coldfield, spoke on the matter in the House of Commons[13]: "Penicillin is controlled under Order No. 731 of 1946. Under that Order if anyone walks into a chemist's shop and says 'Please sell me some penicillin,' unless he tenders a medical prescription, he is guilty of a criminal offence for which he may be severely punished. Even at the time of a shortage of penicillin, to some of us that seemed to be rather a drastic provision, but there is now no longer any shortage of penicillin. Therefore, in my submission, the Order is now quite unjustified."

Mellor then offered some statistics: "In the United Kingdom in January … 225 387 mega units were produced and 85 000 exported. Figures of the quantities distributed to meet demand in January are not yet available, but we are satisfied that there is ample to meet all prescriptions. About 5 mega units were imported for experimental purposes. … I am advised by my right hon. Friend the Minister of Health [Aneurin Bevan] that penicillin should be used only under expert supervision, and at his request my right hon. Friend is retaining the Control Orders until such time as other arrangements can he made."

He then cited the expert opinion: "As I understand the position with regard to medical opinion generally in relation to penicillin, it is that penicillin is in no way harmful, but—and I do not want to under-estimate the importance of the 'but'—the doctors also consider that if penicillin is continually used the body becomes so acclimatised to it that it becomes less susceptible to its beneficial qualities. The reaction of the body to penicillin tends to diminish with frequent use, though I do not think it is contended by the medical profession that any direct harm can come from the use of penicillin." Substitute "bacteria" for "body" and the reasoning is good, as far as it goes.

In reply, Mr John Lewis, MP for Bolton, commented on the availability of low-dose penicillin tablets (500 units each) and, prompted by Mellor, on the use of penicillin cream in dermatology. Wing-Commander Roland Robinson, MP for Blackpool South, then confused matters further by reporting that while in America, he had cured a bad throat by chewing two tablets of penicillin chewing gum.

The joint parliamentary secretary to the Ministry of Supply, a Mr Leonard, then reported that a draft bill had been prepared to control the sale and supply of penicillin other than by Order No. 731.The upshot of that was the Penicillin Act of 1947.[14]

The Penicillin Act 1947

The 1947 Penicillin Act decreed that "no person shall sell or otherwise supply any substance to which this Act applies or any preparation of which any such substance is an ingredient or part unless (a) he is a duly qualified medical practitioner, a registered dental practitioner or a registered veterinary surgeon, or a person acting in accordance with the directions of any such practitioner or surgeon, and the substance or preparation is sold or supplied for the purposes of treatment by or in accordance with the directions of that practitioner or surgeon; or (b) he is a registered pharmacist or an authorised seller of poisons, and the substance or preparation

is sold or supplied under the authority of a prescription signed and dated by any such practitioner or surgeon as aforesaid."

Despite the title of the act, it was intended that it should be applied more widely than to penicillin: "The substances to which this Act applies are penicillin and such other anti-microbial organic substances produced by living organisms as may be prescribed."

In June 1947 Aneurin Bevan moved the second reading of the Penicillin Bill in the House of Lords: "It seemed to us to be highly undesirable that this very valuable substance should be the plaything of quacks with all sorts of ways of advertising it and selling it—penicillin lipstick, penicillin rouge, penicillin powder, and even penicillin waistbands, as we had iodine waistbands years ago. That would be highly undesirable, because hon. Members who have studied the subject will agree that this is one of the most beneficent discoveries in the history of medicine. It would be an appalling thing if, as a consequence of its misuse, the population might, in a period of years, receive no advantage at all from it because it would have developed resistance in those who take it. Therefore, it was decided that we should have a short Bill which would empower the Ministry of Health to control its sale and distribution."[15]

The Penicillin Act was given royal assent in July 1947.

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