

# Commentary: The 1944 patulin trial: the first properly controlled multicentre trial conducted under the aegis of the British Medical Research Council

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The 1948 report of the British Medical Research Council's randomized trial of streptomycin for pulmonary tuberculosis is widely regarded as marking the beginning of the modern history of controlled clinical trials. Four years earlier, however, a methodologically sophisticated multicentre trial conducted under the aegis of the Medical Research Council was reported, which assessed the effects of the antibiotic patulin on the course of common colds. Philip D'Arcy Hart and Joan Faulkner (later Joan Doll) were the secretary and assistant secretary, respectively, to the committee overseeing the trial, and they clearly recognized the importance of preventing foreknowledge of allocations from those admitting patients to the study. To do this and to 'muddle people up', they and Ruth D'Arcy Hart devised a scheme involving the use of two patulin groups and two placebo groups, allocating patients to one of these four groups using strict rotation. Philip D'Arcy Hart believes that this study has been overshadowed by the celebrated streptomycin trial (for which he was also secretary to the oversight committee) because no beneficial effect of patulin was detected, and because the report of the streptomycin trial referred to the use of random sampling numbers to generate the allocation schedule. This article makes clear why we agree with Philip D'Arcy Hart that the 1944 patulin trial deserves wider recognition as the first well controlled, multicentre clinical trial to have been conducted under the aegis of the British Medical Research Council. This status is reflected in the *International Journal of Epidemiology's* reproduction of the full text of the trial report in this issue of the journal.

Sixty years ago, on Halloween 1943, the *Sunday Express* reported that a new cure for the common cold had been discovered. It claimed that a spokesman for the Medical Research Council (MRC) had told the newspaper that the results of tests of the cure would be published shortly (Figure 1). The new remedy was said to be an inhalant made from a mould that killed germs in the nose, tongue and larynx. Sixty years later, a Brazilian website still proclaims that 'the old wives tale of 'an apple a day keeps the doctor away' is true', and that this is because 'the mycotoxin patulin is a strong antiviral agent that is active against the common cold virus'.<sup>1</sup> Unfortunately for those who will suffer from a cold later this year, the evidence suggests otherwise.

The week after the *Sunday Express* report had been published, the Ministry of Supply wrote to the MRC expressing concern

that, if the report was true, they would be expected to supply the raw material for manufacturing the drug.<sup>2</sup> 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's response also remarked:

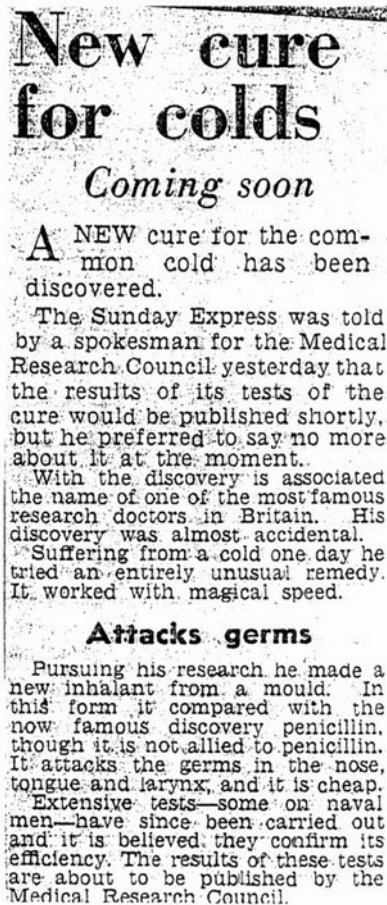
although preliminary observations suggest that this substance may possibly be of value in treating the common cold, one cannot speak with any confidence of that until controlled trials of a sufficient scale have been carried out.<sup>3</sup>

Three weeks later, on 20 November 1943, the *Lancet* did devote six pages to a series of articles describing a drug called patulin.<sup>4</sup> These described the first, very promising studies of its use against the common cold, in particular a controlled trial involving naval personnel.<sup>5</sup> The following week, however, a controlled trial involving army recruits, in which no beneficial effects were detected, was published as a letter to the editor of the *Lancet*.<sup>6</sup>

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**Figure 1** Article published in the *Sunday Express*, 31 October 1943. National Archives, FD1/3155

Within a year, a fuller report of studies in the army<sup>7</sup> and a multi-centre trial carried out under the aegis of the MRC<sup>8</sup> ended hopes that patulin would provide a way of alleviating the considerable personal and national burdens of suffering caused by the common cold. This article makes clear why we believe that the latter deserves wider recognition as the MRC's first well controlled, multicentre clinical trial, as reflected in the *International Journal of Epidemiology's* decision to reproduce the full text of the trial report in this issue of the journal.

## Patulin

Patulin is a metabolic product of the *Penicillium patulum* mould, which grows on apples. It is a colourless crystalline substance, soluble in water. JH Birkinshaw and others at the London School of Hygiene and Tropical Medicine provided considerable information on the chemical properties of the mould in one of the articles in the series published in the *Lancet* of 20 November 1943.<sup>9</sup> Patulin was originally supplied by Harold Raistrick, Professor of Biochemistry at the University of London, to WE Gye, director of the Imperial Cancer Research Fund's laboratories, for testing as a treatment for cancer. Whether or not Gye assessed if patulin had any role in the treatment of cancer, an experiment he performed on himself stimulated the interest and hopes for

patulin as a treatment for the common cold. At the time he had received the patulin, Gye had been stuck indoors for 2 days with a severe cold. He decided to douche his nasal passages with a solution of the drug. Despite some pain from the douching, his blocked up nose cleared within an hour. He repeated the douching twice more that day, using a solution that was a tenth of the strength of the original. The following morning, after what he described as his first night of undisturbed sleep for 3 days, his cold had gone and he returned to work.

Gye reported that several of his friends and colleagues had tried patulin towards the end of 1942, and judged it to have helped them recover from colds. Although he noted that these observations were uncontrolled and of 'no solid scientific value', they nevertheless led to the first controlled trial.<sup>5</sup> The added impetus of the war doubtless encouraged the need to find a successful treatment for such a condition. However, the impact of the war can also be seen in the desire to have proof of patulin's effectiveness before devoting resources to its production. The Directorate of Medical Supplies at the Ministry of Supplies expressed such concerns in November 1943, in correspondence with the MRC.<sup>3</sup>

## First formal studies

### The Navy trial

This first formal study was co-ordinated by Commander WA Hopkins, a surgeon commander in the Royal Navy. In presenting the rationale for his trial, Hopkins noted that the common cold was 'responsible for more absenteeism and loss of efficiency than any other disorder or group of disorders'.<sup>5</sup>

Hopkins' trial was carried out in two parts: the first was a controlled study, using both patulin and a control fluid; the second study had no concurrent controls, 14 people being given a supply of patulin for self-administration. In the controlled trial, volunteers recruited through a broadcast at a naval depot were allocated alternately to receive either a solution of patulin or the buffer solution alone. A sick berth attendant sprayed these into the nasal passages and nasopharynx. The patients all thought they were receiving the same, new treatment and, until the results had been assessed, efforts were made to keep everyone else involved in the trial blind to the identity of the solutions. The desirability of a placebo treatment appears to have been recognized as a way of controlling for the expectations of the patients and the people treating them, as well as providing a control group to show what would happen if the cold were left untreated. As Hopkins reminded readers: 'if a cold is treated energetically it will get well in 7 days, while if left to itself it will get well in a week'.<sup>5</sup>

In Hopkins' trial, cure was judged using self-reports of the patients and clinical signs. The trial involved three series of patients, studied in January, February and April 1943, respectively. The results were striking: 55 of the 95 patients given patulin recovered during the trial, compared with only 8 of the 85 patients in the control group. No explanation is offered of how this quite marked imbalance in the numbers of patients in the two groups could have arisen using 'alternation'. However, the report does note that in the third and final series studied:

To prevent the possibility of any bias on the part of those conducting the trials, until the results of treatment had been assessed, none of them knew which was the treated group and which the control.<sup>5</sup>

In the first and second series, the numbers of patients allocated to patulin and control were not compatible with strict alternation (54 versus 41, and 23 versus 26, respectively). In the third series, there was perfect balance in the number of patients in the two groups (18 patulin versus 18 control), but even in this series there were more cures in the patulin than in the control group (15 versus 4).

If a trial were to be reported today with such a marked difference in outcomes between the two groups, many readers would dispense with formal statistical testing. However, in the last of the series of articles in the *Lancet* published on 20 November 1943, Major Greenwood, Professor of Epidemiology and Vital Statistics at the University of London, did provide a statistical analysis of Hopkins' data, with acknowledgement of arithmetic help received from Dr WJ Martin.<sup>11</sup> Greenwood concluded that a difference as large as 55/95 versus 8/85 would arise about 3 times in 10 000 trials if there was truly no difference between the effects of patulin and control. He makes the added point that:

what the statistician has shown is *not* [his emphasis] that the odds are so and so many thousands to one in favour of the hypothesis that the antibacterial substance does cure, but only so and so many thousands to one against the chance that such results would emerge without *some* [his emphasis] differentiation between the groups.<sup>10</sup>

Of the 14 people with colds who were all given supplies of patulin in the second part of Hopkins' study, 10 reported a complete and rapid recovery. Hopkins also reported that, of 27 women in the Women's Royal Naval Service with colds who had been given patulin, 26 reported 'completely successful results'. In addition, Hopkins seems to have followed the example of Gye by using the patulin on himself, as well as providing it to at least two of his colleagues.<sup>5</sup>

### The Army trial

At the same time as Hopkins was preparing for the third series of patients in his controlled trial of naval personnel, Professor Raistrick made a supply of patulin available for trials in the army. These were sponsored by the Director of Pathology and the Consulting Physician at the War Office, and took place from March to October 1943. As mentioned above, the more disappointing findings were first reported briefly in a letter<sup>6</sup> the week after the excitement of Raistrick's series of articles.<sup>4</sup> Captain JM Stansfeld of the Royal Army Medical Corps and his colleagues published a full report of their trials the following year.<sup>7</sup>

In March 1943, two solutions labelled A and B were made available—one containing patulin, the other buffer solution alone. These were allocated alternately to 50 patients at an army training base, by dripping the solutions into the nose. Five of the 25 given patulin recovered during the trial, compared with none of the 25 patients in the control group. However, the investigators felt that further research was needed, and they undertook another trial, in the late summer and early autumn of 1943, at a different primary training wing. In this later trial, the patulin and control solutions were administered by spraying rather than dripping into the nose, in an attempt to make the study more like Hopkins' trial. The first trial ran from 7 to 29 August, using solutions labelled C and D. The second trial finished on 6 October and used a pair of solutions labelled F and G. Again, efforts were made to conceal the identity of the group allocation

from those administering and taking the solutions, and those assessing the outcomes.

A total of 130 patients took part in the trial. Problems with the follow-up of the first 19 patients recruited led to their exclusion from the analysis, from which a further 11 patients were omitted for other reasons. There is no indication of the distribution of these 30 patients between the allocated groups. One hundred patients remained: 50 in the patulin group and 50 in the control group. Seven of the former had recovered within 7 days, compared with 10 of the latter, a small difference, which was in the opposite direction (that is, favouring control) to that reported in Hopkins' trial of naval personnel and in the authors' earlier trial.

### The Medical Research Council Trial

Following on immediately after Stansfeld's report in the *Lancet* of 16 September 1944 was a report of a trial suggesting that patulin was very unlikely to be a cure for the common cold.<sup>8</sup>

In October 1943, before both the article in the *Sunday Express* of 31 October and the *Lancet* articles published the following month, the manufacturers of patulin, the Therapeutic Research Corporation, approached the MRC to explore whether the Council would be willing to conduct a trial on a larger scale. They were informed that this might be possible, but on condition that the MRC trial would be the only large-scale trial,<sup>11</sup> a condition accepted by the Therapeutic Research Corporation 'if assured that this would involve no delay'.<sup>12</sup>

The MRC accordingly set about establishing a committee to plan the trial. At its meeting on 19 November 1943, the Council approved the plans for the trial and the membership of the Patulin Clinical Trials Committee.<sup>13</sup> 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. Other members included the Chief Medical Officer, Professor Raistrick and Professor Greenwood (who was asked to provide statistical advice to the committee, although, as in Hopkins' trial, the mathematical work is credited to Dr WJ Martin).

The committee met on 25 and 29 November 1943 and approved a design similar to those used for the smaller trials reported above.

Patients would be treated alternately with the Patulin and the control solution and it was agreed that neither the doctor nor the nurse nor the patient should be aware whether patulin or control solution was being used.<sup>14</sup>

A brief form was to be completed for each patient, each of these forms having a serial number. The instructions for treatment allocation were very clear:

Patient will come to nurse having just seen doctor and bringing with him the counterfoil. Nurse must check the latter to see that name and clock number have been filled in. Nurse then takes bottle to be used for patient's treatment from Q, R, S or T group. *It is essential for the success of the trial that the patients be treated in order of the 'serial numbers' on the counterfoils, and that the solutions Q, R, S, and T should be used in strict rotation.* (emphasis in original).<sup>15</sup>

The design of the trial was also novel in testing how successful the attempt to blind the solutions might have been. A study of 29 medical students found that the patulin solution stung more than the control solution.<sup>16</sup> This led the Patulin Clinical Trials

Committee to consider using a control solution that would also sting, but this was not adopted.<sup>14</sup>

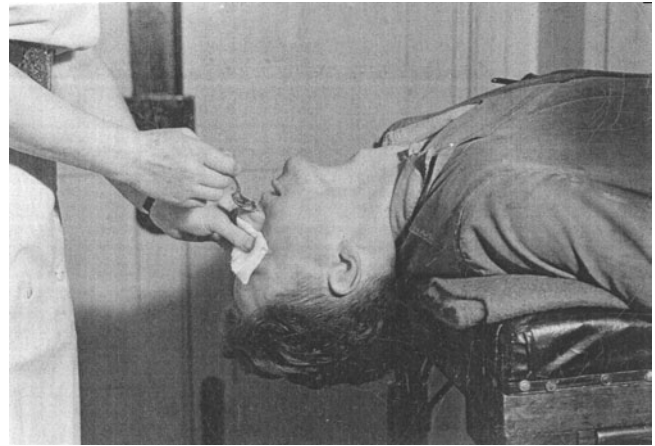
The main trial took place between 18 January and 11 April 1944 at three London units of the General Post Office (Savings Bank Dept, W14; Trunk and Tolls Section, EC4; and Parcels Section, EC1); four Royal Ordnance Factories (in Cardiff, Enfield, Nottingham, and Bishopton); and seven other factories (Rolls Royce at Glasgow, Crewe and Derby; Chloride Electrical Storage (Exide Works) in Manchester; Guest, Keen and Nettlefolds, in Birmingham; Vickers Armstrongs, Newcastle upon Tyne; Enfield Rolling Mills and Cable Works; and Briggs Motor Bodies, Dagenham). There were also studies in two schools, Haileybury College and Rugby School, where the solutions were administered as a spray. Although each centre was organized locally by the medical officer in charge, Joan Faulkner travelled to each centre to supervise the study. None of the centres recruited for the entire 3 months of the study, but there were times when more than one centre was recruiting.

Patients were recruited by advertising for volunteers at each location. This included posters and notices, but also broadcasts on factory radios. On 9 March 1944, for example, Dr Frank Sargent, Medical Officer at the Royal Ordnance Factory in Bishopton, Renfrewshire, broadcast the following message to the employees:

Are any of you suffering from a cold in the head? If so, don't waste it on your family and your friends but take it to the Surgery where they have a use for it. You must have heard of Patulin (lots of people are now asking for a small Patulin and a Pint in Refreshment houses!). Well, we have got Patulin in the Main Surgery and we want to try it on as many people as possible to find out whether it will cure a cold or not. This trial is one of the most important advances that have ever been made in medical practice and we want to make it as good as possible at Bishopton. But the Patulin is no good without the patient. We want hundreds of volunteers, and the more we have the merrier.<sup>17</sup>

Following an assessment by the medical officer to confirm that they really had a cold and not, for example, hay fever, 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 their head tilted back (Figure 2), a method that had been selected from among alternatives by assessing the extent of nasal mucosal anaesthesia after different approaches to instilling cocaine.<sup>8</sup> Patients were told to continue this 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. Recruitment to the trial ceased on 11 April 1944.

A flurry of activity was generated by a letter sent to the MRC the previous week by a chemist at one of the companies manufacturing the drug: his investigations had suggested that the citrate buffer solution used in the MRC trial may have had an adverse effect on the activity of patulin compared with the phosphate buffer used in previous trials. These doubts about the bioavailability of patulin led to further studies at the National



**Figure 2** Photograph illustrating administration of patulin, National Archives, FD1/3155

Institute of Medical Research. These provided reassurance to everyone's satisfaction that the recovery of patulin from citrate and phosphate buffer was 'comparable and satisfactory'.<sup>18</sup> The uncertainty had existed at the time of what turned out to be the last meeting of the Patulin Clinical Trials Committee on 4 May 1944, and this uncertainty had been communicated to Council. The minutes of the Council meeting the following month contained the following entry:

Received: a statement that the uncertainty as to the stability of the preparation used had now been removed (minute 90, 1944); and that the result of the clinical trials of patulin in the treatment of the common cold was therefore conclusively negative.<sup>19</sup>

Interest in the findings of the study extended to Parliament. 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'.<sup>20</sup>

Joan Faulkner sent a draft report to the chairman of the committee, Harold Himsworth, on 8 June 1944, and probably to the other members of the committee as well, because Professor Raistrick suggested some minor changes in wording in a letter to D'Arcy Hart.<sup>21</sup> Himsworth sent a copy of the agreed report to Edward Mellanby, Secretary of the MRC, on 28 June, and Philip D'Arcy Hart sent a copy to the *Lancet* the following day.

The report is a model of clarity and was published virtually unchanged in the *Lancet* 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. Seen in the context of the methodological evolution of controlled trials, the opening

paragraph in the section on dispensing is particularly important:

Previous experience has convinced us that, in a trial of this nature, it is of great importance that both the medical personnel and the patients be prevented from guessing which of the two treatments in genuine and which spurious. It had further been learnt that two solutions are not sufficient to prevent this. In this present trial, therefore, four solutions were used, two of which (R and T) contained patulin and two (Q and S) were simply solutions of the buffer salts used in dispensing patulin.<sup>8</sup>

Nearly 60 years later, D'Arcy Hart emphasized how important these steps to conceal the allocation schedule had been to them. He described how he, Joan Faulkner and his wife Ruth went initially to the Royal Ordnance Factory in Llanishen, Cardiff, to set up the practical procedures for the allocation scheme.

Everyone had thought we would use alternation, and we thought we were very clever in setting up a scheme with two patulin groups and two placebo groups using letters to designate each of the four groups, then using rotation to allocate people to the different groups. We thought we were doing something completely new. We wanted to muddle people up. In fact we succeeded in muddling ourselves up. We didn't always remember what the letters stood for. None of us was a statistician, but we felt that the patulin trial was the first decently controlled trial the MRC had done.<sup>22</sup>

A total of 1449 patients had been treated at the factories and Post Office units, but only 1348 were available for analyses because of problems such as doubtful diagnosis, non-adherence and absence from work in 101 cases (there is no information on how these cases were distributed among the four comparison groups). This left 668 who were treated with patulin and 680 who had received the control solution. The results of each centre were initially analysed separately, but, in the absence of any statistically significant differences among them, the findings from all the centres were combined. Data for only 49 patients were available from the two schools involved, and the results are not given in any detail.<sup>8</sup>

The Table below shows the overall results, as published in the *Lancet*:

	Percentage cured at			Percentage cured or improved at		
	24 hrs	48 hrs	1 week	24 hrs	48 hrs	1 week
Patulin	1.6	13	33	59	73	63
Control	1.2	13	37	64	77	69
Difference	0.4	0 ± 1.9	-4 ± 2.8	-5 ± 2.7	-4 ± 2.5	-6 ± 2.8

Results were also provided for the subgroups of patients who, at the time that they entered the trial, had had a cold for <3 days, or for 3 or more days. These analyses also failed to reveal any subgroup of patients (or outcome) that could confidently be regarded as having benefited from patulin. Two of the 12 comparisons statistically significantly favoured the control group at the one-week assessment, but these differences were deemed irrelevant. The end of the article reads, 'No evidence was found that patulin is effective in the treatment of the common cold'.<sup>8</sup>

## Some reactions

In a letter to D'Arcy Hart at the time the report was published, the chief medical officer at one of the participating factories observed:

It is to be regretted that the work had not produced more helpful results but I do agree that negative results of this kind are very important and I only wish they were more often published since I am sure that a lot of research work is done because other people have not thought it worthwhile to publish their results.<sup>23</sup>

But the fact that the study had found no evidence that patulin was effective did nothing to diminish enthusiasm for the drug in other quarters. A letter to D'Arcy Hart from a doctor at the Imperial Cancer Research Fund at Mill Hill, where Gye's personal anecdote had initiated the series of trials, contained the following request:

Would you please be so kind as to inform me how I may obtain Patulin for personal use? Naturally I am prepared to pay for it, even though it be worth its weight in gold. I shall require enough to last me the remainder of my life, with some over for those friends who beg me to let them have the opportunity of a trial in case they also benefit, as I have done.<sup>24</sup>

The Imperial Cancer Research Fund doctor was not alone in implicitly rejecting the results of the MRC trial. It is D'Arcy Hart's understanding that Professor Raistrick continued to take patulin for his colds for the rest of his life. In a (recorded) discussion we had with him in 2000, D'Arcy Hart observed that the outcome of the MRC trial was one of the two great disappointments of Raistrick's career—the other being his decision not to investigate the biochemistry of penicillin when it was first discovered. D'Arcy Hart's memory was confirmed the following year in a history of the London School of Hygiene and Tropical Medicine.<sup>25</sup> Philip D'Arcy Hart's memory is that there was 'no further interest' in the use of patulin for colds after the results of the MRC trial had been reported.<sup>26</sup>

Nevertheless, some people remained intrigued by the incompatibility between the results of Hopkins trial in the navy and the other trials. In his letter accepting the paper for publication in the *Lancet*, Dr E Clayton-Jones (20 July 1944) observed:

It's very odd, isn't it? What we shall want now is a quick bedside way of telling a naval cold from a military or civilian one. I must own that after the first novelty had worn off I noticed that there was no rush on the office bottle of patulin. As you say, the inquiry has done valuable service in preventing the stuff being put hastily on the market and as hastily withdrawn. We must persuade Prof. Major Greenwood to explain how such things can be.<sup>27</sup>

And a *BMJ* editorial entitled 'The end of patulin', published a few weeks after the *Lancet* report, concluded:

... to explain the conflicting results of the original and subsequent trials remains a problem which no one can positively solve on the basis of published information. There seems to be no further need to study patulin for its own sake, but if further study could throw any light on this discrepancy it might expunge a disturbing question-mark from our records of this form of investigation.<sup>28</sup>

## Discussion

Referring to the misleading article about patulin in the *Sunday Express* with which this article began, Arthur Mortimer of the Directorate of Medical Supplies in the Ministry of Supply wrote:

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.<sup>29</sup>

It is not surprising that the Ministry of Supply was involved from very early on in the patulin story. Because the nation's resources were so stretched during and after the war, it was obviously important to assess therapeutic claims carefully, an approach to value for money which has only recently been reinstated with the creation of organizations such as the Pharmaceutical Benefits Scheme in Australia and the National Institute of Clinical Excellence in England. The MRC patulin trial was designed, implemented, and reported commendably quickly, in contrast to the barriers facing people wishing to conduct controlled clinical trials today. The co-operation between the manufacturers and the MRC is also remarkable. What is markedly different today is that the pharmaceutical industry does not look to the public sector to evaluate the effects of its products, as it did with patulin, let alone acquiesce in disappointing findings, as it appears to have done in respect of the results of the MRC patulin trial.

The impressions left by the early case studies and case series describing the association of patulin administration and the course of colds were extremely promising. The dramatic result in the controlled trial conducted by Hopkins also seemed to point to a wonderful new treatment for a condition that was very debilitating at both a personal and national level. Hopkins' results suggested that patients given patulin were more than six times as likely to recover promptly than controls, with a level of statistical significance much lower than that reported by Major Greenwood ( $P < 0.00001$ ,  $<1$  in 10 000). It does not seem to have taken long for this dramatic result to be dismissed; within a week, the preliminary results of the army trials had cast doubt on patulin's effectiveness, and within a year the MRC's large, multicentre study had ended the early hopes for the drug.

The MRC patulin trial is an early example of a carefully conducted large trial that threw doubt on the validity of the results of a less carefully designed earlier trial. The imbalances between the numbers of patients in the comparison groups in Hopkins' trial suggest that allocation bias may well have been a problem, at least in the first two of the three phases of the trial. The confidence with which a useful effect could be rejected as a result of the MRC trial was an important achievement. More than a decade after it was reported, Professor Ronald Christie, of the Dunn Laboratories at St Bartholemew's Hospital, wrote to Harold Himsforth, chair of the Patulin Clinical Trials Committee (but by then Secretary of the MRC) with a request reflecting this lesson:

I will be very grateful indeed if you can let me have a reprint of the work you did on Patulin. I am anxious to have this since it is so good an example of the type of debunking which is so much needed in therapeutics.<sup>30</sup>

It is not simply because the trial clarified the effects of patulin that it deserves its place in history, however. We believe that

Philip D'Arcy Hart is entirely justified in claiming that the trial was 'the first decently controlled trial the MRC had done'. Until now, history has overlooked that he and Joan Faulkner—apparently entirely on their own initiative—not only identified the crucial importance of concealing the allocation schedule from clinicians and patients, but also devised and implemented a novel method for achieving this. Given that D'Arcy Hart went on to act as secretary for the MRC's trial of streptomycin for pulmonary tuberculosis, it is hardly surprising that careful steps were also taken to conceal the allocation schedule in that study, albeit with the undoubtedly important use of random numbers to help achieve this.

The streptomycin trial tested a treatment that proved effective, and became a key example for the conduct of comparisons of health care interventions. As Philip D'Arcy Hart has noted,<sup>31</sup> the patulin trial might be better known than it is had the drug proved beneficial. Indeed, had it become better known, rotating allocation to four groups might have become adopted more widely in placebo controlled trials, in the mistaken belief that allocation schedules could always be concealed effectively using this approach. Speculation apart, however, the patulin trial appears to be the first, rigorously designed and conducted multicentre trial done under the aegis of the MRC,<sup>32</sup> and it deserves wider recognition than it has received. Even Landsborough Thomson, who played a key brokering role in initiating plans for the trial, makes no mention of it in his two-volume history of the origins and work of the MRC.<sup>33</sup>

We could not have done the research reported in this article had we not had access to original documents held at the National Archives and been able to interview the centenarian Philip D'Arcy Hart. Some very important MRC documents relevant to the history of the evolution of clinical trials have already been mislaid. For example, attempts to trace Bradford Hill's 1933 memorandum commenting on a poorly controlled MRC trial of serum treatment for lobar pneumonia, which was examined by researchers at MRC Head Office in the 1980s, have been unsuccessful.<sup>34</sup> Because the past will often have lessons for the present and the future, more attention should be given to archiving potentially relevant material, including that being generated today.

In view of the key role played by Philip D'Arcy Hart in the design of the study, it seems appropriate to end by quoting the concluding paragraph of the covering letter he wrote to the editor of the *Lancet* when submitting the report of the study for publication:

I am afraid these negative results are rather dull but one can say that the public has been saved possibly from having this being put on the market! The greatest interest to the investigators has been the experience of carrying out a field investigation in industry in which controls were required—the administrative technique may serve as a model for future work of this kind which I suppose is likely to become frequent as new chemo-therapeutics appear.<sup>34</sup>

The patulin trial certainly did serve as a model for the MRC's trial of streptomycin for pulmonary tuberculosis, and many features of its design, conduct and reporting remain exemplary today, 60 years after it was published.

## Acknowledgements

The research reported in this paper is based on published material, unpublished documents in the National Archives and



**Figure 3** Philip and Ruth D'Arcy Hart, London, Summer 2003 (with permission)



**Figure 4** Contemporary photograph of Joan Faulkner (with permission from Richard Doll)

our interviews with Philip D'Arcy Hart over the past four years. We are very grateful to Philip and his wife Ruth for their patience during the meetings we have had with them, for their comments on earlier drafts of our paper and for permission to use a photograph of them taken soon after Philip's 103rd birthday (Figure 3). We were astonished that we were unable to

detect any inconsistencies between Philip's memories of events 60 years ago, as recounted to us, and contemporary documents lodged in the National Archive. We are also grateful to Richard Doll for comments on an earlier draft of this paper and for permission to reproduce a portrait of his wife, Joan Faulkner, taken during the 1940s (Figure 4).

#### KEY MESSAGES

- Promising findings in case reports and small controlled trials must be tested in sufficiently large, properly controlled trials.
- Claims that patulin was an effective treatment for the common cold were tested in a large, multicentre Medical Research Council (MRC) trial carried out during World War II.
- This trial was set up, conducted and reported with remarkable speed, to ensure that scarce resources would be used effectively.
- The non-adversarial collaboration between the manufacturers of the drug and the Medical Research Council to achieve this common purpose is commendable.
- Original documents and recorded interviews with those involved with research are important resources, and more attention should be given to archiving contemporary material.
- The MRC patulin trial served as an important model for the subsequent MRC trial of streptomycin for tuberculosis, and, in several respects, is an exemplar for controlled trials today.

A less detailed commentary on the 1944 MRC patulin trial has been published in the *James Lind Library*: Clarke M. The 1944 patulin trial of the British Medical Research Council: an

example of how concerted common purpose can get reliable answers to important questions very quickly. The James Lind Library ([www.jameslindlibrary.org](http://www.jameslindlibrary.org)).

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