The Royal Society of Medicine

Journal of the Royal Society of Medicine; 2017, Vol. 110(12) 501–502
DOI: 10.1177/0141076817743188

Cushny and Peebles, optical isomers and the birth of modern statistics

Stephen Senn
Competence Center for Methodology and Statistics, Luxembourg Institute of Health, Strassen L-1445, Luxembourg, UK
Corresponding author: Stephen Senn. Email: stephen.senn@lih.lu

Arthur Cushny was born in Fochabers, Scotland, in 1866 and died in Edinburgh in 1926. He had a varied career that included periods in Switzerland, Alsace, America and England. Between 1893 and 1905, he was Professor of Materia Medica and Therapeutics at the University of Michigan and one of his last pieces of research in that post was to collaborate with Alvin Peebles (1884–1917), an instructor at Michigan who had probably been Cushny's student.[1] By the time the paper was published, Cushny had already taken up a chair at University College London.

Arthur Cushny was very interested in optical isomerism, which he regarded as a key sign of living matter. He had previously carried out various researches in vitro and in vivo, using animals. The paper he co-authored with Alvin Peebles[1] describes some of these experiments in dogs and frogs. These are reported concisely in terms of conclusions, but numerical details are largely absent. The paper ends, however, with a quite different sort of experiment, a clinical trial reported in sufficient numerical detail to have been awarded a special place in the history of statistics.

The data reported by Cushny and Peebles were used by 'Student'[2] in his famous paper, 'The probable error of a mean', and subsequently reported by Fisher[3] in his book, *Statistical Methods for Research Workers*. These two works are classics of 20th-century statistics. However, as pointed out by Isidor Greenwald, a biochemist at Bellevue Hospital in New York,[4] 'Student' had actually made a transcription error in the column labels he applied to the data, which Fisher went on to replicate. In this comedy of errors, the experiment was thus interpreted incorrectly by the statisticians Student and Fisher and correctly by the physiologists Cushny and Peebles.[4]

The trial reported by Cushny and Peebles was actually carried out at the Michigan Asylum for the Insane at Kalamazoo by two young doctors, Rudolph Light (1877–1961) and George Gill Richards (1883–1950), under the supervision of the superintendent, William Milan Edwards (1855–1905).[5] Two isomers of hyoscine, the laevorotatory form and the racemate, were compared as hypnotics. Eleven patients in total were studied over several nights, with the hours of sleep they had being noted. Hyoscyamine was also studied, and there were nights without treatment to provide a 'no treatment' control. Thus, from a modern perspective, there were four 'treatments' (including absence of treatment).

The study can be regarded either as an example of a cross-over trial or a collection of n-of-1 trials. However, randomisation was not employed and instead a scheme of systematic alternation was used. Some patterns such as the following seem to have been applied

$$\text{H} - \text{H} - \text{H} - \text{R} - \text{R} - \text{R} - \text{L} - \text{L} - \text{L} - \text{HRLHRLHRL}$$

where H stands for hyoscyamine, L for laevorotatory hyoscine, R for racemic hyoscine and a hyphen, –, for no treatment.

The scheme Cushny and Peebles used can be criticised because, since randomisation was not employed, blinding was not possible and other biases might apply. In particular, treatment was confounded with period of treatment, so some bias due to trends might have occurred. (However, the combination of repeat administration and frequent alteration would probably minimise any such effect.) The absence of a washout period also means that carryover effects might have posed a problem. Nevertheless, the trial also has a number of interesting and valuable features:

1. The presence of a 'no treatment' control allows the sensitivity of the trial to be assessed. This is particularly useful, since, disappointingly, a difference

between the isomers could not be established. However, in their ability to induce sleep, both isomers of hyoscine were judged superior to no treatment and to hyoscyamine.
2. The data are reported in sufficient detail to allow statistical analysis by others. Indeed, the paper is superior to many more modern reports in this respect. Cushny and Peebles did not analyse the data themselves apart from reducing them to summary measures per treatment for each patient, and it is these measures that are reported. However, more modern statistical analysis confirms their conclusions.
3. The conduct of the trial has a feature of many modern trials in that it was conceived by 'laboratory'-based scientists but implemented by clinicians.
4. As is frequently the case in more modern trials, before being used on patients, the drugs had been tested on animals and then healthy volunteers. (Cushny and Peebles themselves tried the drugs first.)
5. Side effects as well as main effects were recorded and reported.
6. A within-patient design permitted more precise conclusions.
7. This precision was further improved by repeated administration of the treatments, which was desirable in view of the small number of participants.
8. L-hyoscine and D-hyoscine were not compared directly, but the L form was compared to the racemate, a mixture of the L and D forms, in order to infer the difference between L and D.
9. Finally, the interest in optical isomerism is a very modern concern, as optically pure treatments may have improved therapeutic ratios.

For all these reasons, the trial at Kalamazoo deserves its place in the history of clinical trials.

An earlier version of this article was published in 2003.

Declarations

Competing interests: None declared

Funding: None declared

Ethical approval: Not applicable

Guarantor: SS

Contributorship: Sole authorship

Acknowledgements: None

Provenance: Invited article from the James Lind Library.

References

1. Cushny AR and Peebles AR. The action of optical isomers. II. Hyoscines. *J Physiology* 1905; 32: 501–510.
2. Student. The probable error of a mean. *Biometrika* 1908; 6: 1–25.
3. Fisher RA. *Statistical Methods for Research Workers*. Edinburgh: Oliver and Boyd, 1925.
4. Senn SJ. A century of t tests. *Significance* 2008; 5: 37–39.
5. Senn SJ and Richardson W. The first t-test. *Stat Med* 1994; 13: 785–803.