The place of clinical trials in the prevention of smallpox and the scurvy: the contribution by military medicine in 18th century England

Bruce Short

People [are] healthy in both ships except a few scourbatics … I have directed constant Bathing in the Warm Latitudes every Evening by the Surgeon's recommendation …

Commodore Edward Hughes RN
Cape of Good Hope, 11th March 1774
Letter to Lord Sandwich, First Lord of the Admiralty[1]

ALTHOUGH KNOWN IN THE 18TH CENTURY as medical experimentation, the initial investigations into two common and disparate diseases of the time, smallpox and the scurvy, were nevertheless done by the application of basic scientific research. Curiosity and discovery of the unknown within the human corpus antedated the 18th century by hundreds of years, but it was not until 1747 that the first true (and exhaustively documented) trial of health care intervention was performed. The importance of interventional trials in the development of treatment protocols is today considered fundamental to modern health care delivery. The linking of trial outcomes with evidence-based best medical practices is pivotal to contemporary Western clinical management.

Nowadays, a new or an established therapy is assessed by the "gold standard" of the randomised controlled trial, involving measurement of the observed effects within a treated group compared with an untreated control group. Members of the latter frequently receive a pharmacologically inert placebo. The allocation of participants to either the control arm or active constituent arm is made randomly, and neither patients nor their physicians will be aware of whether they are receiving an active drug or a placebo — so-called double-blinding. The first modern published randomised controlled trial is generally ascribed to the 1948 United Kingdom Medical Research Council's trial of streptomycin in pulmonary tuberculosis, which is said to represent a model for future therapeutic trials.[2]

Here, I describe the origins of clinical trials in 18th century England and emphasise the important work of naval surgeon James Lind.

An enlightened medicine

Therapeutics during the 18th century, the "Age of Enlightenment", were rudimentary; indeed, very few 18th century scientific advances directly helped to heal the sick. Although the century was regarded as an era of science and

Abstract

- The first modern published randomised controlled trial was the 1948 United Kingdom Medical Research Council's trial of streptomycin in the treatment of pulmonary tuberculosis.
- James Lind performed the first health care intervention trial in the treatment of scurvy in 1747.
- In 1767, William Watson carried out the first true controlled trial in clinical medicine, which was to determine the best source of inoculums to be used in the variolation technique of smallpox prevention.
- Edward Jenner experimented with cowpox in 1796 by inoculating a child with the substance; the child subsequently exhibited smallpox resistance following smallpox variolation. Jenner called the new technique "cowpox vaccination".
- The identification of the anti-scorbutic benefit of citrus fruits was formally documented by Gilbert Blane to the Admiralty almost 50 years after Lind's initial experiment.
- Watson's trials were randomised but not double-blinded, involved a deliberate study design, contained quantitative conclusions with results that were correctly interpreted, and included a control arm.
- The cure of scurvy and the prevention of smallpox provided enormous improvements in the capability of naval and military forces of the past. Military medical science went on to continue the search for prevention and management strategies for the other major military epidemic diseases: malaria, typhus and the enteric diseases, cholera, shigellosis and typhoid fever.

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enlightenment, physicians' therapies remained fundamentally Galenic in character. In regard to the understanding of disease causation, miasmatic germ theory dominated the thinking and practice of 18th century Western medicine.

Medical science during this century nonetheless witnessed the development of numerous new concepts, such as Gabriel Fahrenheit's mercury thermometer in 1714, William Smellie's outline of the first attempted scientific approach to obstetrics in his book *A treatise on the theory and practice of midwifery* in 1752, the first clinical description of diphtheria published in 1748 by John Fothergill as an *Account of the putrid sore throat*, and the first and lasting clinical description of coronary artery disease by the English physician William Heberden in 1772: "There is a disorder of the breast … may make it not improperly be called *angina pectoris*".[3]

The Foundling Hospital in London where William Watson conducted his controlled smallpox trial, involving 38 children, in 1767.

In addition to these achievements, there are two that must rank among the most important landmarks in man's effort to overcome disease up to that time: the putative discovery of the cause of scurvy by James Lind in his *Treatise of the scurvy*,[4] published 6 years after his experimentation in 1747; and the prevention of smallpox, first by variolation and later by the safer vaccination technique of Edward Jenner in 1796.

How important was the control of these common and deadly diseases?

Smallpox, known to the ancient Egyptians since the 12th century BC, brought down at least three empires, and some estimates suggest that 10% of all human deaths worldwide each year were caused by smallpox.[5] On average, smallpox killed at least 20%–30% of the people it infected, the figure rising during severe epidemics. In 18th century England, 90% of the victims were under the age of 10 years; smallpox became the leading cause of childhood deaths in London, with about one in four children dying.[6] Throughout Europe in the 18th century, about 400 000 people a year died from smallpox.[7]

Scurvy was no less fatal. It too is an ancient disease, but rose to prominence during the great "Age of Exploration" beginning in the 15th century. More sailors were killed by scurvy than by misadventure or as the result of naval engagements. The Royal Navy's special interest in scurvy followed a particularly disastrous expedition to the Pacific regions in 1740 by Commodore George Anson RN. Nearly 90% of a total crew of 1400 died from scurvy alone, and only one of his original five ships was sufficiently crewed to permit its safe return to England in 1744.[8] Scurvy, which also occurred among land dwellers during winter, was known throughout the world by many different names: scarby, scorbus, scarbuck, scourby and the "scorbutic taint".[8] As a result of great distances, bad weather and currents, or strategic sea duties, Royal Navy crews were frequently away from landfall for months.[1] Merchant navies, and particularly those involved in the burgeoning industry of slave transportation, suffered similar scorbutic adversities.

Why are humans so susceptible to these two diseases?

Variola major, smallpox virus, is a member of the diverse *Orthopoxviridiae* family that affects humans exclusively and has no non-human reservoir.[9] Smallpox, cowpox, monkey pox and vaccinia are the only orthopoxviruses to infect humans.[10] Smallpox is primarily a respiratory disease, but skin-to-skin transmission is also important in disease communication.

Humans, certain other primates, bats and guinea pigs all share the same biochemical defect: they are unable to synthesise vitamin C and are entirely dependent on dietary ascorbic acid. Rosehips (the ripe fruit of the rose) are probably the richest natural source of ascorbates. In common with other water-soluble vitamins, the body's storage of vitamin C is relatively slight. Collagen synthesised in the absence of ascorbate is insufficiently hydroxylated, such that the abnormal collagen cannot properly form fibres, thereby causing abnormal skin and blood vessel fragility.[11] Haemorrhage into the major body cavities is the main cause of death from scurvy. At sea, the deficiency of ascorbic acid was frequently accompanied by other serious deficiencies, including thiamine, niacin and riboflavin.

Smallpox contagion in 18th century England

Fear of the smallpox epidemic that broke out in England in 1721 stimulated widespread acceptance of the very recently imported variolation or inoculation technique. Spread of the variolation procedure also occurred throughout Europe, as well as to America. General George Washington, a survivor of teenage smallpox, swiftly adopted the practice and ordered compulsory variolation of all new at-risk recruits.[9] During the 1721 epidemic, the Prince of Wales (the future King George II) permitted the variolation of his two daughters, fortunately with an uncomplicated outcome, thereby enhancing the reputation of the technique.[12] To further endorse the benefits of variolation, James Jurin carried out a statistical analysis of the native disease and inoculation in 1722. He found that smallpox killed one-fourteenth of the inhabitants of London during the 42-year period before 1722, and that during bad epidemics up to 40% of those affected died.[13]

This 1802 caricature by British satirist James Gillray depicts Edward Jenner calmly vaccinating a fearful group of people, with cows erupting from various parts of their bodies — a popularly rumoured effect of Jenner's cowpox vaccine.
Source: Library of Congress, Prints & Photographs Division, LC-USZC4-3147.

The ancient variolation technique of introducing a small amount of necrotic material from a smallpox pustule into a small cut to the arm had been imported into England from Turkey 3 years previously.[12] English variolators, particularly the doctors, developed costly and complicated interventional schedules to accompany the procedure, such as the use of "antimonial and mercurial medicines" and "bleeding some and purging all" patients.[14] Variolation's major disadvantage was that it resulted in a potentially infectious recipient during the subsequent development of the rash. The procedure was also attended by a 1%–2% mortality rate. Balanced against these complications was the production of lifelong immunity, together with limited or absent body-wide pock marking.

Dr William Watson (1715–1787), physician to the London Foundling Hospital, carried out perhaps the first controlled trial in clinical medicine. Watson had previously experimented with the nature and properties of electricity, and was a botanist and a keen supporter of the new Linnaean classification system and its introduction to England. On the 12th of October 1767, he "experimented" on 31 non-immune children aged between 6 and 11 years, divided into three separate trial groups. The children were the abandoned waifs of the Foundling Hospital and all highly vulnerable to smallpox. The trial objective was to answer two questions: What was the best source of the inoculums? Was mercury (as calomel), taken as a pre-treatment, of any benefit? Most importantly, his trials included a control group of children who were given no medication before or after the variolation.[14] Watson graded the clinical response in all three groups by quantifying pustule size and number, as well as documenting accompanying symptoms.[14]

In his treatise published the next year, Watson correctly concluded that mercury added no benefit and that fluid used from both an early and mature pox were superior to that taken from a late lesion.[14] He also advised against inoculating children younger than 3 years of age.

As Boylston notes, when Watson's data are analysed today using the Kruskal–Wallis test, a non-parametric method of comparing independent groups, it shows that there were no significant differences between any pre-treatment and no pre-treatment or between any of the sources of the inoculums.[6] Importantly, however, Watson's experiments were characterised by a deliberate study design, contained quantitative conclusions, had results that were correctly interpreted, and, significantly, included a control arm.

It was 28 years later, on the 14th of May 1796, that Edward Jenner performed another experiment — but today this is not considered a clinical trial. In the process, however, Jenner introduced a new word into the English vocabulary, "vaccination", derived from the Latin, *vacca*, a cow. Louis Pasteur in the next century used the term "vaccine" to apply to all antigenic agents introduced percutaneously in recognition of Jenner's ground-breaking experimentation with cowpox vaccine.

Following wide-ranging discussion among his peers, Jenner introduced material taken from a cowpox-infected cow's udder into a small incision on the arm (by inoculation) of 8-year-old James Phipps. The child suffered no ill effects and some 6 weeks later he proved to be smallpox-resistant to

variolation. Following Jenner's scholarly treatise of 1798 entitled *An inquiry into the causes and effects of the variolae vaccine*, the story of smallpox prevention in England was marked by vigorous scientific and sociopolitical controversy lasting into the middle of the 19th century. Immediate scientific controversy following this seminal document was unfortunately exacerbated by Jenner himself when he asserted, subsequently shown to be incorrect, that primary cowpox vaccination conferred lifelong immunity to smallpox.[15]

Nineteenth-century public health measures in England continued the controversy surrounding smallpox vaccination by the introduction of the second Vaccination Act (1853), containing measures for compulsory smallpox vaccination. Free but compulsory vaccination was offered to the poor with calf-lymph vaccine administered by the Poor Law Guardians. Later amendments to the Vaccination Act outlined very unpopular penalties for non-compliance.[16] The 1853 and 1867 Vaccination Acts declared the inoculation technique illegal within Britain but also throughout the colonies.[17]

The last naturally occurring case of smallpox, in 1977, occurred in the African nation of Somalia. The last smallpox fatality ironically occurred in Birmingham, England, a year later, when a hospital worker was accidentally infected from the hospital laboratory.[12]

Portrait of naval surgeon James Lind (1715–1794). Source: Wellcome Library, London (no. 5826i).

The cure of the "scourby"

The narrative of the cure of scurvy is similarly vexed by 50 years of ensuing controversy, mainly scientific, but also by the important economic issue, namely the financial rewards to be gained by the first nation that could successfully and reliably protect their merchant and combat navies against the scurvy.

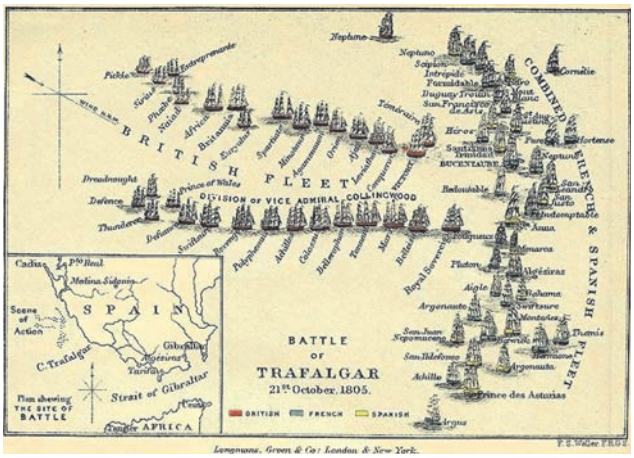
Some 3 years after Commodore Anson's single surviving ship limped back to England in 1744, the crews of the other four having been lost to the scurvy during the 4-year voyage, Surgeon James Lind, after receiving his captain's permission, commenced the first investigation into the cause of scurvy. Lind was a practical and dutiful Scot who wrote of the reason for his interest in discovering the cure for scurvy:

> After the publication of the Right Honourable Lord Anson's voyage by the Reverend Mr Walter … Some time afterwards, the society of surgeons of the Royal navy published their laudable plan for improving medical knowledge … It appeared to me [that scurvy was] a subject worthy of the strictest inquiry.[4]

Lind, with sea-duty experience of scurvy since the late 1730s, first searched for, abstracted and evaluated previous reports of the disease and drew on accounts sent to him by members of the Society of Naval Surgeons. All these data were meticulously recorded for the first time as the *Bibliotheca scorbutica*, an appendix to the first edition of his treatise.[4]

Lind, a ship's surgeon of relatively low professional status in the medical hierarchy of the day, commenced his work in a small ship of the line on station with the Channel Fleet on the 20th of May 1747. Six pairs of severely scorbutic sailors were mustered in the small cockpit, forward in the dank, dark orlop deck (the lowest deck over the ship's hold), and fed six different remedies during a 14-day trial. This experimentation by Lind may today be described as a form of "controlled empiricism", as he gave no

James Lind feeding citrus fruit to a scurvy-stricken sailor aboard HMS Salisbury *in 1747 (Artist: Robert A Thom).*
Source: http://education.vetmed.vt.edu/Curriculum/VM8054/Labs/Lab5/Notes/scurvy.htm (Originally from: A history of medicine in pictures*, published by Parke, Davis & Co. in 1960.)*



The attacking columns of the British fleet at the Battle of Trafalgar. Despite being outgunned, the British fleet had very few cases of scurvy compared with the Franco-Spanish fleet — a factor that helped to seal the outcome of the battle.

reason for his choice of possible remedies. The anti-scorbutic benefits of citrus fruit had been known since the early 1600s[18] but, curiously, were ignored by later seafarers. In his trial, Lind prescribed oranges and lemons for one lucky pair of subjects, but only 6 days' supply could be spared from the ship's stores. A second pair received an extemporaneous concoction of seven substances. A third pair were given straight sea-water, erroneously believed to be useful in scurvy prevention, while a fourth pair sipped two spoonfuls of vinegar three times a day. The unfortunate fifth pair were given 25 drops of an *elixir vitriol* (caustic sulphuric acid) three times a day, and the final pair were fed each day with a quart of slightly alcoholic cider. All 12 sailors were fed the same diet throughout the fortnight.[4] Unfortunately, due to the exigencies of the Service, the cramped conditions of the cockpit, or simply due to oversight, but not because of an insufficiency of cases of scurvy on board, Lind did not include a control group. The results of his investigation were immediate — so much so that the pair given the daily dose of two oranges and a lemon were deemed fit for full ship duties and were promptly set to nurse their 10 seriously ill shipmates. By serendipity, the trial succeeded simply because one of the treatments happened to contain vitamin C.

In 1753, the first edition of Lind's scientific analysis was published in a large, 400-page, three-part tome.[4] Yet in spite of the length and depth of his discourse, it seems that both Lind and his contemporaries thought that a simple dietary deficiency was too simple an answer to account for the cause of scurvy. In 1772, Dr Lind, now chief physician at the Royal Hospital Haslar, published the third edition of his *Treatise of the scurvy*; but he again remained unsure of the precise remedy for scurvy. On pages 537 to 540, Lind outlined the details of a further trial using an unfermented or fermenting infusion of malt, known as "wort", as a possible anti-scorbutic agent. On this occasion Lind did perform a controlled therapeutic trial, but concluded his report with the non-committal statement: "it is a very nourishing liquor and well adapted for scorbutic patients". Today's analysis of the wort's benefit relate to its high vitamin B complex content, thereby correcting the common accompanying vitamin B deficiencies of late 1770s shipboard-scurvy diets.

Further trial-and-error experiments at sea were continued by the explorer James Cook on his voyages between 1768 and 1779, some 16 years after Lind's initial publication. Cook carried a battery of anti-scorbutics; his favourite was a mixture of malt and sauerkraut. In spite of a remarkably scurvy-free crew, Cook too remained unable to identify the precise anti-scorbutic foodstuff with the richest vitamin C content. Ultimately, it was a third investigator, Gilbert Blane, whose lengthy research data convinced the Admiralty by 1795, almost 50 years after Lind's initial experiments, to order the Sick and Hurt Board to provide daily rations of citrus juice for crews of the Royal Navy and transport support ships.[8]

In a rising swell in the late morning of the 21st of October 1805, off Cape Trafalgar, near the southern Spanish port of Cadiz, Vice Admiral Viscount Nelson, Commander-in-Chief, Mediterranean, may very well have taken for granted the high level of fitness and training of his ships' crews when he signalled the fleet, by now splitting into two attacking squadron columns slowly sailing in line-ahead formation, that "England expects that every man will do his duty". This famous signal would have had far less effect and meaning had Lind, Cook and Blane not previously signalled the Navy that "Every man will now expect England to give him fresh food and citrus fruits daily". At the outset of the engagement, Admiral Villeneuve had a clear superiority in ships and guns — 33 sails of the line bearing 2632 guns to Nelson's 27 with 2148 cannon — however, his entire Franco-Spanish fleet was smitten by scurvy. The French flagship of Rear-Admiral Magon, the *Algésiras,* a 74-gun first of the line in the rear squadron, contained several hundred sailors with scurvy who were unfit for full sea duty, amounting to 37% of the crew.[1] Nelson's fleet, by comparison, had only isolated cases of scurvy. Far superior efficiencies and fitness among the ratings and leadership by battle-experienced captains and officers who followed a straightforward dedicated battle plan — the Nelson touch — sealed the outcome at Trafalgar. By 4:30 in the afternoon, all firing had ceased, 20 ships of the combined fleet were lost (although none by England), and Nelson had just died. Thereafter, the scurvy-free Royal Navy achieved and maintained a comfortable superiority over the combined navies of France, Spain and the Netherlands.

Conclusion

Both smallpox and scurvy remain highly fatal diseases, and early in the 18th century both were without known cure. That century witnessed the first applications of scientific experi-

mentation in the process of investigating disease causation and measures of prevention of both diseases. For both diseases, the publications of the original scientific reports were followed by vigorous controversy, lasting, in the case of Lind and Jenner's works, at least 50 years. England, like other nations, had a national interest in eradicating both diseases: smallpox and scurvy had always and readily undermined the national defence through sporadic outbreaks within the Army and Navy. Curiously, both diseases had known preventive strategies before the 18th century, but these were unknown to enlightened England. English seafarers had forgotten the 16th century knowledge of the anti-scorbutic effect of citrus fruits. England only become aware of variolation-induced smallpox immunity as late as the early 1700s, when this had been known in the Orient, India and the Middle East possibly for centuries.

The measures unearthed in 18th century England to combat these two scourges were universally successful, highly effective, entirely safe in the case of scurvy and associated with up to a 2% mortality rate following variolation for smallpox, were simple measures to apply, and cheap to implement. The cure of scurvy and the prevention of smallpox provided enormous improvements in the capability of naval and military forces of the past. Military medical science went on to continue the search for prevention and management strategies for the other major military epidemic diseases: malaria, typhus and the enteric diseases, cholera, shigellosis and typhoid fever.

As to the ethics of the experiments involving participant coercion, individual rights, experimental risks, informed consent and group monitoring, among other issues, little can be said except that the Watson trial participants were all non-immune deserted and abandoned children of the London Foundling Hospital who were susceptible to a common, highly fatal infectious disease. The same susceptibility applied to the below-deck seamen during the 1700s, who, particularly in times of the many wars, often suffered impressment into a Royal Navy vessel, typically out of the crew of a returning merchantman. The sailor thereby commenced his next, often long commission with either acute or subacute scurvy, to be once again fed a vitamin C-deficient ship's diet.

The 1747 scurvy trial by Lind lacked a control group, but not the later 1772 trial of the anti-scorbutic value of wort. At the time, James Lind's 1772 trial was only the second documented clinical trial designed with a control arm to have been undertaken in Western medicine. The 1767 experiments undertaken by Dr William Watson (later Sir William when a Vice President of the Royal Society in 1785)[19] were randomised but not double-blinded. Importantly, however, they were characterised by a deliberate study design, quantitative conclusions, results that were correctly interpreted and, significantly, by the inclusion of a control arm. His three mini-trials represent the first known randomised interventional clinical trials, which would wait, as would the development of the ethics of experimentation, another two centuries to become embedded within the framework of contemporary evidence-based clinical medicine.

Competing interests

None identified.

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