

The James Lind Library: explaining and illustrating the evolution of fair tests of medical treatments

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ABSTRACT The James Lind Library (www.jameslindlibrary.org) has been established to improve public and professional general knowledge about fair tests of treatments in healthcare and their history. Its foundation was laid ten years ago at the Royal College of Physicians of Edinburgh, and its administrative centre is in the College's Sibbald Library, one of the most important collections of historic medical manuscripts, papers and books in the world. The James Lind Library is a website that introduces visitors to the principles of fair tests of treatments, with a series of short, illustrated essays, which are currently available in English, Arabic, Chinese, French, Portuguese, Russian and Spanish. A 100-page book – *Testing Treatments* – is now available free through the website, both in English and in Arabic and Spanish translations. To illustrate the evolution of ideas related to fair tests of treatments from 2000 BC to the present, the James Lind Library contains key passages and images from manuscripts, books and journal articles, many of them accompanied by commentaries, biographies, portraits and other relevant documents and images, including audio and video files. New material is being added to the website continuously, as relevant new records are identified and as methods for testing treatments evolve. A multinational, multilingual editorial team oversees the development of the website, which currently receives tens of thousands of visitors every month.

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INTRODUCTION

The Library at the Royal College of Physicians of Edinburgh was founded in 1682 when Sir Robert Sibbald (1641–1722) donated 'three shelves full of books' to the College. Since then, the Library has grown to become one of the most important collections of historic medical manuscripts, papers and books in the world, and the historical collections were renamed the Sibbald Library in 2008. The idea for an online library emerged in the mid-1990s when two of the co-authors met during a tour of the College for newly elected Fellows. They found that they shared an interest in the history of medicine and recognised that the web offered great potential for making available to a worldwide readership some of the contents of the College Library's historic collection. With initial help from a historian with an interest in the history of controlled trials,¹ a website called Controlled Trials from History was created. It was launched in 1998 at a meeting convened in London by the *British Medical Journal* to mark the 50th anniversary of the publication of the Medical Research Council's (MRC) celebrated randomised trial of streptomycin for pulmonary tuberculosis.²

Five years later, the website was redesigned substantially with a view to improving public and professional general

knowledge about fair tests of treatments in healthcare, and the history of their evolution. Explanatory essays were added and a wider variety of records were included, with commissioned commentaries, biographical pieces and other material. The website was relaunched as the James Lind Library (www.jameslindlibrary.org) at a College symposium to mark the 250th anniversary of the publication of James Lind's *Treatise of the Scurvy*.³ Lind's *Treatise*, which was written while he was resident in Edinburgh and a Fellow of the Royal College of Physicians, contains not only his celebrated account of a controlled trial showing that oranges and lemons were dramatically better than the other supposed treatments for the disease, but also a systematic review of what had previously been written about scurvy. Lind was Treasurer of the College at the time; he resigned to take up the post of Chief Physician at the Royal Hospital at Haslar, near Portsmouth.

The content of the James Lind Library reflects its twin objectives of improving public and professional general knowledge about fair tests of treatments in healthcare, and illustrating the history of their evolution. It explains and illustrates fair tests of medical interventions for prevention and treatment, and provides an internet archive of methodologically relevant records, from antiquity to the present.

Explaining and illustrating fair tests of treatments

Occasionally the result of a medical treatment is so dramatic that its effects are clear, without the need for further testing. The James Lind Library contains several examples of such treatments, including Lind's use of oranges and lemons to treat scurvy.³ The effects of most treatments are not so obvious, however, and biased information or the play of chance can lead us astray. As a consequence, we may sometimes conclude that an intervention is useful when it is not, or worse, when it is actually harmful. Conversely, we may sometimes dismiss as useless or harmful something that is actually helpful. It is in these circumstances that unbiased, fair tests of treatments are so important. Misleading claims about the effects of treatments are common. Knowledge about fair tests helps us to sort the kernels of 'information wheat' from the plethora of 'disinformation chaff'.

A number of agencies acting on behalf of the public (for example, drug licensing authorities and organisations preparing clinical guidelines) reach their decisions after considering evidence from research assessing the desired and undesired effects of medical and other treatments. Increasingly, these agencies require that research evidence is generated in ways intended to ensure that tests are fair, and that they avoid biases of various kinds.

Although these requirements have been introduced to protect the public's interests, the public's as well as sometimes the professionals' knowledge about the steps required to achieve fair tests remains very limited. This lack of public knowledge and understanding presents a challenge that the James Lind Library is helping to address.

The James Lind Library contains a series of short explanatory essays to promote wider understanding of why fair tests of treatments are needed and their methodological features. The essays explain why treatment comparisons are essential, what is needed to achieve unbiased comparisons, the identification of unanticipated effects of treatments and how to interpret unbiased comparisons reliably. They also explain why, when assessing the effects of treatments, it is important to review systematically all of the relevant, reliable evidence. The texts of the explanatory essays are freely available for use by others under a Creative Commons Attribution 3.0 Unported Licence. Through the good offices of the World Health Organization and its regional offices, the James Lind Library's explanatory essays are now available not only in English, but also in Arabic, Chinese, French, Portuguese, Russian and Spanish.

To illustrate how current ideas about fair tests of treatments reflect principles and practices that have evolved over the past millennium, the James Lind Library's explanatory essays draw on hundreds of texts from manuscripts, books, articles and other documents. We select records for inclusion in the Library both to illustrate the evolution of

principles of fair tests of treatments, and to illustrate the application of these principles in practice.

In addition to the explanatory essays (which total about 8,000 words), the James Lind Library provides access to a 100-page book – *Testing Treatments: Better Research for Better Healthcare* – initially published by the British Library in 2006.⁴ Translations of the book have been, or are being, published in Arabic, Chinese, German, Italian, Japanese and Spanish. *Testing Treatments* in English and translations into Arabic and Spanish are also freely available for use by others.

An internet archive from antiquity to the present

The explanatory material in the James Lind Library draws on material in the 'backbone' of the Library – a searchable internet archive of hundreds of documents of methodological relevance, from antiquity to the present. These records can be selected not only using textword searches, but by the methodological principles that they illustrate. The records can also be listed chronologically, alphabetically by the names of their authors and by the country of authors. The Library also contains a wealth of material linked to these records – commentaries, biographies, portraits and other images, audio and video recordings, and so on.

Our oldest record, from an Egyptian papyrus of about 1550 BC, describes (in hieratic and in hieroglyphs) how to reduce a dislocated mandible.⁵ It is an example of a record included in the James Lind Library to illustrate a treatment with a dramatic (and intended) effect, just as thalidomide has been included to illustrate a dramatic unintended effect.⁶

An analysis of studies following the introduction of sulphonamides in the 1930s provides an illustration of treatments that have dramatic effects in some conditions but not in others, showing why carefully controlled trials are needed.⁷

The need for comparison in assessing less dramatic effects of treatments was recognised at least as early as the tenth century: al-Razi⁸ referred to a comparison between a treated group and an untreated group as the basis for his conclusion about the effects of treatment for early meningitis. However, the earliest examples of formally justified, quantitative treatment comparisons in the James Lind Library occurred during the first half of the eighteenth century. They were designed to assess the effects of inoculation against smallpox,⁹ the relative merits of different surgical approaches and techniques for lithotomy and ways to perform limb amputations.¹⁰⁻¹²

From the mid-eighteenth century on, there was a steady growth in quantitative assessments of treatments, a development in which Lind and other Edinburgh graduates played leading roles.^{10,11} The manuscripts of William

Cullen's clinical lectures, held in the Sibbald Library, have provided the earliest example identified so far of the use of the word 'placebo' in the sense of an inactive treatment given to please the patient,^{13,14} and there were some examples of the use of blinding and placebos to test treatments at the end of the eighteenth century.^{15–18}

Proposals were made at least as early as the seventeenth century to use lottery to create 'fair' treatment comparison groups to resolve differences of opinion about the relative merits of alternative therapeutic approaches.^{16,19–21} There are examples of lottery and alternation being applied in practice during the first half of the nineteenth century,^{22,23} and in 1835 a 'society of truth-loving men' in Nürnberg, Germany, reported a meticulously designed and conducted placebo-controlled trial to assess the effects of homeopathy.^{24,25} At about the same time, Jules Gavarret was stressing the need to study sufficiently large numbers of patients.^{26,27} As the nineteenth century progressed into the twentieth century, increasing numbers of records contained in the James Lind Library illustrate the gradual appreciation and application of these important methodological characteristics of fair tests, until their widespread acceptance during the second half of the twentieth century.

We include records in the James Lind Library to illustrate the application of the methodological principles underlying fair tests of treatments up to the point at which the principles appear to have become widely accepted, for example, by their appearance in textbooks. For instance, by the 1960s, there was wide acceptance of the need to generate comparison groups using alternation or random allocation – so that like would be compared with like. Biases in assessing treatment outcomes had also been recognised by then, along with the steps needed to reduce these, sometimes by using placebos.²⁸ By the end of the twentieth century, people had realised that it is important to assess treatment effects using systematic reviews of all the relevant evidence, published and unpublished. At the beginning of the twenty-first century, there is an increasing awareness of the various biases associated with commercial sponsorship of tests of treatments.²⁹ The most recent record in the Library at the time of writing is an important and rare example of a formal attempt to assess the extent to which animal models for testing treatments are reflected in subsequent studies in patients.^{30,31}

It is clear that the principles of fair tests of treatments continue to evolve. We try to reflect this continuing evolution in the James Lind Library and to identify relevant records from around the world. Although we do not attempt to be exhaustive, we are constantly assessing additional material for possible inclusion in the James Lind Library, and we welcome suggestions for additional 'candidate' records, and other comments through feedback@jameslindlibrary.org.

Contributions to the history of medicine

The James Lind Library contains several doctoral theses by medical historians who have researched aspects of the history of clinical trials, one of whom is a member of the editorial team,¹⁰ and several other historians have made important contributions to the Library. However, the James Lind Library has also been able to contribute to the history of medicine by drawing attention to previously insufficiently recognised evidence of methodological thinking, particularly in documents published in languages other than English. Forty of the 206 records published before the end of the Second World War which have been selected for inclusion are in languages other than English, including:

- a reference, in Arabic, to an untreated comparison group when discussing the validity of a treatment for early meningitis in tenth-century Baghdad;^{8,32}
- a comparison, reported in French, of different ways of administering mercury for preventing venereal disease in eighteenth-century Geneva;^{33,34}
- the use of placebos in a trial of homeopathy in St Petersburg in 1832, reported in Russian;^{35,36}
- perceptive comments published in German and Danish at the end of the nineteenth century about the use of statistics in evaluating treatments;^{37–39}
- a Dutch report of scrupulous efforts to avoid bias in research to identify nutritional solutions to beriberi in the Dutch East Indies.^{40,41}

The collection of records in the James Lind Library makes clear that the controlled clinical trial is not, as has often been assumed, a strictly British invention. By the beginning of the 1920s, controlled trials had been reported from Britain,⁴² the United States,⁴³ Denmark,⁴⁴ France⁴⁵ and Germany.⁴⁶ In particular, work on early twentieth-century material in the James Lind Library has drawn attention to several interrelated American researchers (Jesse Bullowa and Russell Cecil in New York in the 1920s, and James Doull, Pearl Kendrick and Joseph Bell at Johns Hopkins University in the 1930s, for example) who were pioneers in the development of methods for testing treatments. Perhaps surprisingly, these researchers appear to have been largely overlooked in previous histories of clinical trials^{47–51} – an omission that has now begun to be addressed in Scott Podolsky's 2006 book *Pneumonia before antibiotics*.⁵²

Other research using material in the James Lind Library⁵³ builds on earlier work⁵⁴ exposing the lack of evidence to support assumptions that statistical theory was important in the design of the iconic MRC trial of streptomycin for pulmonary tuberculosis.² By focusing on random allocation some historians seem to have overlooked its inextricable connection with alternate allocation in the development of unbiased methods to generate comparison groups.

Material published during the 1940s and later has offered the possibility of obtaining and publishing

accounts from individuals who were involved in some pioneering studies. For example:

- Guy Scadding provided details of the sulphonamides trials that he had conducted in the early 1940s;^{55,56}
- Philip D'Arcy Hart⁵⁷ told us about the steps he and his colleagues had taken to conceal the treatment allocation schedule in the MRC trial of patulin;^{58,59}
- John Crofton provided an account of what it was like being at the clinical front line during the MRC trial of streptomycin for pulmonary tuberculosis;⁶⁰
- Richard Doll wrote about the introduction of randomised factorial trials;⁶¹
- William Silverman provided an account of the crucial importance of controlled trials in the chequered history of innovation in neonatal medicine;⁶²
- Peter Elwood recorded the origins of the first controlled trial of aspirin to prevent cardiovascular disease and how it led to one of the earliest meta-analyses in medicine;⁶³ and
- Milos Jenicek has provided an account of how he came to write (in French) the first book on systematic reviews and meta-analysis in medicine.⁶⁴

Reception and possible future development

We have been encouraged by the way that the James Lind Library has been received. In 2003, *Scientific American* awarded the Library a Sci/Tech web award. Judges representing the journal considered 1,000 websites across all of science, and selected 50 for awards. Only five of these were in the medicine category, and the James Lind Library was the only one of these to have been created outside the US. Since its launch, the James Lind Library has been welcomed in lay media, such as the *Guardian* and *Videnskab*, the BBC website and various blogs, and professional publications such as *The Lancet*, *Hospital Doctor* and *Controlled Clinical Trials*. Indeed, this publicity led 20 May to be designated International Clinical Trials Day, because James Lind's celebrated controlled trial began on that day in 1747.

The James Lind Library website is used by visitors from around the world. In the second quarter of 2008 the site was visited more than 100,000 times by people from 112 countries. More than half came from Europe, a third from the Americas and the remainder from across the globe: Asia (including Bahrain, China, Hong Kong, India, Iran, Israel, Japan, Kuwait, Pakistan, the occupied Palestinian territory, Saudi Arabia, South Korea, Syria, Taiwan, Turkey and the United Arab Emirates), Oceania (including Australia and New Zealand) and Africa (including Algeria, Egypt, Ghana, Ivory Coast, Malawi, Morocco, South Africa, Sudan and Tunisia). With material now being available in seven languages, we anticipate a further growth in the numbers of visitors.

The explanatory essays and the book *Testing Treatments: Better Research for Better Healthcare* are the most popular



FIGURE 1 The editorial team of the James Lind Library, with a bust of Robert Sibbald, founder of the library at the Royal College of Physicians of Edinburgh, and an autographed copy of James Lind's *Treatise of the Scurvy*. (Left to right): Alfredo Morabia, Ulrich Tröhler, Iain Milne, Iain Chalmers, Estela Dukan, George Tait, Jan Vandenbroucke.

elements of the Library. More than 20,000 copies of the book were downloaded during the first half of 2008. We have been encouraged that organisations promoting public engagement in science and clinical research – the Pan American Health Organization/World Health Organization and the UK Clinical Research Collaboration, for example – have added their endorsements of the James Lind Library to that of *Scientific American*.

Because of the high quality and general interest of the material published in the James Lind Library, several journals, including the *Journal of the Royal College of Physicians of Edinburgh*, have republished articles commissioned originally for the James Lind Library. *The Journal of the Royal Society of Medicine*, for example, has been republishing James Lind Library commentaries every month since October 2005.

Over the next few years, we plan to develop a new section of the Library to promote wider understanding of the evolution of ideas and methods used in epidemiological research, incorporating reproductions of original papers representing milestones, together with related commentaries. A substantial amount of basic material has already been collected and structured by one of us,⁶⁵ and we are currently seeking resources to support this further development of the James Lind Library.

Finally, we wish to reiterate that we welcome comments and suggestions, particularly if they draw our attention to relevant material published in languages other than English.

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