‘Controlled trials before Archie Cochrane’

Iain Chalmers
Editor, James Lind Library

‘The effectiveness of interventions for addictions: The Cochrane Drugs and Alcohol Group Contribution’
Roma, 24 October 2008
I became desperate. I was severely jaundiced and had pitting oedema above the knees. I argued in vain with the Germans. I decided that something must be done, and that I was the only one who could do it. I had a vague memory of the phrase “wet beri-beri,” so I decided to see if I could show that the oedema was due to a vitamin deficiency. That night I bought some yeast on the black market and the next morning I recruited 20 young prisoners. There seemed little wrong with them except emaciation above the waist and pitting oedema to above the knees. I gave them a short talk about my medical hero James Lind and they agreed to cooperate in an experiment. I cleared two wards. I numbered the 20 prisoners off: odd numbers to one ward and evens to the other. Each man in one ward received two spoonfuls of yeast daily. The others got one tablet of vitamin C from my “iron” reserve.
James Lind (1716-1794)
HMS Salisbury
A TREATISE
OF THE
SCURVY.
IN THREE PARTS.

An inquiry into the Nature, Causes, and Cure, of that Disease.

Together with
A Critical and Chronological View of what has been published on the subject.

By JAMES LIND, M. D.
Fellow of the Royal College of Physicians in Edinburgh.

EDINBURGH:
Printed by Sand, Murray, and Cochran
For A. Kinsale & A. Donaldson,
MDCCCIII.
TRAITÉ
DU
SCORBUT,
DIVISÉ EN TROIS PARTIES.
CONTENANT
Des recherches sur la nature, les causes
& la curaition de cette Maladie.

Avec un Tableau chronologique & critique de
tout ce qui a paru sur ce sujet.

Traduit de l'Anglois de M. Laxo, D. M. Membre
du Collège Royal de Médecine d'Édimbourg.

Auprès en a joint la Traduction du Traité du Scorbut
de Boemarave, commencé par M. Van Swieten.

TOME PREMIER.

A PARIS,
Chez Gavez, Libraire, rue Saint Severin;
chez Armes de Dombes.

M. DCC. LVI.
Avec Approbation & Privilège du Roy.
“....I took twelve patients in the scurvy... Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of their knees. They lay together in one place, being a proper apartment for the sick in the fore-hold; and had one diet common to all.”
Lind allocated two sailors with scurvy to each of:

“a quart of cyder a day”
“twenty-five gutts of elixir vitriol three times a-day”
“two spoonfuls of vinegar three times a-day”
“a course of sea water… half a pint every day”
“two oranges and one lemon every day”
“the bigness of a nutmeg three times a day”
“The most sudden and visible good effects were perceived from the use of oranges and lemons.”
Treatments with dramatic effects don’t need carefully controlled trials
Case 25. Edwin Smith Surgical Papyrus (c 2000 BCE)
“If you examine a man having a dislocation in his mandible and his mouth does not close for him, you then place your thumb on the back of the two rami of the mandible inside his mouth, your two groups of fingers under his chin, you cause the two mandibles to fall so they lie in their correct place!”
Recognising the need for comparisons
Abu Bakr Muhammad ibn Zakariyya al-Razi
(865-925 CE; 251-313 AH)
Kitab al-Hawi fi al-tibb
[The comprehensive book of medicine].
“So when you see these symptoms, then proceed with bloodletting. For I once saved one group [of patients] by it, while I intentionally neglected [to bleed] another group. By doing that, I wished to reach a conclusion.”
Recognising the need to compare like with like
Francesco Petrarca (1364). Letter to Boccaccio, Rerum Senilium V.3
Francesco Petrarca
(1304-1374)

Giovanni Boccaccio
(1313-1375)
"I solemnly affirm and believe, if a hundred or a thousand men of the same age, same temperament and habits, together with the same surroundings, were attacked at the same time by the same disease, that if one half followed the prescriptions of the doctors of the variety of those practising at the present day, and that the other half took no medicine but relied on Nature's instincts, I have no doubt as to which half would escape."
Leonardo Fioravanti (1517-1588)
A u. d'Aprile, 1573,

che il Prothofisico Boldone, et l'Almutio
s'informi del supp. et uferescano, al quale si
concede che possa fare le sue difese in quiete,

Vescovano
‘...that there be consigned to me alone twenty or twenty-five sick people with diverse ailments, and an equal number with the same infirmities to all the physicians of Milan, and if I don't cure mine faster and better than they do theirs, I am willing to be banished forever from this city....'
Using alternation, rotation and random allocation to ensure fair treatment comparisons
Johannes Baptista Van Helmont
(1579-1644)
ORIATRIKE
OR, Phylick Refined.
The common ERRORS therein
REFUTED,
And the whole ART
Reformed & Rectified:
BEING
A New Rise and Progress of PHILOSOPHY
and MEDICINE, for the Destruction of
Diseases and Prolongation of Life.

Written
By that most Learned, Famous, Profound, and Acute Philosopher, and Chymical Phystitian,
John Baptista Van Helmont,
Treasur or Governor, in Medicines, Reprobates, Oamor, Pellagre, &c.
And now faithfully rendered into English, in tendency to a common good, and
the increase of true Sciences: By
J. C. Sometime of M. H. Oxon.

Job 14:4. There is a Spirit in Man, and the Inspiration of the Almighty giveth
Understanding.
Pro Bona. I. Wisdom dwells with Prudence, and fond out knowledge of witty Inventions.
Altemanum eam sem contemptu co ephi, uraeon sapientia sapientem, ut Divinitus
Magistrum; utamur de rebus Naturae subjctis, que tam reperierunt sunt, quam
proprietas Alterius, &c.

LONDON,
Printed for Ludovici Lloyd, and are to be sold at his Shop next the Castle in
Cordwalk, 1662.
“Let us take out of the Hospitals, out of the Camps, or from elsewhere, 200, or 500 poor People, that have Fevers, Pleurisies, etc. Let us divide them in halfes, let us cast lots, that one half of them may fall to my share and the other to yours; I will cure them without bloodletting and sensible evacuation; but do you do as ye know......we shall see how many Funerals both of us shall have.”
Dissertatio medica
inauguralis
De synocho castrensi;
quae,
annuente summo numeri,
ex auctoritate reverendae aedaeum vini,
d. georgii baird, ss. t. p.
academiae edinburgensis prefecta;
sequent
amplissimi senatus academicorum consensu, et
nobilissimae facultatis medicae decreto;
pro gradu doctoris,
ademque in medicina honoribus ac privilegiis,
bite et longius consequendis;
exhibitum examinis sui subjicit
alexander hamilton,
status,
ad exercitum britannicum
chirurgus.

...
“It had been so arranged, that this number (366) was admitted, alternately, in such a manner that each of us had one third of the whole. The sick were indiscriminately received, and were attended as nearly as possible with the same care and accommodated with the same comforts.

“Neither Mr. Anderson nor I ever once employed the lancet. He lost two, I four cases; whilst out of the other third [treated with bloodletting by the third surgeon] thirty five patients died.”
Comparing like with like and controlling observer bias by using placebos
Die homöopathischen Kochsalzversuche zu Nürnberg.
Von einer Gesellschaft wahrheitsliebender Männer veröffentlicht durch Dr. George Löhner, Redakteur der „Allgemeine Zeitung v. u. f. Bayern.“

Als Anhang: Ein Beispiel homöopathischer Heilkunst.

Nürnberg im März 1835.
Löhner G, on behalf of a Society of truth-loving men, 1835.
Die Homoööopathischen Kochsalzversuche zu Nürnberg.
[The homeopathic salt trials in Nuremberg].
“100 vials, 50 for filling with the potentiation, 50 for filling with pure distilled snow water, are labelled consecutively by Dr. Löhner with the numbers 1 – 100, then mixed well among each other and placed, 50 per table, on two tables.”

“Those on the table at the right are filled with the potentiation, those on the table at the left are filled with pure distilled snow water.”
10
“Dr. Löhner enters the number of each bottle, indicating its contents, in a list, seals the latter and hands it over to the committee, the members of which also affix their seals thereto."

11
“The filled bottles are then brought to the large table in the middle, are once more mixed among each other and thereupon submitted to the committee for the purpose of distribution.”
Recognising the need for large numbers
Recognising the dangers of false positive inferences
Louis-Dominique-Jules Gavarret
(1809-1890)
PRINCIPES GÉNÉRAUX
DE
STATISTIQUE MÉDICALE
OU
DÉVELOPPEMENT DES RÈGLES QUI DOIVENT PRÉSIDER
À SON EMPLOI.
Par Jules Cavarret,
ANCien ÉLÉVE DE L'ÉCOLE POLYTECHNIQUE.

Plus les yeux ont vu, plus l'esprit voit grand.
Zimmermann, Traité de l'Expérience, etc.

PARIS
BECHET JEUNE ET LABÉ,
LIBRAIRES DE LA FACULTÉ DE MÉDECINE DE PARIS,
4, PLACE DE L'ESCALAIS DE MÉDICINE,
1840
The principles of the law of large numbers are strictly applicable to therapeutic research and they alone can furnish the solution of these two important problems.
To be able to decide in favour of one treatment method over another, it is not enough for the method to yield better results; the difference found must also exceed a certain limit, the extent of which is a function of the number of observations.
Recognising the dangers of false negative inferences
Thomas Graham Balfour
(1813-1891)
“There were 151 boys of whom I had tolerably satisfactory evidence that they had not had scarlatina; I divided them in two sections, taking them alternately from the list, to prevent the imputation of selection.

To the first section (76) I gave belladonna; to the second (75) I gave none; the result was that two in each section were attacked by the disease....”
“...The numbers are too small to justify deductions as to the prophylactic power of belladonna, but the observation is good, because it shows how apt we are to be misled by imperfect observation.

Had I given the remedy to all the boys, I should probably have attributed to it the cessation of the epidemic".
Assessing the likelihood that observed differences can be explained by chance
THE SERUM TREATMENT AND ITS EVALUATION IN LOBAR PNEUMONIA *

JESSE G. M. BULLOWA

Clinical Professor of Medicine, New York University

Delivered November 2, 1928, in the Friday afternoon lecture series of The New York Academy of Medicine
Table 8.—Deaths per Hundred Patients, (Deaths Within Twenty-Four Hours of Admission Excluded)

<table>
<thead>
<tr>
<th>Type</th>
<th>(a) With Serum</th>
<th>(b) Without Serum</th>
<th>Ratio of Difference in Case Fatality to Its Error</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases Deaths</td>
<td>Deaths per 100</td>
<td>Cases Deaths</td>
</tr>
<tr>
<td>I</td>
<td>25</td>
<td>10</td>
<td>33</td>
</tr>
<tr>
<td>II</td>
<td>26</td>
<td>6</td>
<td>38</td>
</tr>
<tr>
<td>III</td>
<td>24</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>IV</td>
<td>54</td>
<td>7</td>
<td>33</td>
</tr>
</tbody>
</table>

Without going into technical details, I may explain that the relative spread or flatness of the curve is measured by what is called the standard error of the measurements, which is to the probable error as 3 to 2. In order that the difference between measurements in two separate materials shall be recognizable as definitely significant, the distance between the peaks of the two curves must satisfy a certain statistical test; namely, that the difference between the average measurements in the two cases shall be at least equal to twice the “standard error” of that difference.
When were controlled clinical trials first used in Italy?
Febrile patients yielding positive blood findings were assigned alternately to the atebrin and to the atebrin-plasmoquine group in the order of their arrival, irrespective of the degree of gravity of the case.
Torpé, Sardinia
Applying all the principles of good clinical trial design
Joseph Asbury Bell
(1904-1968)
Public Health Reports

Vol. 56 • AUGUST 1, 1941 • No. 31

PERTUSSIS PROPHYLAXIS WITH TWO DOSES OF ALUM-PRECIPITATED VACCINE

By Joseph A. Bell, Passed Assistant Surgeon, United States Public Health Service
“A numbering machine was used to stamp a serial number after each name in the above order. **Using the "Random Sampling Numbers"** as assembled and published by L.H.C. Tippett, the allotted numbers in each section were divided at random into two equal groups.”
“Since the "V" and "N" groups of children in this study were strict random samples of the combined groups, since the observation of each group was pursued with equal diligence and uniform criteria were used to enumerate cases, and since the only known difference between the groups was the injection of alum-precipitated pertussis vaccine into a large proportion of the "V" group of children, whereas only a small proportion of the "N" group of children were so injected, it is believed that the vaccine used was responsible for the disproportionately smaller number of cases of pertussis observed in the "V" as compared with the "N" group or with the combined groups.”
The James Lind Library has been created to help people understand fair tests of treatments in health care. The principles of fair tests are explained in essays containing many examples. These essays are available in Arabic, Chinese (中国), English, French (français), Russian (русский язык), Portuguese (Português) and Spanish (español).

The text of ‘Testing Treatments’ - a 100-page book published by the British Library in 2006 - is available here without charge, in the original English, and in Arabic, Chinese, and Spanish translations.

To illustrate the evolution of fair tests of treatments from 1550 BCE to the present, the James Lind Library contains key passages and images from manuscripts, books and journal articles. The website also contains many commentaries, biographies, portraits, doctoral theses and other relevant material about the history of fair tests.

The James Lind Library is dedicated to patients and professionals who have contributed evidence about the effects of treatments in health care. For a full description the James Lind Library, click here. Comments are welcome, and should be sent to feedback@jameslindlibrary.org.