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The Medical Research Council (MRC) trial of patulin,¹ as a possible treatment for the common cold, is an exemplar of researchers, research funders, manufacturers, patients and government working together with a common purpose to pose and answer an important healthcare question. To do this within less than 2 years seems remarkable today, and is something that everyone currently involved in healthcare research, policy and decision making would do well to learn from.

On 31 October 1943, the *Sunday Express* reported that a new cure for the common cold had been discovered. It claimed that a spokesman for the MRC had told the newspaper that the results of tests of the cure would be published shortly. The new remedy was said to be an inhalant made from a mould that killed germs in the nose, tongue and larynx. The true source of the newspaper story is unclear, but it referred to patulin, a metabolic product of the *Penicillium patulum* mould, which grows on apples. Within a year, however, the drug had been assessed in the first large, well-designed, multicentre controlled trial conducted by the MRC. The trial showed that any beneficial effect of patulin was likely to be small, negligible or non-existent.¹

The week after the *Sunday Express* report, the Ministry of Supply wrote to the MRC expressing concern that, if the report were true, they would be expected to supply the raw material for manufacturing the drug. The MRC denied any involvement in the *Sunday Express* story, but noted, 'the newspaper appears to have got hold of a garbled version of the contents of a paper which is expected to appear in the *Lancet* in the course of a few weeks'. The MRC also commented,

' . . . although preliminary observations suggest that this substance may possibly be of value in treating the common cold,

one cannot speak with any confidence of that until controlled trials of a sufficient scale have been carried out'.

The *Lancet* paper mentioned by the MRC appeared on 27 November 1943, amidst several pages devoted to a series of articles about patulin.² This collection of papers described the first, very promising studies of the use of patulin against the common cold, in particular a case report of its benefits and a small, controlled trial involving naval personnel.³ The following week, however, another controlled trial, this one involving army recruits, was published as a letter to the editor of the journal and it failed to detect any beneficial effects.⁴

Patulin was originally supplied by Harold Raistrick, Professor of Biochemistry at the University of London, to W E Gye (director of the Imperial Cancer Research Fund's laboratories) for testing as a treatment for cancer. At the time Gye received the patulin, he had a severe cold and decided to douche his nasal passages with a solution of the drug. His blocked nose cleared within an hour. He repeated the douching twice that day and, the following morning, his cold had gone and he returned to work. Enthused as he was by this piece of personal research, Gye recognized the need for a controlled trial to assess the possible benefits of patulin. The first formal, controlled study was coordinated by Commander W A Hopkins, a surgeon commander in the Royal Navy.³ The trial was done in early 1943 and used alternation to allocate patients to patulin or a placebo control group. The results were striking: 55 of the 95 patients given patulin recovered during the trial, compared to only eight of the 85 patients in the placebo control group. (The article does not explain how this imbalance in the numbers of patients in the two groups could have arisen using 'alternation'.)

Towards the end of the Hopkins trial in the navy, a supply of patulin was also made available for trials in the army. These took place from March to October 1943. As mentioned above, the relatively disappointing findings were reported briefly in the correspondence pages of the *Lancet* a week after the excitement of Raistrick's series of articles.⁴ A fuller report with additional patients appeared the following year,⁵ in the same issue of the *Lancet* as the report of the MRC trial. The army trial found that colds among patients allocated patulin lasted somewhat longer than those

among control patients, but the difference probably reflected the play of chance.

In October 1943, after the navy and army trials had finished but before either had been published, the manufacturers of patulin, the Therapeutic Research Corporation, approached the MRC to explore whether they would be willing to conduct a trial on a larger scale. On condition that no other large trial was done, the MRC agreed and set up a committee to plan the trial. Professor Harold Himsworth (Head of the Medical Unit at University College Hospital) was appointed chair; Dr Philip D'Arcy Hart, Director of the MRC Tuberculosis Research Unit at Mill Hill, secretary; and Dr Joan Faulkner, later Lady Doll, assistant secretary.

The committee met in November 1943 and approved a design similar to those used for the smaller trials reported above. Alternation (or more precisely, rotation) was used to allocate patients to patulin or placebo control, but with the twist of using two treatment groups and two control groups. In the words of Philip D'Arcy Hart, interviewed sixty years later, this was 'to muddle people up', and so reduce the likelihood of foreknowledge of the allocations among those recruiting participants.

The trial took place between January and April 1944 at three London units of the General Post Office; four Royal Ordnance Factories; and seven other factories. Patients were recruited by advertising for volunteers at each location. Following an assessment by the medical officer to confirm that they really had a cold, the experiment was explained and a trial card completed before each patient received the relevant solution from the factory nurse or sick bay attendant. Each patient was given his or her own bottle of solution to look after. While at work, a teaspoonful of solution was run into each nostril three times a day for 2 days, with the patient lying down and his head tilted back. This method had been selected from among alternatives by assessing the extent of nasal mucous anaesthesia after different approaches to instilling cocaine. Patients were told to continue their treatment at home, about once every 4 hours. The medical officer, the nurse and the patient did not know what was in the solution used for each individual. The patient returned to the medical officer after 1, 2 and 7 days, when their progress was recorded on their record card. There were also studies in two schools, Haileybury College and Rugby School, where the solution was administered as a spray. But, only 49 patients were available for analyses from these two schools and their results were not reported in detail.

Given the personal and national burden of the common cold, and the possibility of a successful treatment for it, there was wide interest in the findings of the trial. This extended to parliament and, on 4 May 1944, a parliamentary question put by Colonel Lyons to the Lord

President of the Council (Clement Atlee) requested a statement on the results of recent trials of patulin and whether large-scale manufacture was being encouraged. Atlee responded that the results of the trials were currently being analysed and that patulin was not generally available, and 'unless there is definite evidence of its value it would not be justifiable under existing conditions to encourage production on a large scale'.

On 29 June 1944, the analysis completed, Philip D'Arcy Hart sent the manuscript that was to become the *Lancet* article to the journal. The report is a model of clarity and was published virtually unchanged on 16 September 1944. The introductory paragraphs set out the methodological challenges faced by the investigators and the way they had been addressed—by studying sufficiently large numbers of patients, ensuring unbiased allocation to drug or placebo controls, and by developing a simple, standard way of recording symptoms. The methods adopted are described in great detail.

A total of 1449 patients had been treated at the factories and Post Office units, but 101 were not available for analyses because of problems such as doubtful diagnosis, non-adherence and absence from work. This left a total of 1348 patients: 668 who were treated with patulin and 680 in the control group. The report presents the results at 1, 2 and 7 days for both recovery and improvement. The control patients actually did somewhat better than those in the patulin group, although the difference is easily compatible with chance. The article concludes:

'No evidence was found that patulin is effective in the treatment of the common cold'.¹

Within less than 2 years, during the Second World War, the battle against the common cold had brought together researchers, research funders, manufacturers, patients and government to test a treatment that, at first sight, had looked very promising. On the basis of the results obtained in a sufficiently large, multicentre controlled trial, evidence had been generated that continued use of the drug would not be a sensible use of limited national resources.

Of course, such evidence is not universally accepted and, 60 years after the trial, a Brazilian website still proclaims that:

'The old wives tale of 'an apple a day keeps the doctor away' is true . . . because the mycotoxin patulin is a strong antiviral agent that is active against the common cold virus'.⁶

However, maybe the final words are best left to those in a letter written by Arthur Mortimer of the Directorate of Medical Supplies in the Ministry of Supply, in the interval between the *Sunday Express* article in October 1943 and the first articles in the *Lancet* the following month. On 10

November 1943, in a letter to Dr Landsborough Thomson at the MRC, he remarked 'I assume that the statement in the *Sunday Express* was as accurate as most of the news in that paper. In fact, for some time I have come to the conclusion that the title of the paper, the price, and the date, were about the only accurate things it contained'.

Acknowledgments This article is dedicated to Philip D'Arcy Hart, who died on 30 July 2006, aged 106. Philip's help and remarkable memory made a vital contribution to telling this story. A fuller account of the patulin trial is available, along with a reprinting of the 1944 *Lancet* paper, in the *International Journal of Epidemiology*.⁷

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