

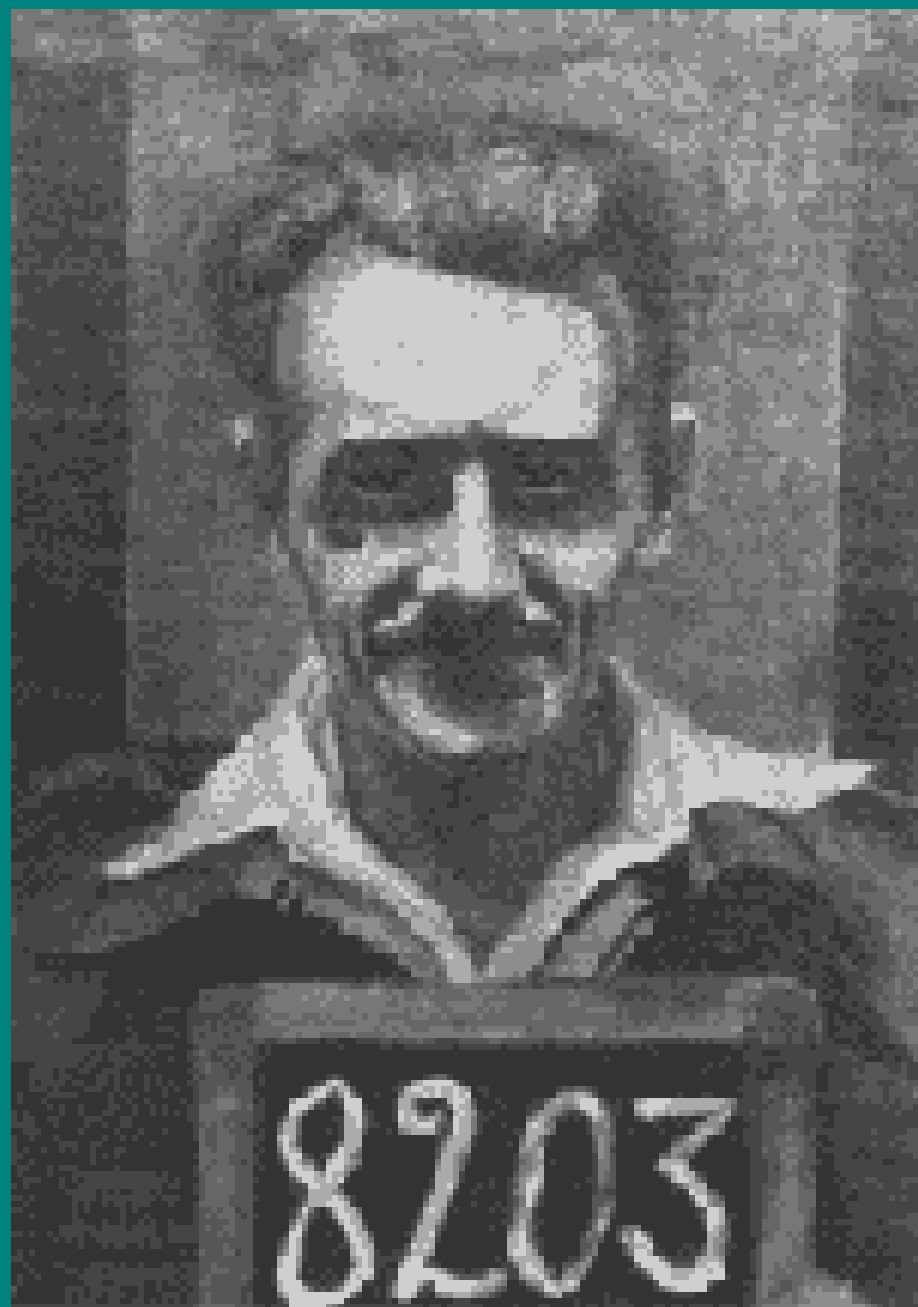
'Controlled trials before Archie Cochrane'

Iain Chalmers

Editor, *James Lind Library*

**'The effectiveness of interventions for
addictions: The Cochrane Drugs and
Alcohol Group Contribution'**

Roma, 24 October 2008



Sickness in Salonica: my first, worst, and most successful clinical trial

A L COCHRANE

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



Edin. King
In Libris & Bibliotheca

T R E A T I S E

*In Libris OF THE College Regi
Medic. Edinburg.*

S C U R V Y.

I N T H R E E P A R T S.

Prætic CONTAINING *Prætic*

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

Medicor. Together with *Edinburg*

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.

E D I N B U R G H:

Printed by SANDS, MURRAY, and COCHRAN

For A. KINCARD & A. DONALDSON.

MDCCLIII.

TRAITÉ
DU
SCORBUT,
DIVISÉ EN TROIS PARTIES.

C O N T E N A N T

Des recherches sur la nature, les causes
& la curation de cette Maladie.

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

Traduit de l'Anglois de M. LIND, D. M. Membre
du Collège Royal de Médecine d'Edimbourg.

Aussi on a joint la Traduction du Traité du Scorbut
de BOERHAAVE, commenté par M. VAN SWIETEN.

TOME PREMIER.



A PARIS,

Chez GANEAU, Libraire, rue Saint-Severin,
aux Armes de Dombes.

M. D C C. L V I.

Avec Approbation & Privilège du Roi.

*"....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"*

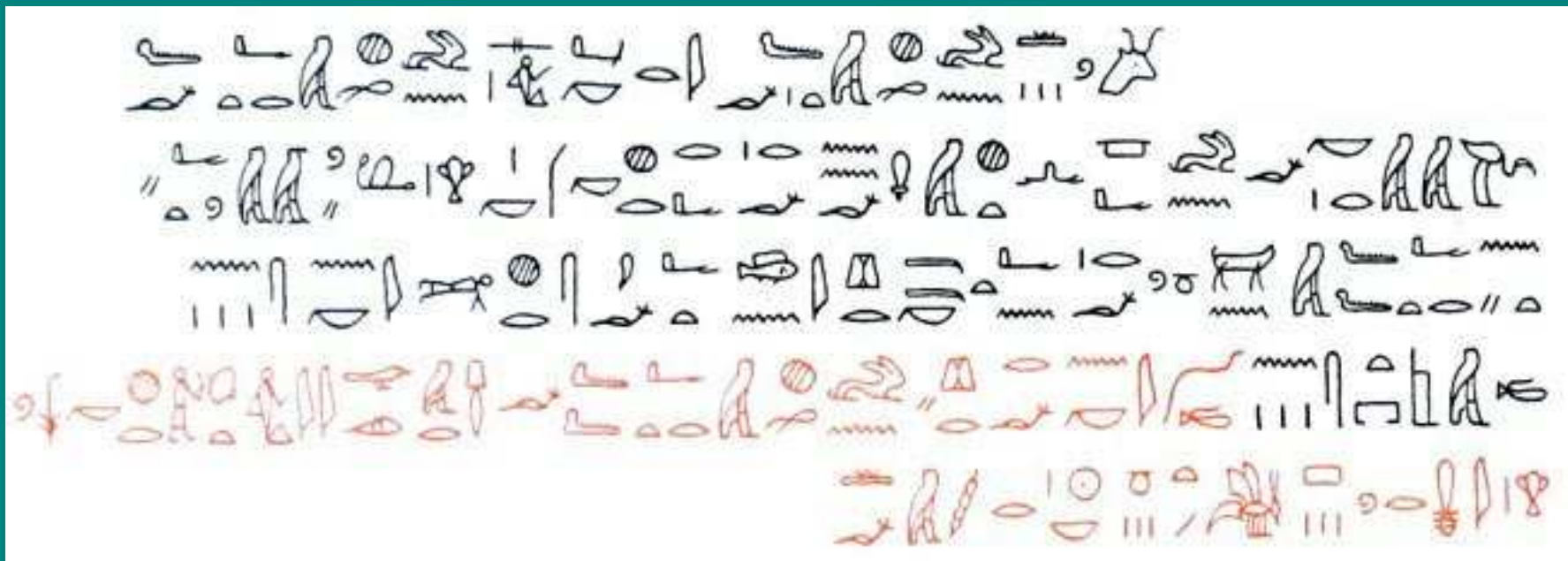
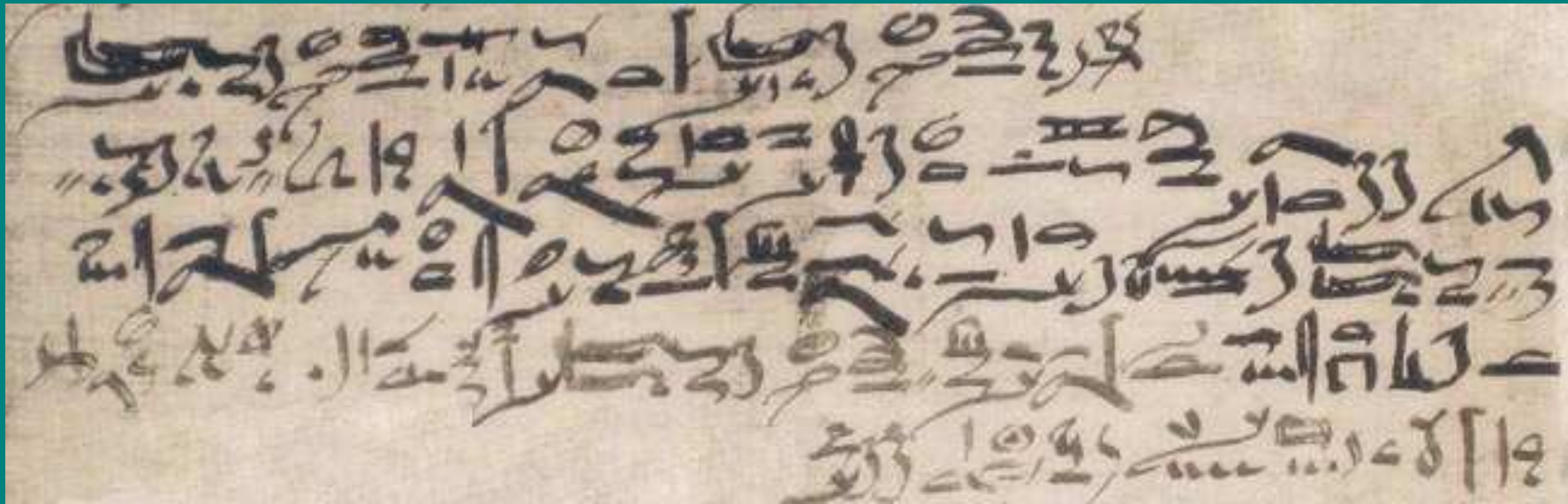
*"the bigness of a **nutmeg** three times a day"*

*"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].

بمذاذ ادم الثقل والوجع في الرأس والعنق ^{بين}
ثلاثة واربعه وخمسه وكثير وحيد الصرع والضو وقد الروع ويكثر التثاوب والنطى وشهس شديد به ويجد مس
لاعياء الشديده فانه ينتقل العليل بعد ذلك الى السوساء فقيده كالسكران ولا يتينه لطعام ولا الشراب الى ان يجيه
الجيران فان كان الثقل في الرأس اكثر من الوجع ولم يكن سهو لكن نوم فكانت الحرارة اسكن والنبض عظيم غير سريعاً مثل
اليه ليرعش في رايه هذه العلامات تنفد في الضد فاني قد حصلت جماعة به وتركت شعرا جماعة استوى بذلك
راي فسن هو كلهم وقد يكون هذا في الحميات الدوسية فاذا رايت في الحميات علامات الخدر في فاعلم انه ينقل اليه وان را
هذه العلامات غالية تنقل

*"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

tas aut cunctis affectibus p̄ferenda est. Itaq̄
sic sentio, hoc affirmo. Si centū aut mille
hōes b̄ni' etatis ac nate, et b̄ni' uirt'
b̄no similitōis morbo correpti esset. Quis
q̄ pars dimidia s̄lmo staret. Talis
qualis h̄t etas n̄a. Nūc n̄o sine
illis medicis n̄ali īstinctu et p̄pa dis
cretōe se regēt. Nulla m̄ dubitatio est, quin
ex illis p̄tes morerēt, plures ex illis euade
rent. // Aliū quōdam hōem p̄līmū litterarū



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)

Fl. Cava. & Fioravate

Cons.^o

A v. d' Aprile . 1573.

Che M^o Sebastiano Boldone, et S^o Albutio

^{Le et del suo Diploma di Dottore}
s' informino del supp. et uferiscano. al qual si
concede, che possa far le sue difese fuor di prigione,

Valeriana

Fioravanti L (1573). Communication addressed to "Illustrissimo e Eccellentissimo Signor Al Protofisico Boldon e al Vicario di Giustizia", 22 xxxx 1573.

*che mi siano consignati 20/25
amalati di diverse infermita a me solo, et altri tanti delle istesse infermita
a tutti li medici di milano, et se io no curo li miei piu presto, et meglio di
loro voglio esser bandito per sempre di questa, citta,*

'...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)**

ORIENTAL

OR,

Physick 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 Philoso-
pher, and Chymical Physitian,

John Baptista Van Helmont,

Toparch or Governor, in *Moreda, Royenborch, Oorschot, Pellines, &c.*

And now faithfully rendred into *English*, in tendency to a common good, and
the increase of true Science; By

J. C. Sometime of M. H. Oxon.

*Job 32. 8. There is a Spirit in Man, and the inspiration of the Almighty giveth
understanding.*

*Pro. 8. 12. I Wisdom dwell with Prudence, and find out knowledge of witty Inventions.
Aeternarum rerum seria contemplatio eo usq; animum nostrum subvecit, ut Divina
loquuti videamur de rebus Naturae subjectis, quae tantò perfectiores sunt, quanto
propriores Aeternis, &c.*

LONDON,

Printed for Lodowick Loyd, and are to be sold at his Shop next the Castle in
Cornhill. 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 halves, **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;

QUAM,

ANNUENTE SUMMO NUMINE,

EX AUCTORITATE REVERENDI ADMODUM VIRI,

D. GEORGII BAIRD, SS. T. P.

ACADEMIÆ EDINBURGENÆ PRÆFECTI;

NECNON

AMPLISSIMI SENATUS ACADEMICI CONSENSU, ET
NOBILISSIMÆ FACULTATIS MEDICÆ DECRETO;

Pro Gradu Doctoris,

SUMMISQUE IN MEDICINA HONORIBUS AC PRIVILEGIIS,

RITE ET LEGITIME CONSEQUENDIS;

ERUDITORUM EXAMINI SUBJICIT

ALEXANDER HAMILTON,

Scotus,

AD EXERCITUM BRITANNICUM

CHIRURGUS.

Πολλοῖς ἀνιλιόγειν μὲν ἔθος περὶ παντὸς ὁμοίως
Ὁρθως δ' ἀπὸ λόγου, ἀπὸ τῆς ἰν ἔθει :
Καὶ πρὸς μὲν τούτους ἀρκεῖ λόγος ὡς ο παλαιος
ΣΟΙ μὲν ταῦτα δοκεῖ ἴσθι, ΕΜΟΙ δὲ ἴαθε.

EVENUS PARIUS.

Deficient inopem vena te, si Cibus atque
Ingens accedat stomacho fullura ruenti.
Quid cessas? Agedum, sume hoc Ptisanarium oryza.

HORAT.

Kal. Aug. hora locoque solitis.

EDINBURGI:

EXCUEBANT JAC. BALLANTYNE ET SOCIJ.

MDCCCXVI.

Alexander Lesassier Hamilton
(1787-1839)



*"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 „Allgemeinen Zeitung v. u. f. Bayern.“

Als Anhang:

Ein Beispiel homöopathischer Heilart.

Nürnberg im März

1835.

**Löhner G, on behalf of a Society
of truth-loving men, 1835.**

Die Homoöopathischen
Kochsalzversuche zu Nürnberg.
[The homeopathic salt trials in
Nuremberg].

8

*"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."*

9

*"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

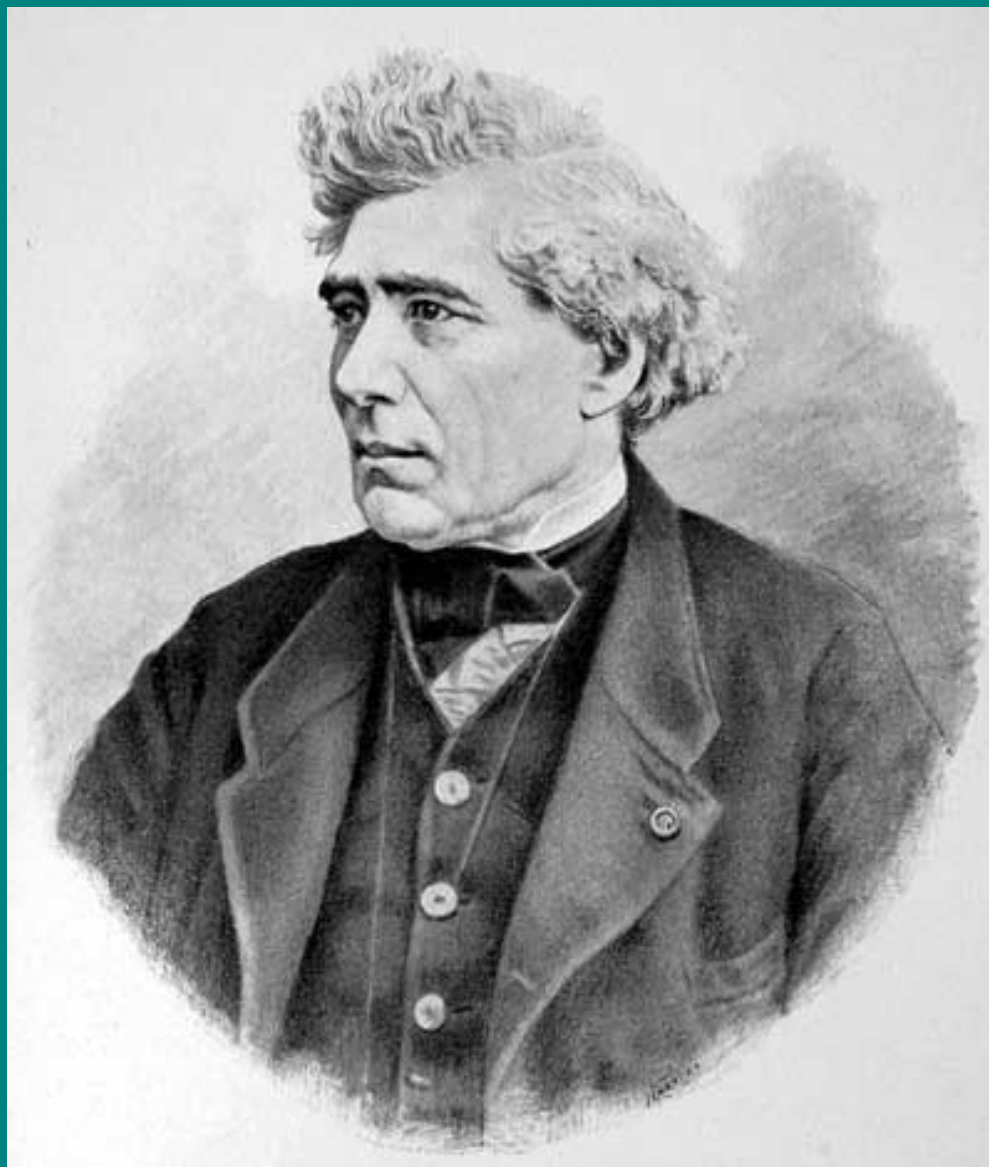
"Dr. Löhner **enters the number of each bottle**, indicating its contents, in **a list**, **seals** the latter and hands it over to the committee, the members of which also **affix their seals** thereto."

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
A SON EMPLOI.

Par Jules Gavarret,

ANCIEN ÉLÈVE DE L'ÉCOLE POLYTECHNIQUE.

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

PARIS

BECHET JEUNE ET LABÉ,
LIBRAIRES DE LA FACULTÉ DE MÉDECINE DE PARIS,
4, PLACE DE L'ÉCOLE DE MÉDECINE.

1840

BIBLIOTH
COLL. REG
M.D. EF

Les principes de la loi des grands nombres sont rigoureusement applicables aux recherches de thérapeutique, et peuvent seuls donner la solution de ces deux problèmes importants.

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.

Pour qu'il y ait lieu de préférer une méthode thérapeutique à une autre, il faut, non seulement, que ses résultats soient plus avantageux, mais encore que la différence constatée surpasse une certaine limite, dont la valeur dépend des nombres de cas recueillis.

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**

Jesse Bullowa (1879-1943)

328 BULLETIN *of the* NEW YORK ACADEMY *of* MEDICINE

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)

Type	(a) With Serum			(b) Without Serum			Difference in Case Fatality (a — b)	Ratio of Difference to Its Error
	Cases	Deaths	Deaths per 100 Cases	Cases	Deaths	Deaths per 100 Cases		
I	55	10	18 ± 5.2	53	16	34 ± 6.5	-16 ± 8.3	1.9
II	20	0	23 ± 8.3	18	14	37 ± 7.8	-14 ± 11.4	1.2
III	24	11	46 ± 10.2	17	7	41 ± 11.9	5 ± 15.7	0.3
IV	54	7	13 ± 4.6	52	7	9 ± 3.2	4 ± 5.0	0.7

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?

Bastianelli G, Mosna E, Canalis A (1937). Prevention and treatment of malaria by synthetic drugs. Bulletin of the Health Organisation of the League of Nations 6:822-891.

PREVENTION AND TREATMENT OF MALARIA BY SYNTHETIC DRUGS.

Field Experiments

carried out under the Direction of

Professor G. BASTIANELLI

by

Dr. E. MOSNA,	and	Dr. A. CANALIS,
(Malaria Laboratory, Institute of Public Health, Rome)		(Institute of Malariology " Ettore Marchiafava ", Rome).

Febrile patients yielding positive blood findings were assigned alternately to the atebtrin and to the atebtrin-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

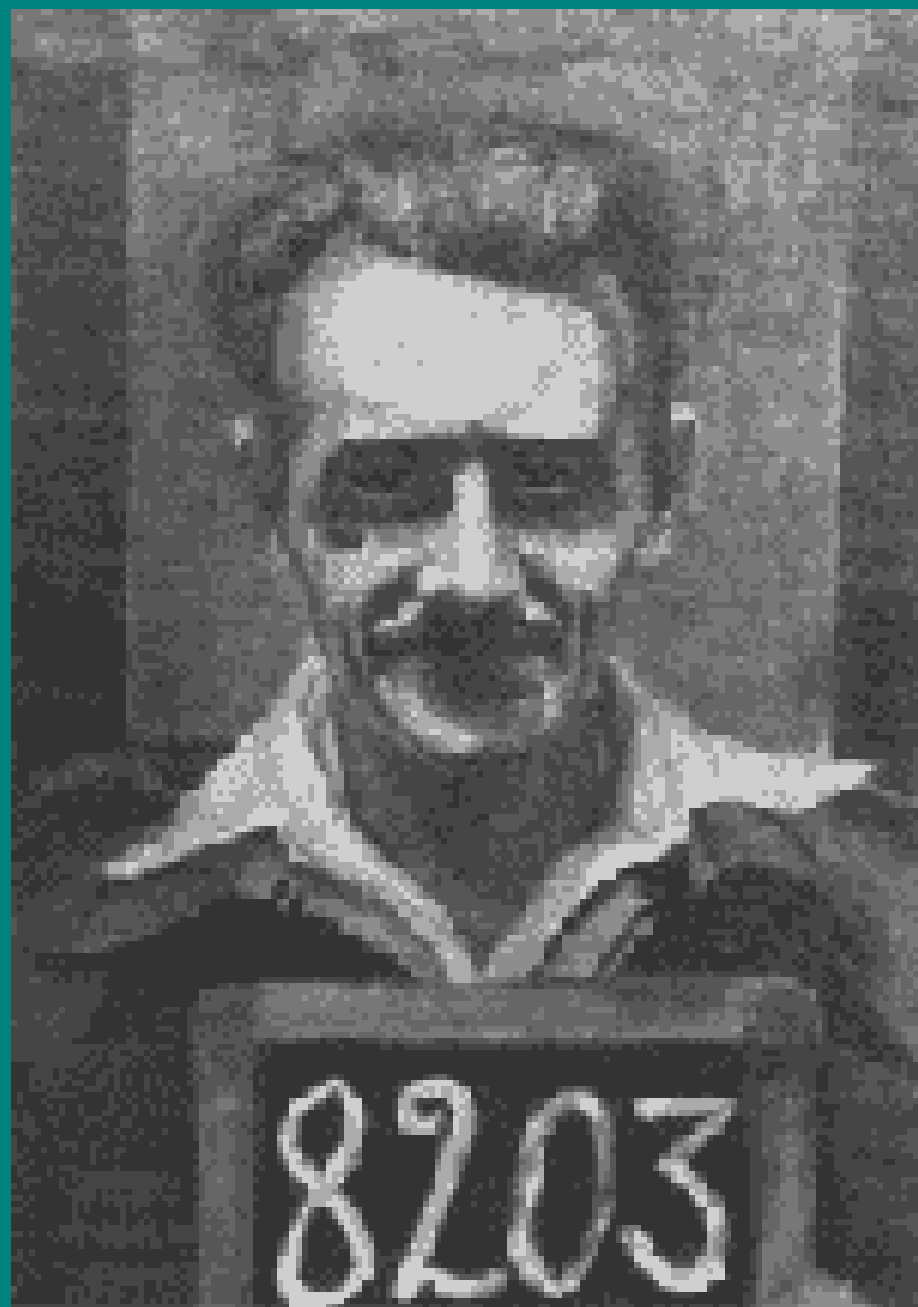
Vol. 56 • AUGUST 1, 1941 • No. 31

PERTUSSIS PROPHYLAXIS WITH TWO DOSES OF ALUM- PRECIPITATED VACCINE¹

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.”



www.jameslindlibrary.org

The James Lind Library

Explaining and illustrating the development of
fair tests of treatments in health care

Enter Text Search:

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.



[what is a fair test](#) [contents](#) [browse records](#) [what's new](#) [building the Library](#) [about us](#)



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