The Science Communication Competition is now in its fifth year. As in previous years, it aims to find young talented science writers and give them the opportunity to have their work published in *The Biochemist*. In 2015, a new branch of the competition was launched to include video entries. Overall, this year's competition attracted 47 entries and these were reviewed by our external panel of expert judges. The second prize in the written category was awarded to Paul Brack from Loughborough University, whose article is presented here.

Norman Heatley: the forgotten man of penicillin

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Seventy years ago, three men shared the Nobel Prize in Physiology or Medicine. Their names were Alexander Fleming, Howard Florey and Ernst Chain, and they had all played their part in the discovery and development of penicillin, the wonder drug that has saved tens of millions of lives. Honours and accolades were to follow them for the rest of their lives. Fleming was lionized and given a knighthood, 25 honorary degrees, 26 medals, 18 prizes, 13 decorations and honorary membership of an astounding 89 scientific societies[1]. Florey, far less interested in publicity, was still knighted, then later elevated to a Lord; Chain was also knighted.

There was, however, a fourth man. Quiet, unassuming and modest, his name was Norman Heatley. In the words of the late great Oxford Professor Sir Henry Harris, "without Fleming, no Chain or Florey; without Chain, no Florey; without Florey, no Heatley; without Heatley, no penicillin."[2]. Yet it was not until 1990, at the ripe old age of 79 and a full 45 years after the award of the Nobel Prize to his colleagues, that Heatley's contribution was recognized with a major honour: Oxford University presented him with an honorary Doctorate of Medicine, the first to be awarded to a non-medic in the entire 800-year history of the institution[3].

So why was Heatley's work so important? To understand that, we need to go back to the beginning of the penicillin story. In 1928, Alexander Fleming was working at St Mary's Hospital in London. He was not a particularly tidy scientist, and had a tendency to leave things lying around, including the plates on which he grew bacteria. In July, he went on holiday and did just this. When he returned in September, he began checking his plates for anything interesting and disinfecting them so he could use them again. As he was doing this, an assistant came by, and Fleming decided to show him one of the plates he was disinfecting. He noticed that the plate had been contaminated by a mould, and around that mould was an area free from bacteria[1]. Fleming realized that he had found something that could kill bacteria. That something was penicillin.

Fleming extracted the 'mould juice' which contained the penicillin, and tested it on further bacterial samples. Even at a dilution of 800 to 1, the bacteria still died. This got Fleming excited. However, he was not a chemist, and did not have the skills to extract and purify the penicillin from the 'mould juice'. He was also unable to generate much interest from other scientists in his work. He kept a culture of the *Penicillium* mould, but after publishing his findings in a low-key paper in 1929[4], he moved on to other things.

Our story moves on too, to Oxford University. In 1935, Howard Florey, an Australian, started there as the Chair of Pathology. He had long thought that there ought to be more chemistry applied to the field of pathology, and thus set about recruiting some chemists. One of these was Ernst Chain, a Jewish refugee from Nazi Germany. Despite their conflicting personalities, Florey and Chain made a good team. In 1938, they decided to study some natural antibacterial compounds. Chain, his interest piqued by Fleming's 1929 article, suggested penicillin, and Florey went along with him. Chain was pleasantly surprised to find that he did not even have to go anywhere to get hold of the *Penicillium* mould that Fleming had worked with; the laboratory at Oxford had been using it for several years to keep Petri dishes free of contamination. As Chain put it later, "I was astounded at my luck in finding the very mould about which I had been reading, here, in the same building, right under our very noses"[1].

Enter Norman Heatley. Recruited by Florey not long after Chain, Heatley was an Englishman with a PhD in biochemistry from Cambridge University. Heatley was assigned by Florey to come up with a method to produce and extract enough penicillin (the challenge that had defeated Fleming) for Chain to study. In March 1940, Heatley succeeded. Penicillin is destroyed by strong acids or alkali, heat and many chemicals. To avoid having to use any of these, Heatley invented a technique called back-extraction. In the first step, cooled 'mould juice' was mixed with ether. The penicillin was taken up into the ether

and some of the impurities left behind. Despite Chain's misgivings, Heatley then took the ether and mixed it with slightly alkaline water, pulling the penicillin back into the water. Next the watery mixture was freeze-dried, giving a brown powder that was later found to be about 1% pure penicillin. Using this method, Heatley was able to make enough penicillin to allow him and the rest of the team to conduct the first animal tests of its antibacterial properties[3].

Heatley himself monitored the experiment in which penicillin was administered to animals for the first time. On 25 May 1940, eight mice were infected with *Streptococcus*. An hour later, four of them were given penicillin. Heatley stayed in the laboratory until 3.45 a.m., by which time all four of the mice which had not received penicillin were dead. In the morning, he was able to tell Florey that the four treated with penicillin were still alive[1]. With typical understatement, Heatley wrote in his diary that "it really looks as if P. [penicillin] may be of practical importance"[3].

Florey realized that penicillin could make a huge impact in the war if they could prove it would treat infections effectively in humans as well and, as Head of Department, was able to throw resources at this challenge. In order to have enough penicillin to test in humans, the Oxford team would have to produce 500 litres of 'mould juice' every week. With the outbreak of war, resources were limited, and thus the mould had previously been grown in whatever they could lay their hands on such as pie dishes, biscuit tins, petrol cans, sterilized bottles and even 16 old-fashioned bed pans borrowed from the Radcliffe Infirmary[3]. However, this would not be adequate to produce 500 litres a week. They needed a way to make more.

Again, Heatley solved the problem. He was a supreme improviser, known for using his skills in optics, glass and metal work, plumbing, carpentry and rudimentary electronics to cobble together functional efficient laboratory set-ups from whatever he could lay his hands on. He worked out that, of all the makeshift vessels they had tried, the bed pans worked best, so 500 stackable ceramic 'bed pans' were designed and developed. On Christmas Day 1940 he added mould to them, and within a month, helped by six 'penicillin girls' Florey employed to operate the homemade factory, they were producing enough penicillin to start clinical trials[3].

As part of this scaling up of penicillin production, Heatley also managed to mechanize his extraction process, constructing a machine out of milk churns, drinks bottles and rubber and glass tubing, with a doorbell to signal when a bottle was full or empty. It stood six feet [1.8 m] tall upon a stand made from an old bookcase discarded by the Bodleian Library. Using Heatley's homemade contraptions, the Oxford penicillin factory was able to provide 2 million units of the drug in the spring of 1941, sufficient to treat a few patients and prove beyond any doubt that the stunning antibacterial properties of penicillin had the potential to revolutionize the whole of medicine. In June 1941, Heatley and Florey took their methods to America. The Americans were (having found a more potent mould on a rotten cantaloupe) able to devise a method to make penicillin on a huge scale, the drug was rapidly deployed to treat soldiers, and the rest, as they say, is history.

Alexander Fleming discovered penicillin. Howard Florey brought together a great team of scientists, and at first permitted and then embraced the work they were doing on penicillin. Ernst Chain brought penicillin's potential as an antibacterial agent to the attention of Florey. All of this was undoubtedly crucial in taking penicillin from a laboratory curiosity to a wonder drug. However, without the contribution of Norman Heatley, without his extraction and purification method and his homemade penicillin factory, there would never have been enough to test in a human being. It was these tests in humans that proved beyond doubt that penicillin was an effective antibiotic and enabled Florey and Heatley to convince the Americans to find and use a way to manufacture and deploy penicillin on a huge scale. And it was this that changed the world. Truly, "without Heatley, no penicillin"; let us give him the huge amount of credit his contribution deserves. ■

Further links

Heatley's achievements are celebrated by a Biochemical Society Medal and Prize for exceptional work in applying advances in biochemistry, and especially for developing practical uses that have created widespread benefits and value for society
www.biochemistry.org/Awards/TheHeatleyPrize.aspx
Dr Norman Heatley obituary – The Guardian
www.theguardian.com/news/2004/jan/08/guardianobituaries.highereducation
Discovery and Development of Penicillin – American Chemical Society
www.acs.org/content/acs/en/education/whatischemistry/landmarks/flemingpenicillin.html

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2. Harris, H. (1999) Notes Rec. R. Soc. Lond. **53**, 243–252
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4. Fleming, A. (1929) Br. J. Exp. Pathol. **10**, 226–236