Penicillin's Forgotten Man: Norman Heatley

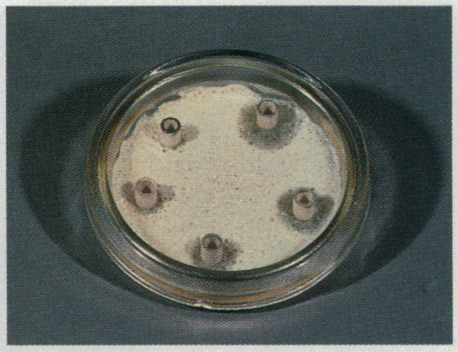
Although he's been overlooked, his skills in growing penicillin were a key to Florey and Chain's clinical trials

FOR HALF A CENTURY, NORMAN HEATLEY has lived in the shadow of Alexander Fleming, Howard Florey, and Ernst Chain. A soft-spoken biochemist, Heatley was a key member of the Oxford University team that helped launch a new era of medicine 50 years ago, when it proved that a substance—penicillin—secreted by an obscure mold has remarkable healing powers. But while Fleming, who discovered the mold in 1928, and Florey and Chain, who demonstrated penicillin's medicinal properties 12 years later, went on to receive fame, glory, and the Nobel Prize, Heatley had gone largely unrecognized—until recently. Last October, Heatley, now 80 years old, was awarded an honorary Doctorate of Medicine from Oxford. What makes the honor particularly remarkable is that Heatley is the only person to receive that award in the university's 800-year history.

The honor recognizes Heatley's singular contribution to the penicillin project: to produce the compound in sufficient quantities to carry out the first clinical trials. Bulk production of penicillin had defeated previous workers, but Heatley did it by devising new extraction methods and by cobbling together an amazing array of makeshift equipment. "All of us following the Oxford project knew Norman Heatley's exceptional work," says Rollin D. Hotchkiss, emeritus professor of Rockefeller University who worked on gramicidin in 1939–40. But Hotchkiss also recalls that once the 1945 Nobel Prize was awarded to Heatley's colleagues and postwar jockeying for market share of penicillin began, "Norman's crucial role faded in world memory."

Notable for his modesty, Heatley shows not a trace of bitterness. Speaking of his award, which was presented during penicillin's golden jubilee year, Heatley says in a gentle voice, choosing his words carefully: "This is an enormous privilege, since I am not medically qualified....I have been picked out to represent the whole team involved in the difficult process of extracting and purifying penicillin. I am absolutely staggered that this award has been made at all."

Heatley is a small, almost vanishingly thin, spry man with elfin twinkles around his eyes and mouth. His specialty, for which he was duly honored, was in training things to grow. Indeed, he still does it, proudly exhibiting an immense espaliered pear tree in his garden, one of the largest he knows. The one exception to his desire to see things grow is apparently his own renown: When it comes to discussing the precious units of penicillin he grew at Oxford in 1940–41, Heatley becomes reticent: "I was a third-rate scientist whose only merit was to be in the right place at the right time." Not so. What his modesty will not allow him to admit is that he was also just the right person.



© Lawrence R. Moberg

Green thumb. *Heatley's penchant for training things to grow extends from penicillin cultures to a four-tiered espaliered pear tree in the garden of his Oxford home.*

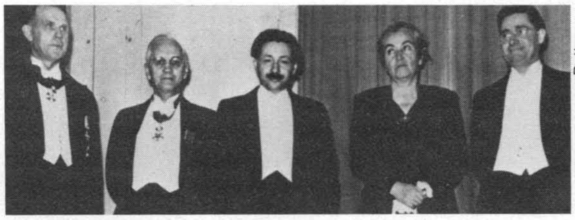
In 1939, when Florey assembled a group to study antimicrobial substances, including the penicillin discovered 11 years earlier by Fleming in London, he selected Chain, a chemist, to analyze the nature of penicillin and to try to purify its active ingredient. Florey appointed himself to head a small team that investigated penicillin's biological, and later clinical, effects. And he chose Heatley as his personal assistant and put him in charge of producing enough penicillin for the researchers to study.

At that time, a crude mold juice containing penicillin could be easily grown. But no one knew how to extract an active substance from temperamental mold cultures. Earlier chemists had tried, had encountered penicillin's notorious instability, and concluded penicillin vanished while they looked on.

Heatley was well suited to Florey's task and team. This Cambridge-trained biochemist, according to Florey's biographer, historian Gwyn Mcfarlane, had "technical skills of optics, glass- and metal-working, plumbing, carpentry, and as much electric work as was needed. Above all he could improvise—making use of the most unlikely bits of laboratory or household equipment to do a job with the least possible waste of time." Heatley's gifts of improvisation and micro-engineering were to prove invaluable in establishing the world's first penicillin factory in the laboratories of Oxford's Sir William Dunn School of Pathology.

Heatley's initial contribution—the first in a remarkable series—was the "cylinder plate," or "penicillinder," to determine how powerful this unknown substance was. The assay plates contained short lengths of glass tubing embedded into bacteria-laden agar, and each tube was filled with a different penicillin solution. The diameter of the growth-free circle of agar around each tube was measured from a glass scale illuminated from underneath. The assay gave rise to the "Oxford unit" of penicillin, essentially the standard adopted a few years later by the League of Nations. Historians acknowledge this assay alone gives Heatley claim to recognition for developing the first essential step in producing an antibiotic.

The assay had another important capability: It indicated the critical time when a culture should be harvested at the peak of antibacterial activity. Furthermore, Heatley discovered growing time could be substantially reduced by reusing the fungus and producing up to twelve crops of the penicillin fluid underneath a single fungal mat.


Bettmann

Richly rewarded. *Fleming* (second from left), *Chain* (third from left), *and Florey* (far right) *at the Nobel ceremony.*

Then, in March 1940, while trying to increase output, Heatley devised an ingenious method to separate the active penicillin from the yellow mold juice. Penicillin's instability, which had defeated earlier scientists including Fleming, precluded conventional separation techniques. The penicillin is destroyed by heat, strong acids or alkali, some metals, and numerous chemicals. Heatley pioneered a gentle two-stage, liquid-into-liquid technique called back-extraction. In the first step, the cooled and slightly acidified culture was mixed with ether, or later amyl acetates, which took up the penicillin and left impurities behind. Then, Heatley hit on what today may seem an obvious next step, although he remarked that Chain initially "considered the deduction unsound." The ether solution was back-extracted into slightly alkaline water.

Heatley's back-extraction method worked brilliantly. The resulting watery solutions of penicillin were freeze-dried into a stable brown powder that was remarkably powerful in a dilution of one to a million. Yet—as the Oxford team later learned—the powder contained only 1% pure penicillin. Nevertheless, this method produced enough penicillin in 7 weeks for Florey to test the effects of the antibiotic in animals.

The crucial protection experiment was performed on 25 May 1940. Eight mice were infected intraperitoneally with a virulent streptococcus, and an hour later four were given the first test doses of penicillin subcutaneously. In this experiment, Heatley kept the death watch. "The controls were looking very sick," he wrote in his diary, "but the treated animals seemed very well. I stayed at the lab until 3:45 [a.m.] by which time all four control animals were dead. It really looks as if P. may be of practical importance."

The Oxford team's paper on the therapeutic power of penicillin appeared in *The Lancet* on 24 August 1940 and listed the seven members alphabetically, according to Florey's rule: Chain, Florey, Gardner, Heatley, Jennings, Orr-Ewing, and Sanders.

Florey immediately wanted to extend the trials to man, but this demanded great quantities of the drug. The 600 units of penicillin used in the mouse protection experiment represented at least a week's production. "Even so," Heatley remembered, "the dose was scarcely adequate, and preparation of enough material for tests on man (3000 times the size of a mouse) presented a ormidable problem." English factories under harsh wartime conditions could not help, so Florey hired a few "penicillin girls" to help Heatley. To have enough penicillin for treating six patients within the next few months, the Dunn School factory would have to produce 500 liters of mold filtrate per week.

Two production methods were upgraded. "Clearly some kind of mechanization was badly needed here," Heatley said. First, he automated his back-extraction process with available equipment. This apparatus consisted of milk churns and soft drink bottles connected with yards of glass and rubber tubing, and included "a warning bell, indicator lights, etc., on a stand made from a bookcase discarded from the Bodleian Library." The "counter current" machine's six columns of amyl acetate extracted penicillin from uniform droplets of acidified culture. The penicillin-rich solvent flowed in a counter current direction to the top of a column where it was collected while the spent watery liquid was discharged below.

Next, Heatley needed to grow more mold juice to keep pace with his extraction machine that processed 12 liters of medium an hour. "Because it was wartime," Heatley remembered, "there were great scarcities of everything. We had to get containers to brew thousands of liters of medium for a very low yield of the drug." He had already pressed into service an astonishing assortment of sterilized bottles, trays, pie dishes, gasoline cans, and biscuit tins. "The best of these makeshift culture vessels," he explained, "was the old-fashioned enamel bedpan with a side arm through which the culture could be inoculated and harvested."

Inspired by the bedpan, Heatley designed a square-sided ceramic vessel that could be quickly and inexpensively made by a slipcast process. Each utensil held a liter of medium and could be stacked horizontally in the incubator, vertically in the autoclave, and in neat rows lining the walls of the Dunn School operating theater. Heatley fetched the first 174 (of 500) bespoke bedpans from a nearby pottery, in a "bull-nosed Morris two-seater groaning under the weight," and incubated them with the mold on Christmas Day 1940.

Within a month, the now famous "bedpans" produced enough penicillin to justify the beginning of Florey's clinical trials. The antibiotic had also been purified of pyrogens by chemist Edward Abraham, who collaborated with Chain. The six patients treated during the spring of 1941 at Oxford's Radcliffe Infirmary used a total of nearly 2 million units of penicillin. Even so, one patient died when supplies ran out before curing his infection. Nonetheless, these Oxford clinical trials, published in *The Lancet* in August 1941, established penicillin as a powerful and safe cure for bacterial infections. (Remarkably, the Oxford team's entire research effort to this point took just 18 months and was based on a mere 4 million units of Heatley's handmade penicillin, an amount that today represents a daily dose for a single person.)

Florey planned an even larger trial, but the problem once again was to obtain enough penicillin. In June 1941, he and Heatley came to the United States to seek help from the chemical industry, a visit that galvanized mass production with a deep tank fermentation process. However, when the United States entered the war in December 1941, all of its penicillin was appropriated for treating battle casualties, and the supplies hoped for in Oxford never arrived. By that time, Heatley had conveyed his technical expertise to American penicillin producers whose large-scale manufacture at last stimulated British production.

Heatley's assemblage of bottles, tubes, and bedpans continued in use until adequate commercial supplies were available. For his resourceful factory, Heatley was again honored at Oxford's "Penicillin 50" celebration this spring in the only toast from High Table at Lincoln College. The rector, raising his glass, paid tribute "to Norman Heatley and his bedpans." ■ CAROL L. MOBERG

Carol L. Moberg is co-editor with Zanvil A. Cohn of Launching the Antibiotic Era *(Rockefeller University Press, 1990).*