

Commentary: MRC Patulin trial

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The MRC Patulin trial¹ was undertaken in 1943–1944 to investigate a proposed remedy for the common cold. Only a few clinical trials took place before the second world war and they often had serious defects of planning or execution. The Patulin trial, it is claimed, was the first to meet the rigorous requirements for a scientifically acceptable trial with concurrent controls, as set out originally by Bradford Hill^{2,3} in 1937. The findings were disappointing; the treatment had no detectable effect on the natural course of the disease. Not surprisingly, Patulin as a cold cure has long since been forgotten, but the huge step forward in methodology demonstrated in this trial was also not generally recognized or remembered until recently. Credit for the advance was given instead to the first MRC trial of streptomycin in pulmonary tuberculosis⁴ three years later in 1946–1947. In that trial streptomycin showed substantial but temporary benefits, and two major disadvantages, toxicity and the early emergence of drug resistance, were identified. The scientific contribution of the Patulin trial might have been overlooked partly because the findings were wholly negative. The streptomycin trial was justly praised for using an allocation procedure ‘based on random sampling numbers’, in place of the strict alternation of treatment and control in the Patulin trial. How do the effects of these two procedures differ?

The answer is—surprisingly little. Each is a valid and acceptable method of dividing a sequence of patients without bias into two (or more) series for treatment or control. In the present context, randomization involves converting a series of random sampling numbers into an ordered sequence of allocations which is fully random. Strict alternation (or rotation) is already an ordered sequence of allocations which is effectively, though not strictly, random. The design of the Patulin trial went a considerable way towards ensuring a strict adherence to the prescribed sequence by concealing the alternation in a strict rotation of the patients into four coded treatment series, as a separate procedure and in a separate room. In the streptomycin trial the prescribed sequence was incorporated in a series of sealed envelopes which were

opened individually, and only by the trial co-ordinator, following the admission of each patient.

D’Arcy Hart⁵ has recently suggested that randomization may completely replace systematic allocation procedures in future clinical trials. There are, however, many investigations, especially in trials of vaccination or other interventions, where a strictly applied systematic procedure (preferably a lot less obvious than alternation) would have practical advantages. D’Arcy Hart describes the step from a systematic to a random procedure as a ‘change in scientific approach’ but the near equivalence of the two approaches as scientific methods means that it would be fairer to describe the step as a valuable development in trial practice.

To sum up, randomization would be the method of choice in a situation where a potentially effective treatment for a serious disease is under study, emotions are involved and the number of patients may be limited, as in the streptomycin trial. With less serious conditions and larger numbers of patients it might be more practical to use a systematic procedure, as in the Patulin trial. In conclusion, each of the two trials is a model of its kind. The Patulin trial emerges from relative obscurity as the first rigorously controlled clinical trial in modern times. The streptomycin trial retains its place as the earliest randomized controlled clinical trial.

References

- 1 MRC Patulin Clinical Trials Committee. Clinical trials of Patulin in the common cold. *Lancet* 1944;**ii**:373–75. Reprinted *Int J Epidemiol* 2004; **33**:243–46.
- 2 Hill AB. Principles of medical statistics 1. The aim of the statistical method. *Lancet* 1937;**i**:41–43.
- 3 Hill AB. The principles of medical statistics. 1st edn. *Lancet* 1937.
- 4 MRC Streptomycin in Tuberculosis Trials Committee. Streptomycin treatment of pulmonary tuberculosis. *Br Med J* 1948;**ii**:769–83.
- 5 D’Arcy Hart P. A change in scientific approach: from alternation to randomised allocation in clinical trials in the 1940’s. *Br Med J* 1999; **319**:572–73.