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THE FIRST *t*-TEST

STEPHEN SENN AND WILLIAM RICHARDSON

Medicine and Clinical Development Department, CIBA, CH4002 Basle, Switzerland

SUMMARY

The data with which Student illustrated the application of his famous distribution are examined from a number of aspects. Central to the discussion is the within-patient clinical trial at Kalamazoo whose results were published by Cushny and Peebles and misquoted by Student and Fisher. This trial is discussed from historical, pharmacological and statistical perspectives. Student's and Fisher's analyses and a more modern analysis by Preece are considered as is Cushny's and Peebles's interpretation. Brief biographies of the five physicians involved in running the trial are presented.

INTRODUCTION

In 'The probable error of the mean', a paper which appeared in *Biometrika* in 1908,[1] Student not only derived and tabulated the *t*-distribution but presented the first practical example of its application: an illustration of what we should now call a 'matched pairs', 'paired samples' or 'correlated' *t*-test. Section IX of his paper showed how the tables which he had calculated could be applied to the analysis of a physiological experiment. As Student put it:

> *Illustration I.* As an instance of the kind of use which may be made of the tables, I take the following figures from a table by A. R. Cushny and A. R. Peebles in the *Journal of Physiology* for 1904, showing the different effects of the optical isomers of hyoscyamine hydrobromide in producing sleep. The sleep of ten patients was measured without hypnotic and after treatment (1) with D. hyoscyamine hydrobromide, (2) with L. hyoscyamine hydrobromide. The average number of hours' sleep gained by the use of the drug is tabulated below
>
> The conclusion arrived at was that in the usual dose 2 was, but 1 was not, of value as a soporific.

Student then went on to list the data, illustrate the analysis and present his conclusions. The data, as he listed them, are reproduced in Table I.

Thanks to Fisher,[2] Student's data were to become well known to many who had never read his paper, let alone the original article by Cushny and Peebles.[3] Fisher quoted Student's table in his extremely influential book *Statistical Methods for Research Workers*,[2] the work in which many statisticians and scientists between the two wars first encountered the *t*-test. Fisher's analysis differed from Student's in ways we shall discuss in due course, but his conclusions were identical to Student's, namely that the two optical isomers of hyoscyamine differed in their ability to induce sleep.

These conclusions were, however, wrong. On 31 December 1934, by which time *Statistical Methods for Research Workers* was in its fifth edition, Fisher received a letter from Isidor

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Table I. Data from the hyoscine trial at Kalamazoo as reported by Student[1]

Additional hours' sleep gained by the use of hyoscyamine hydrobromide

Patient	1 (dextro-)	2 (laevo-)	Difference (2 − 1)
1	+ 0·7	+ 1·9	+ 1·2
2	− 1·6	+ 0·8	+ 2·4
3	− 0·2	+ 1·1	+ 1·3
4	− 1·2	+ 0·1	+ 1·3
5	− 0·1	− 0·1	0
6	+ 3·4	+ 4·4	+ 1·0
7	+ 3·7	+ 5·5	+ 1·8
8	+ 0·8	+ 1·6	+ 0·8
9	+ 0	+ 4·6	+ 4·6
10	+ 2·0	+ 3·4	+ 1·4
Mean	+ 0·75	+ 2·33	+ 1·58
SD	1·70	1·90	1·17

Greenwald of the University and Bellevue Hospital Medical College, New York University, pointing out that the original Cushny and Peebles data were not correctly labelled in Student's paper and that, as a consequence, Fisher's and Student's interpretation of the experiment was quite wrong. Greenwald wrote:

> I was curious to see just what conclusion Cushny and Peebles had drawn . . . I found that they stated that the levo- and racemic (not dextro-) forms of hyoscine (not hyoscyamine) had about the same influence in inducing sleep . . . What 'Student' and you have done, apparently, is to misread their column 'L-hyoscyamine' as 'D-hyoscyamine' and their column 'L-hyoscine' as 'L-hyoscyamine' (Reference 4, p. 54)

Of course, these data had a purely illustrative value for Student and he had no particular interest in the analysis as such. He admitted the error in a letter to Fisher of 7 January 1935:

> . . . of course it doesn't really matter two straws . . . I have no recollection at all of having selected two columns out of a four column table and if I had not such a genius for making slips I should be inclined to think that I had taken the figures from a notice of the paper . . . I remember I had a good deal of difficulty in getting any figures to illustrate with but I haven't the faintest recollection of how I managed to run across Cushny and Peebles. (Reference 4, p. 54; see also Reference 5, p. 141)

The second of Student's lapses of memory is most curious because Arthur Cushny was the first Professor of Pharmacology and Materia Medica at University College, London, occupying that chair from 1905 to 1918. He was thus teaching and researching at University College during the period (September 1906 to spring 1907) in which Student studied there with Karl Pearson.[4] It is not implausible that Student knew Cushny. (An interesting coincidence is that Fisher was made Galton Professor of Eugenics in 1933 and so was working at Cushny's old address, University College, at the time of Greenwald's letter.) It is also possible (but this is mere speculation) that Student did not read the original Cushny and Peebles paper, but obtained the data directly from the authors or, indeed, 'from a notice of the paper', and that the mislabelling might not be his mistake. It is interesting to note that the date which Student gives for the paper is wrong. It was

not published in 1904 as he states but 1905.[6] Furthermore, Cushny himself, when he returned to the topic of the optical isomers of hyoscine several years later, did not cite his own paper correctly, listing it as 'Peebles and Cushny' (Reference 7, p. 61). In any case by 1935 there would have been little possibility of Student's clearing the matter up, had he wished to, as Cushny died in 1926.

Fisher replied to Isidor Greenwald on 10 January 1935 explaining that he would remove specific references to the drugs in future editions. He also claimed that Student had pointed out a further error to him: Student should have referred to hydrobromate and not hydrobromide. Student's letter of 7 January 1935 does not mention this, however, and presumably it was Fisher himself who spotted it.

In this article we review the paper by Cushny and Peebles,[3] discussing its background as well as its findings. In particular, we discuss the 'Cushny and Peebles data' from the pharmacological as well as the statistical point of view, quoting extensively. We also present biographical details of the scientists involved in obtaining these data.

Our justification for doing this is to make known to a statistical audience the work of an important pharmacologist: Arthur Cushny. The paper by Cushny and Peebles[3] has an interest which goes far beyond that of the use which Student and Fisher made of it. It provides an early example of a crossover trial in clinical research, and one of the earliest of all investigations in humans of differences in the pharmacological effect of optical isomers. Crossover trials and chirality (not to mention 'dirty' data!) are matters which will be recognized by those who work in drug development (as we do) as being of importance today.

Before we do so we comment briefly on the title of our paper. Student's analysis of the Cushny and Peebles data may, of course, not be his first application of the method. He is often represented as having developed the *t*-test because his work for Arthur Guinness and Company required him to use small samples. It may well be that he would not have had 'a good deal of difficulty in getting any figures to illustrate with' had he been able to use data from his own work. However, the same considerations which required W. S. Gosset to publish as 'Student' made it impossible to publish these data (Reference 4, p. 17). In any case, as is discussed below, Student's analysis does not exactly constitute a *t*-test as we know it today. Nevertheless, given a little licence, we feel one may justifiably describe Student's analysis of the Cushny and Peebles data as 'the first *t*-test'.

OPTICAL ISOMERS AND OTHER MATTERS

The terms used by the organic chemist to distinguish between different molecular species can be confusing to the non-chemist. Some of the more basic concepts in stereochemistry would therefore benefit from explanation to allow better understanding of the data which Student used in his paper.

In the early nineteenth century chemists recognized that structurally different molecules existed which were made up of exactly the same atoms in terms of their number and their identity. Such molecules were called structural isomers. The differences in the spatial arrangement of the atoms of structural isomers are easy to depict. Stereochemistry is concerned with isomeric relationships which require an appreciation of three-dimensional molecular structure for the differences between stereoisomers to be understood.[8] Stereoisomerism, therefore, transcends simple structural isomerism. Stereoisomers are different molecular species, each comprising the same atoms, in which the interconnections between constituent atoms are the same. This concept is perhaps best illustrated using the example employed by Student[1] himself, namely atropine. Atropine is a mixture of equal parts of two stereoisomers, D-hyoscyamine and L-hyoscyamine (Figure 1). Pharmacologists use the terms *racemate* and *racemic mixture* interchangeably to describe a mixture of equal proportions of a pair of enantiomers (see below) such as the mixture of D- and

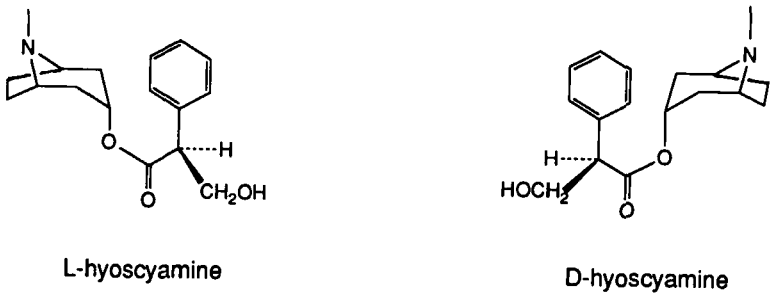

Figure 1. The two enantiomers of atropine: D-hyoscyamine and L-hyoscyamine. The asymmetric carbon atom is at the junction of the dashed bond and the bold triangular bond, and is joined to four different molecular subgroups. The bold triangular bond attempts to represent the three-dimensional depth of the molecule, placing the CH_2OH moiety in front of the rest of the molecule. No matter how L-hyoscyamine is rotated or otherwise manipulated, whilst preserving the integrity of the molecule, it cannot be made to appear identical to D-hyoscyamine

L-hyoscyamine which comprises atropine. Since the interconnections between the atoms in each of these stereoisomers are identical, they are identified as being structurally different by using the prefixes D- and L- by convention. A molecule which cannot be superimposed on its mirror image is described as being *chiral*. The word *chirality* describes the phenomenon and is derived from the Greek word for hand, *cheir*. This derivation is entirely appropriate; the left hand is the mirror image of the right and the one cannot be superimposed on the other. Chiral molecules generally have a centre of asymmetry: a central carbon atom bound to four different molecular subgroups. Chiral molecules are subclassified by their asymmetry. D- and L-hyoscyamine fall into the subcategory called *enantiomers* because they are mirror images of one another (Figure 1). Whilst it is not the case with hyoscyamine, it is not unusual for molecules to have more than one asymmetric carbon atom. A molecule with two asymmetric carbon atoms, for example, exists as two pairs of enantiomers. Collectively these are known as diastereomers.

An inherent property of chiral molecules is optical activity. When polarized light passes through a pure solution of a stereoisomer, it will be rotated in one direction or another to a varying degree. There are various conventions for expressing the direction of rotation. This paper will use only the notations D- (dextro-) to imply rotation of the plane of incident light to the right, L- (laevo-) to imply rotation to the left and R- (racemic) for the mixture. (Note that Cushny and Peebles mainly used lower-case l-, d- and r- prefixes in their paper. In the quoted passages we have changed the prefixes to upper case.)

THE TRIAL

There was, indeed, a paper comparing the action of the two optical isomers L-hyoscyamine and D-hyocyamine in the *Journal of Physiology* in 1904, and it did conclude that there was a difference in activity between the two, but the paper was by Cushny[9] alone and the experiments were carried out on animals (mainly frogs) and not on humans. Cushny compared the effect of L-hyoscyamine (somewhat confusingly referred to simply as hyoscyamine) with the racemic form, atropine, and later to D-hyoscyamine. His major conclusion was that some physiological responses are identical for L- and D- forms of a chiral drug whereas others vary according to which enantiomer is used.

Cushny had established the existence of a phenomenon which is the reason why chirality is an issue in drug development today. Where optical isomers exist, the properties of the enantiomers

may differ qualitatively or quantitatively in a number of ways. Both isomers of an enantiomeric pair may have identical actions, or one enantiomer may be active pharmacologically whilst the other has no detectable activity, or both enantiomers may be pharmacologically active but their effects may be different, or finally one enantiomer of a pair may be toxic whilst the other is not. Depending on which of these conditions apply to any given enantiomeric pair, a decision has to be made as to whether to develop an optically pure drug or to produce a racemate.[10] This is an important decision. Because the physicochemical properties of enantiomers, such as melting point, boiling point, solubility and so forth, are usually identical, production of an optically pure drug is technically very demanding and very costly.

Having studied one pair of optical isomers it was logical for Cushny to want to see if the results were more general by examining the effects of the related compound, hyoscine, which also exists as two enantiomers:

> The study of atropine and hyocyamine led naturally to that of laevorotatory and racemic hyoscine, and the fact that the presence of the dextrorotatory body in atropine lends it a more excitant action on the central nervous system than is possessed by hyoscyamine suggested that racemised hyoscine might have less hypnotic action than the laevorotatory base and this might explain the frequent failure of hyoscine to act in insomnia (Reference 3, p. 502).

To test this theory Cushny and Peebles performed various animal experiments, concluding:

> In these experiments no unquestionable evidence of a depressant action on the central nervous system was obtained, and in order to determine whether the natural base and the racemic form were equally available as hypnotics a number of trials of their usefulness for this purpose were made in the Michigan Asylum for Insane at Kalamazoo. The harmlessness of small doses of both alkaloids were first ascertained on ourselves, and then a number of tablets each containing 0·6 mg of L-hyoscine or R-hyoscine hydrobromate were used as hypnotics in the wards of Drs Richards and Light under the general supervision of Dr. W. M. Edwards. We are much indebted to these physicians for the results recorded by them. Instead of hyoscine, a certain number of tablets contained 0·6 mg of hyoscyamine hydrobromate, as its usefulness as a hypnotic has not yet been determined. In all, ten patients were treated with the tablets. (pp. 508–509).

We shall present what little we have managed to uncover about the background to this trial in the biographical section below, and in particular how it was that a professor of pharmacology at a university in London came to use data from an insane asylum in the USA, a connection which, on the face of it, seems to require more explanation than how Student 'managed to run across Cushny and Peebles'. For the moment, however, we return to Cushny's and Peebles's discussion of the trial at Kalamazoo:

> As a general rule a tablet was given on each alternate evening and the duration of sleep and other features were noted and compared with those of the intervening control night on which no hypnotic was given. Hyocyamine was thus used on three occasions, and then racemic hyoscine, and then laevohyoscine. Then a tablet was given each evening for a week or more, the different alkaloids following each other in succession. The results may be given shortly in tabular form, details being reserved for publication elsewhere. (Reference 3, p. 509)

This further publication does not appear to exist or, if it does, Cushny is not a co-author, since it is not listed among his papers and, although Cushny refers to his paper with Peebles subsequently,[7,11] he does not in these papers cite any other paper in connection with this trial. The data presented by Cushny and Peebles are reproduced here as Table II. This may be compared with Student's[1] version given as Table I, thus confirming Isidor Greenwald's claim. Note also that eleven patients were treated, not ten as Cushny and Peebles claimed, although the eleventh has far fewer recorded observations.

The details of the trial are not perfectly clear but evidently it was what we should now refer to as a crossover trial, or possibly, since each patient is given each treatment a number of times, a series of '*N* of 1' trials (see Reference 12, Chapter 7). If we use the symbol _ to stand for 'control night', H for hyoscyamine, R for R-hyoscine and L for L-hyoscine, a typical sequence seems to have been of the form

H_H_H_R_R_R_L_L_L_H R L H R L H R L

This would correspond to both the description and the number of observations for patients 1 and 2. If the final control night was dropped, the number of observations collected for patient 3 would arise. Omitting all observations in the series beyond the final control would produce the numbers obtained for patients 4 and 5, and omitting the final control also would produce the number of observations recorded for patient 7. The number of observations recorded for patients 8, 9 and 10 would be obtained if the basic sequence above were used and data were occasionally missing. Preece[6] supposes that a slightly different possible sequence may have been used starting with a control night rather than with hyoscyamine.

By modern standards the design is not perfect. Nowadays, we should more usually use a placebo to provide a control rather than simply omitting treatment. We should also usually balance the treatments for period to be able to eliminate efficiently any secular trends. It seems unlikely, however, that such a trend would severely affect the conclusions of this experiment, since the total length of the series is long compared with the average time difference between treatments. Where, however, period effects may be ignored altogether, we should now randomize the order of treatments subject to the restriction regarding the total number of each treatment each patient was to receive; and, even where it could not be ignored, we should allocate patients at random to the given sequences chosen. Some degree of randomization would be indispensable if we were to blind the treatments, as would nowadays usually be done. Another point is that it would be unusual in a modern crossover trial to have such variation in the number of observations obtained per patient.[6,12] Also the fact that more control observations were obtained than observations under active treatments might be appropriate if the main object were to compare each active treatment to control, but is not efficient if the main object is to compare L-hyoscine and R-hyoscine. (Note, however, that with repeated measures what constituted an 'optimal' design would itself depend on the relative importance of various components of variation.)

It would also be usual in a modern crossover to employ a wash-out period between treatments. In a case like this an intervening night in which no measurements were made might be employed. Preece[6] has also pointed out that the design does not allow efficient estimation and elimination of residual or carryover effects. It is, however, a matter of some controversy as to whether such elimination is ever possible (except, of course, by wash-out) unless rather simple and unrealistic forms of carryover apply.[12,13]

A modern clinical trial would also have much more attention paid to various details of conduct. In particular one wonders just how easy it was to establish the time for which patients slept. The definition of inclusion criteria would also form an important part of any modern-day protocol. On the whole it is noticeable in the trial at Kalamazoo that the patients have very little

Table II. Data from the hyoscine trial at Kalamazoo as reported by Cushny and Peebles[3]

Patient	Controls (no hypnotic)		0·6 mg L-hyoscyamine HBr			0·6 mg L-hyoscine HBr			0·6 mg R-hyoscine HBr		
	No. of observations	Average hours of sleep	No. of observations	Average hours of sleep	Increase over controls	No. of observations	Average hours of sleep	Increase over controls	No. of observations	Average hours of sleep	Increase over controls
1	9	0·6	6	1·3	0·7	6	2·5	1·9	6	2·1	1·5
2	9	3·0	6	1·4	− 1·6	6	3·8	0·8	6	4·4	1·4
3	8	4·7	6	4·5	− 0·2	6	5·8	1·1	6	4·7	0·0
4	9	5·5	3	4·3	− 1·2	3	5·6	0·1	3	4·8	− 0·7
5	9	6·2	3	6·1	− 0·1	3	6·1	− 0·1	3	6·7	0·5
6	8	3·2	4	6·6	3·4	3	7·6	4·4	3	8·3	5·1
7	8	2·5	3	6·2	3·7	3	8·0	5·5	3	8·2	5·7
8	7	2·8	6	3·6	0·8	6	4·4	1·6	5	4·3	1·5
9	8	1·1	5	1·1	0·0	6	5·7	4·6	5	5·8	4·7
10	9	2·9	5	4·9	2·0	5	6·3	3·4	6	6·4	3·5
11	—	—	2	6·3	—	2	6·8	—	2	7·3	—

sleep on control nights and presumably this corresponds to their usual pattern. However, patients 4 and 5 enjoyed an average of 5·5 and 6·2 hours respectively on control nights. It is possible that these patients usually slept fairly well, hence forming poor subjects for study, and might have been eliminated from the study by choice of appropriate inclusion criteria.

ANALYSES

We now consider various possible analyses of the Cushny and Peebles[3] data. Our discussion relies heavily on Preece's[6] detailed examination as well as on commentaries by Eisenhart,[14] Pearson[4] and Fisher Box.[15,16]

Cushny and Peebles themselves considered that the message from the data was self-evident. The only calculations they undertook appear to have been those underlying Table II, that is they reduced the original observations to arithmetic means by treatment and patient and took the useful step of eliminating between-patient variation by calculating the differences from control. This was apparently sufficient for their purposes, and indeed, having presented the table, the only further comment they give directly concerning the data is the one sentence 'From these results it is evident that hyoscyamine is of no value in the dose given as a hypnotic, while the laevorotatory and racemic forms of hyoscine have about the same influence in inducing sleep' (Reference 3, p. 509). Curiously, the further step of directly comparing the two forms of hyoscine by reducing the results to a difference does not seem to have occurred to them. This was in fact noted by Student, who wrote: 'But I take it the real point of the authors was that 2 is better than 1. This we must test by making a new series, subtracting 1 from 2' (Reference 1, p. 31). This difference in attitude towards using data from clinical trials, with the statistician stressing differences between treatments and the life scientist more prepared to consider results for individual treatments, is a distinction which is still commonly encountered today.[17] Note, however, that Student was more than just a statistician, having obtained a first-class degree in chemistry at Oxford in 1899 and being, through his own work at the Guinness brewery, a practising scientist.[4]

As Isidor Greenwald pointed out, what Student thought he was comparing here were the *dextro* (treatment 1) and *laevo* (treatment 2) forms of hyoscyamine hydrobromide, whereas what he was in fact comparing were the laevo enantiomers of hyoscyamine hydrobromate and *hyoscine*. We now consider this comparison.

First we may note that Student ignored the data from patient 11 which are not even reproduced in his table. In fact there was less reason for him to ignore these data than for Cushny and Peebles to do so. In their table they only formed differences from control and, since no control values were obtained for patient 11, were unable to calculate differences for this patient. Student, although he also analysed the original differences, differenced again and, since such further differencing eliminates the control values, making them irrelevant, could perfectly well have included the data from patient 11, using the treatment means to form the differences. (But he could not have compared the two treatments individually to control using patient 11, and in any case as we have noted above he may never have read the paper.) In our further discussions of these data we too shall ignore patient 11, simply noting, however, that it is *not* our general practice in analysing clinical trials to ignore data from individual patients.

Student calculated the mean and standard deviation s of the differences (2 − 1) for patients 1 to 10, obtaining values of 1·58 hours and 1·17 hours respectively. Note that Student calculated s using the divisor n not $n - 1$, where n is the sample size. Next, Student formed the ratio of the mean to the standard deviation, obtaining the value 1·35, a calculation which, in view of modern practice, needs some explanation. In Student's notation, he calculated the ratio $z = x/s$; where x is 'the distance of the mean of the sample' (Reference 1, p. 17), that is the difference between the

sample mean and the supposed population mean, the latter being 0 when testing equality of treatments. This is because, in Student's own words, in the paper 'The equation is determined of the curve representing the frequency distribution of a quantity z, which is obtained by dividing the distance between the mean of a sample and the mean of the population by the standard deviation of the sample' (p. 12).

The consequence of this is that z does not exactly have a Student's t-distribution as we now know it but is related to the t-statistic by [4,14,15]

$$z = t/\sqrt{(n-1)} \quad \text{or} \quad t = z\sqrt{(n-1)}, \tag{1}$$

so that the probability density function of z is

$$f(z) = \frac{\Gamma(n/2)\ (1+z^2)^{-n/2}}{\pi^{1/2}\Gamma\{(n-1)/2\}} \quad \text{for} \quad -\infty < z < \infty. \tag{2}$$

Student's probability table presents values of the integral of (2) from $-\infty$ to x, where x runs from 0·1 to 3·0 in intervals of 0·1 for values of n of 4, 5, 6, 7, 8, 9 and 10. (Had Student decided to include patient 11 in his analysis he would, therefore, have had to calculate a further column to his table.)

By modern standards, of course, this table is rather crude since by (1) the difference of 0·1 for z for $n = 10$ correspond to differences of 0·3 in t. Interpolating, Student finds 'From the table the probability is 0·9985, or the odds are about 666 to 1 that 2 is the better soporific', noting later 'Of course odds of this kind make it almost certain that 2 is the better soporific, and in practical life such a high probability is considered a certainty' (p. 31). Student is sometimes described as a Bayesian and statements such as this support the designation. Clearly Student calculated $0{\cdot}9985/(1 - 0{\cdot}9985) = 666$ and interpreted the result as odds in favour of one of the treatments. Student's probability calculation is remarkable for its accuracy since the correct figure to six places is 0·998584, although even this small difference in the probability changes the odds to 705 to 1.

Before leaving Student's treatment of the data it is worth noting one comment. Student observed that the standard deviation of the difference between the two 'soporifics' is less than either of the standard deviations of the difference to control (1·17 hours as opposed to 1·70 hours and 1·90 hours).[6] He remarked: 'The low value of the S.D. is probably due to the different drugs reacting similarly on the same patient, so that there is correlation between the results' (p. 31). Note that, since the values under treatment have themselves already been related to control, the pure between patient error is already eliminated. Furthermore, because both series of results are expressed as differences from the same control, a correlation between the two is induced. This particular correlation, which (given equal numbers of observations) might be expected to equal 0·5 cannot however be the explanation for the reduced variance. There must be a further source of correlation. Quite clearly the phenomenon which Student identified is a patient by treatment interaction, and this must constitute a further component of variation which is eliminated by comparing values taken under treatment. There are, however, two difficulties. As the table of Cushny and Peebles shows, more observations were obtained on control nights than on treatment nights. Other things being equal we should expect the difference between two treatments to have a higher variance than the difference between treatment and control. The fact that Student does not note this is further circumstantial support for the hypothesis that he had not read Cushny and Peebles.[3] The second difficulty is that partial elimination of a patient by treatment interaction in this way is only plausible if treatment 1 is partially effective. Treatment 1 is, however, L-hyoscyamine hydrobromate, judged by Cushny and Peebles (and later Greenwald!)

to be ineffective. Student himself considers that the effectiveness of the treatment (which of course he supposes to be D-hyoscyamine) is such that it is 'very likely that 1 gives an increase of sleep, but would occasion no surprise if the results were reversed by further experiments'.

As we have already noted, Fisher[2] used the data from Student's paper to illustrate the t-test in *Statistical Methods for Research Workers*. Fisher's notation differs from Student's in that he used the symbol n for the degrees of freedom and not the sample size (so that Fisher's n is 9 where Student's is 10). To calculate the sample variance s^2 he used the divisor 9 and divided further by 10 and took the square root to obtain an estimated standard error of 0·3890 hours and hence t as 1·58/0·3890 = 4·06 (Reference 18, p. 121). This is the usual method of calculation today, and the fact that it is so is a tribute to Fisher's influence. The result is simply three times the value obtained by Student, which agrees with equation (1) above.

It seems probable that Fisher decided to perform the calculations in this alternative way at least as early as 1922. A letter from Student to Fisher dated 5 May 1922 refers to the possibility of 'tabulating your integral', that is in Fisher's alternative form (Reference 4, p. 49). However, in a paper[19] which was received by the editors of the *Proceedings of the Cambridge Philosophical Society* on 16 July 1923, Fisher was still using notation and formulae which agreed with Student.[1] Fisher's paper of 1924 already showed most elements of his later usage in *Statistical Methods for Research Workers*, reserving n for degrees of freedom and defining s^2 as 'the best estimate from the sample of the true *variance*, σ^2', that is using the degrees of freedom as the divisor for the corrected sum of squares (Reference 20, p. 807). He also used the symbol t rather than z for Student's statistic, having

$$t = \frac{x\sqrt{n}}{\sqrt{S(x^2)}}.$$

Here $S(x^2)$ is the corrected sum of squares and x is to be understood to be any (independent) quantity such that $\text{var}(x) = E\{S(x^2)/n\}$. For the particular application which Student had in mind originally, one would thus substitute $(n+1)^{1/2}$ times the sample mean for x. By Fisher's extremely important paper of 1925, 'Application of "Student's" distribution' the revolution was complete and the calculation was performed in the usual modern way, the formula being expressed (Reference 21, p. 91) in terms of n', the sample size, as

$$t = (\bar{x} - m)\frac{\sqrt{n'}}{s}.$$

To return to Fisher's analysis of the Cushny and Peebles data, having calculated the t-statistic as 4·06 he noted that 'For $n = 9$ only one value in a hundred will exceed 3·250 by chance so that the difference between the results is clearly significant' (Reference 18, p. 122). The value of 3·25 is the value cutting off the top 0·5 per cent of the t-distribution, so that Fisher used what we should now call the two-tailed critical value at the 1 per cent level to establish that $p < 0{\cdot}01$.

Fisher also carried out a sign test on the data, conditioning on the nine non-zero values and noting: 'of the 9 values other than zero, however, all are positive, and it appears from the binomial distribution,

$$\left(\frac{1}{2} + \frac{1}{2}\right)^9,$$

that all will be of the same sign, by chance, only twice in 512 trials'. Rather confusingly, since for the t-test he had merely established that $p < 0{\cdot}01$ whereas for the sign test he obtained $p = 0{\cdot}004$, he then commended the former on the grounds that 'it is the more sensitive method when the actual values are available'.

Table III.

Source of variation	Degrees of freedom	Sums of squares	Mean square
Between patients	9	89·500	9·9444
Between treatments			
Between forms of hyoscine (X)	1	0·005	0·0005
Hyoscyamine versus hyoscine (Y)	1	16·5375	16·5375
Control versus others (Z)	1	24·3000	24·3000
Patients × treatments			
Patients × X	9	1·6445	0·1827
Patients × Y	9	9·7775	1·0864
Patients × Z	9	24·9200	2·7689
Total	39	166·6800	

Preece[6] made an extensive analysis of the data as recorded in Student[1] and also as recorded in Cushny and Peebles,[3] to which we refer the reader for details. For the ;latter he produced the analysis of variance shown in Table III. Preece (Reference 6, p. 193) concluded that there is a 'clear non-homogeneity of the interaction between patients and treatments: each of the main effect components X, Y, Z should be assessed by comparing it with the corresponding interaction component.' Clearly this is the same phenomenon of 'correlation between the results' to which Student[1] drew attention. We note, in passing, that most modern statisticians prefer to use degrees of freedom to chase period and carryover effects and that unlike Student (and Preece) they commonly ignore the problem of patient by treatment interaction.[22]

It is interesting to note, however, that Fisher himself, as a further hypothetical illustration, carried out an independent samples *t*-test on the Cushny and Peebles data as quoted by Student, writing: 'Let us suppose that the above figures . . . had been obtained using different patients for the two drugs; the experiment would have been less well controlled, and we should expect to obtain less certain results from the same number of observations, for it is *a priori* probable, and the above figures suggest, that personal variations in response to the drugs will be to some extent correlated' (Reference 2, p. 110). This statement survived to 1934 and the fifth edition (Reference 23, p. 122). For the sixth edition of 1936, in which Student's labels for the Cushny and Peebles data were removed, the word 'correlated' was changed to 'similar' (Reference 24, p. 130), perhaps because Fisher had realized, having now seen the Cushny and Peebles paper, that the data would in any case be correlated by virtue of being expressed as differences from control even if there were no differences between patients (see our comments above).

Fisher seems to be implying that it is legitimate to perform an independent analysis only if the data come from two independently obtained series. Later in the same chapter, however, using another example where the data may be matched in pairs, Fisher says that in such cases, 'if either method indicates a definitely significant difference, its testimony cannot be ignored' (Reference 2, p. 113). Student later criticized this: 'faced with this choice, I personally choose the method which is most likely to be profitable when designing the experiment rather than use Prof. Fisher's system of *a posteriori* choice which has always seemed to me to savour too much of "heads I win, tails you lose" (Reference 25, p. 206).

In the case of the Cushny and Peebles data, however, Fisher and Student agree, and, although Preece's orthogonal decomposition above does not correspond to Student's analysis (but see his paper for further details), his findings both justify the use of a matched pairs *t*-test for this example

and amply confirm Cushny and Peebles[3] conclusions: hyoscine is a more effective hypnotic than L-hyoscyamine and there is no evidence of any difference between racemic hyoscine and the single enantiomer, L-hyoscine. His analysis also confirms a further opinion of Cushny's whose lecture notes at Edinburgh,[26] under the section on atropine, contain a reference to hyoscine as follows: 'CNS activ. different – tends more to fatigue and drowsiness sleep – *good deal of variation in individuals*' (our italics).

THE TREATMENTS

To this day neither of the enantiomers of hyoscyamine which form atropine is considered to have useful hypnotic properties.[27] D-hyoscine is considered nowadays to have little activity of any sort.[28, 29]

The pharmacological actions of hyoscine and atropine are due to their ability to interfere with the activity of acetylcholine, a chemical transmitter which is widely distributed in the peripheral nervous system. The actions of these drugs on the eye are due to the same mechanism and their actions on the central nervous system are almost certainly mediated through this mechanism. The differences between the effects of atropine and hyoscine in man can be accounted for by differences in the degree of penetration to different sites within the body, and different affinities for various receptors.[27]

The pharmacology of these substances is extremely complex. The differences in the actions of atropine and hyoscine are usually a question of the degree of response elicited in the end-organ. The magnitude of the response also varies with the administered dose and the route of administration. In general, however, hyoscine has a greater effect on the central nervous system, causing more sedation and having greater anti-emetic properties than atropine. Compared with atropine, the action of hyoscine on peripheral nerve transmission is greater on the internal muscles of the eye (causing dilation of the pupil), and on sweat glands, salivary glands and the glands of the gut and airways (causing reduced secretion). Atropine, on the other hand, is more potent on the muscles of the gut, the bladder and the airways (causing relaxation), and on the heart (causing an increase in heart rate).

The time-course of action of these drugs varies depending on the end-organ response being studied, However, intravenously administered atropine has a half-life of elimination of 13–38 hours.[30] The fate of hyoscine in the body is similar to that of atropine[27] except that it is more completely metabolized, mainly by the liver. The lack of a wash-out period in the study may therefore have had an influence on the outcome. Both atropine and hyoscine are well absorbed orally. Only a proportion of the orally administered dose of both drugs reaches the general circulation intact, since the blood returning from the gut must first pass through the liver, where atropine and hyoscine are broken down before being distributed to their sites of action.

It is perhaps surprising that Cushny and Peebles[3] came to the conclusion that racemic hyoscine 0·6 mg was as effective a hypnotic as 0·6 mg of the single active enantiomer L-hyoscine, since the 0·3 mg of D-hyoscine in the racemic hyoscine should not have contributed to its effect. They even stated in their paper that the expected outcome would have been that L-hyoscine was a better hypnotic than racemic hyoscine. There are, however, plenty of reasons to suspect that the trial, as it was designed and conducted, would not have been sensitive enough to detect any difference in the hypnotic effects of racemic hyoscine and L-hyoscine. These have been discussed in some detail in the third part of this paper. In addition to these factors, the variability introduced by choosing the oral route to administer the drugs would have tended to reduce the sensitivity of the trial to detect differences between comparators. Another plausible explanation would be that the L-hyoscine employed in the experiment was not as optically pure as Cushny and Peebles[3] claimed it was. The

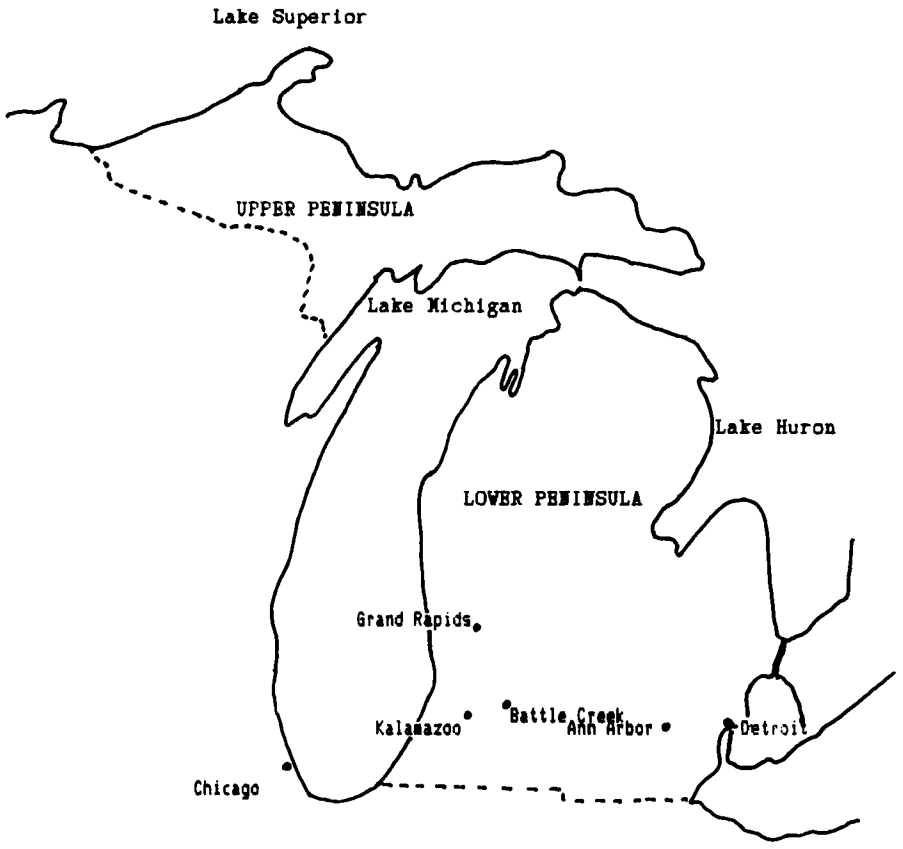

Figure 2. Map of Michigan showing location of Kalamazoo, Ann Arbor and other towns mentioned in the biographical section

L-hyoscine was said to be 98 per cent pure. If it were to have been even more contaminated with the D-enantiomer its effects would more closely have resembled those of the racemate. Finally, it is possible (if not plausible on the basis of what we know today) that Cushny and Peebles had reached the top of the dose–response curve. They did not prove that 0·6 mg L-hyoscine was more effective than 0·3 mg L-hyoscine.

THE SCIENTISTS

Introduction

Fisher (1890–1962) and now Student (1876–1937) have been made the subject of excellent biographies[16, 4] and there is in any case no need to present them to the statistical reader. We provide instead a brief biography of Cushny, and what little we have managed to discover concerning Peebles and the doctors at Kalamazoo: Edwards, Light and Richards. Before we do so, however, some brief explanation of the geography of Michigan is relevant (Figure 2).

Michigan is a state of the American Midwest in the area of the Great Lakes comprising two peninsulas: the smaller Upper Peninsula between Lakes Superior and Michigan and the larger

Lower Peninsula between Lakes Michigan and Huron, St Clair and Erie. Ann Arbor and Kalamazoo are two towns in the Lower Peninsula on the railway line between Detroit and Chicago (which is, however in Illinois). The distance from Ann Arbor to Kalamazoo is about 100 miles and the distance from Kalamazoo to Chicago a little more. There was a regular rail service between Detroit and Chicago by 1905, the railway link being opened in 1852. Battle Creek is a town about 25 miles east of Kalamazoo. Grand Rapids is a town 50 miles to the north of Kalamazoo.

Cushny

Arthur Cushny was born at Fochabers in Morayshire on 6 March 1866 as the fourth son of the Reverend John Cushny and his wife Catherine Ogilvie Brown, of the manse Speyside, and died in Edinburgh on 25 February 1926 (some sources state 24 February but this is incorrect) of a cerebral haemorrhage. Although his life began and closed in Scotland, and his education was also Scottish, at Fochabers Academy, the University of Aberdeen (MA 1886) and its medical school, Marischal College (Bachelor of Medicine and Master of Surgery 1889), his career in pharmacology included periods in Switzerland, Alsace, the USA and London before it finally brought him back to Scotland as Professor of Materia Medica at Edinburgh.[31]

Cushny's first position was in the physiological laboratory of Hugo Kronecker at Bern, from October 1889 to November 1890,[32] after which he went to work with Schmiedeberg in Strasbourg, 'then the most famous centre of pharmacological teaching and research in Europe' (Reference 33, p. xix). In 1893 when Abel, himself a former student of Schmiedeberg, moved to Johns Hopkins, he persuaded Cushny to take up the chair of Materia Medica and Therapeutics at the University of Michigan, Ann Arbor, which he had vacated. 'And so the young Aberdonian of twenty-seven who was later to attain an almost unrivalled position in physiological pharmacology came to this country and gave it twelve fruitful years full of inspiration to others' (Reference 34, p. 268). At Ann Arbor, Cushny did important work on the action of digitalis on the heart and also on urinary secretion, topics that were to continue to retain his interest. His extremely influential *A Textbook of Pharmacology and Therapeutics* appeared in 1899 and at the time of his death had run to eight editions. Dale says of it: 'it may safely be claimed for Cushny's great work that it was the first textbook of the subject in any language to consider and to meet the needs of the student and scientific physician alike' (Reference 33, p. xxiii).

Shortly after moving to Ann Arbor, Cushny married Sarah Fairbank, an Englishwoman whom he had met in Strasbourg, They had one daughter, Helen, born in 1898. Her biographical memoir[35] is a moving account of her father's life.

On 21 March 1905 Cushny set sail from New York with his family on the *SS Cedric* for Liverpool to take up a post as the first professor of pharmacology at University College, London. He had already begun his work on the biological effects of optical isomers at Ann Arbor, however, and this presumably explains why, despite the fact that Cushny's address in Cushny and Peebles[3] was given as University College, data were quoted from Kalamazoo. According to Dale (Reference 33, p. xx) Cushny had early determined 'to seek opportunity for combining laboratory research with clinical work in a hospital and consulting practice'. Clearly, the Michigan Asylum provided such an opportunity.

Cushny was elected to fellowship of the Royal Society on 2 May 1907 (Dale, who wrote the obituary of Cushny for the Society, gives the date as 1906 but this is incorrect[33]). He was then 41 years old and it is interesting to note that when Fisher was elected to the Royal Society in 1929 he was roughly the same age (39). Cushny seems to have been extremely active administratively, establishing the New Institute of Pharmacology at University College[36] and serving on the

Proprietary Drugs Committee (1906), The Royal Commission on Whisky and other Potable Spirits (1908) and the Central Control Board (Liquor Traffic).[37,38] Thus, like Student, but from a different viewpoint, he too had an interest in alcohol! Cushny's fellow professor, Karl Pearson, was also, through his statistical researches, involved in controversy over alcohol.

During the Great War, Cushny's Institute of Pharmacology housed Lt. Col. E. F. Harrison's Anti-Gas Department, which carried out important war work,[39] and Cushny himself served on the Poison Gas Committee at the War Office and later the Antigas Committee.[35] He continued his researches into the effects of optical isomers. In a letter to Abel he wrote: 'Optical activity interests me very much. It is the one sign of living matter that we have, it seems to me, but it is still so obscure physically that not much is to be done with it'.[40]

In 1918 Cushny moved to a chair at Edinburgh where, in keeping with his reputation as a sceptic in matters pharmacological, he revolutionized the syllabus. 'Gone was the host of time-honoured drugs whose only qualification was founded on a hazy empiricism; and their place was taken by a comparatively few substances of their number which were well tested in the laboratory, and whose therapeutic action could be accurately foretold' (Reference 41, p. 202). Apparently the revolution was welcomed by the students who also appreciated his open attitude: 'Professor Cushny himself would have been the first to welcome any disproof founded on the experimental method' (p. 202).

In 1925 he was again in the States receiving an honorary degree from the University of Michigan and delivering the Dohme memorial lectures at Johns Hopkins, the topic of his lectures being optical isomers.[28]

In his many travels Cushny seems to have retained 'something of a Scotsman's hunger for the air of his native land' (Reference 33, p. xxvi). He was able to establish himself at Craigmillar near Edinburgh in a fine country residence, Peffermill House (the Dumbiedykes of the *Heart of Midlothian*), where his 'home life was one of serene happiness and charming hospitality to his students and colleagues'. He did not have many years left to him, however, and 'the blow fell suddenly, and he passed from the fullness of his powers into the final sleep' (Reference 33, p. xxvii). As did his daughter in her biographical memoir, we give the final word to *The student*:

> Long after doses and actions have faded from the memory will there remain in the mind the vision of a true scientist . . . of one who founded the modern science of Pharmacology, and filled his students with his own enthusiasm . . . We, too, have our giants, and in the days to come we will look back upon Cushny as one of the greatest of them all (Reference 41, p. 204)

In addition to the sources we have cited, Cushny's time at Michigan is covered in Shaw,[42] and an extremely thorough (and critical) evaluation of his role in the development of the specific receptor theory of pharmacological action has been made by Parascandola.[43] The further primary material which we have consulted will be found in the special collections of the University of Edinburgh Library and in the Contemporary Medical Archives Centre of the Wellcome Institute for the History of Medicine (183 Euston Road, London NW1 2BP, U.K.).

Peebles

Alvin Roy Peebles was born in Battle Creek, Michigan in 1884 and attended the Michigan High School at Grand Rapids. He studied Medicine at Ann Arbor, where presumably Cushny was one of his teachers, graduating MD in 1906.[44] He then took a post graduate course at Johns Hopkins (with Abel perhaps?), returning to Michigan as an instructor.[45] He was licensed as a medical practitioner in the state of Colorado in 1908 and became an instructor at the Medical University

of Colorado at Boulder.[44] He married Miss A. R. Elizabeth Barrett in 1910. The couple moved to Europe where he undertook research but we do not know where. They had a daughter, Sally.[45, 46] He was subsequently a professor of preventive and experimental medicine and director of the clinical laboratories at the University of Colorado. He died on 22 October 1917 aged 33.[44]

Edwards

William Milan Edwards was born in Peru, Indiana in 1855[47] and, having trained for a while as a teacher, entered the Department of Medicine and Surgery in the University of Michigan in 1881, graduating in 1884. He started work at the Michigan Asylum for the Insane (now the Kalamazoo Regional Psychiatric Hospital) on 1 May of that year and was made superintendent on 1 June 1891.[48]

He appears to have been a man of great energy with a considerable interest in organizational matters ranging from the heating of the asylum to the organization of a 'colony' system of caring for the patients. By 1900 he was also a non-resident lecturer in the Medical Department of Ann Arbor and would, therefore, have had ample opportunity to meet Cushny.

Edwards married Emma A. Merrit in 1897. Their marriage was marked by tragedy as their only son died aged 3 in 1902 and Edwards himself died on 11 April 1905, only three weeks after Cushny's departure for Britain.

Light

S. Rudolph Light was born on 2 March 1877 in Lebanon, Pennsylvania as the seventh of eight children. While still at school he determined to be a dentist and worked for seven years as assistant to a dentist to save money for his education. However, just as he was about to take up his studies he changed his mind and enrolled in the medical school at the University of Michigan in 1899.[49] Apparently Cushny was one of his teachers.[50] He continued to work to support himself while studying and discontinued his studies for a year in order to set up a laundry in Dayton to secure funds.

He graduated in 1904 and started work straight away as a resident physician at the Kalamazoo State Hospital (that is, the asylum). Cushny and Peebles refer to both Edwards and Light, so that the study must have been undertaken between Light's arrival in 1904 and Edwards's death on 11 April 1905. The likeliest time, perhaps, would then be the middle or perhaps second half of 1904 but possibly even early 1905. (See note on Richards below.)

Light stayed at the hospital for three years, joining the Upjohn Company on 1 October 1907. His subsequent career was an extremely successful combination of business and medicine. He was made president of the American Manufacturers of Medical Products in 1920 and was appointed to the board of Upjohn in 1937. He had many other business interests and was successful enough to be able to set up a trust endowed with $1.5 million for Kalamazoo College scholars and another of $350,000 for a surgical research laboratory at Vanderbilt University. It is tempting to speculate that his early exposure to the scientific value of the controlled clinical trial in investigating pharmaceuticals was what launched him on his successful career in drug development!

He had a keen interest in aviation and was a friend of the Wright brothers. He was also at one time or another acting president of the American National Bank (during World War II), a director of the Federal Home Loan Bank and mayor of Kalamazoo.

He married Winifred Upjohn Smith on 25 June 1908. Both of their sons became prominent members of the medical profession. S. Rudolph Light died in January 1961.

Richards

We have not established the identity of Richards with certainty. The Kalamazoo directory lists a G. G. Richards as resident in the town in 1905 (but not 1904 or 1906), and this makes it plausible that he is George Gill Richards, born in Mendon, Utah on 5 September 1883.

George Gill Richards studied at the University of Utah 1898–1902 and at the University of Chicago 1903–1904. He graduated MD at New York University and Bellevue Hospital in 1906. (Isidor Greenwald's address!) where he was also an intern. His dates of birth and graduation are thus almost identical to those of Peebles. It is conceivable that his studies at Chicago were followed by a period at Kalamazoo, and if so this would bring him to the hospital at the right time to be involved in the hyoscine trial. Residency in Kalamazoo from mid 1904 to mid 1905 might well be consistent with only appearing in the 1905 directory.

His career included two spells in Vienna and work at the Utah Valley Hospital, in Provo. From 1942 until his death on 20 April 1950 he was clinical professor of internal medicine at the University of Utah.[51]

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