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Although numerical approaches were used by John Graunt to analyse patterns of mortality in 17th-century London,[1] it was not until the early 18th century that numbers began to be used to assess the effects of medical interventions.[2–7] This development occurred chiefly, but not exclusively, in Britain.[8–27] In 1731, for example, Francis Clifton published a book entitled *Tabular observations recommended as the plainest and surest way of practising and improving physick*,[28] followed by a work entitled *The state of physick, ancient and modern, briefly considered: with a plan for the improvement of it*.[29] Clifton pointed out that, instead of assessing the worth of therapies by whether they accorded with theories, physicians needed to base their judgements about the effects of treatments on a sufficient number of their own (or otherwise testified) observations, organized in tables.[30]

Clifton was followed later in the 18th century by others emphasizing similar principles: for example, William Hillary's *Inquiry into the means of improving medical knowledge*;[31] Thomas Percival's commentary on the 'dogmatist' and the 'empiricist' physician in his *Essays medical and experimental*;[32] John Gregory's *Observations on the duties and offices of a physician*;[33] James Sims' *Discourse on the best method of prosecuting medical enquiries*;[34] a section in John Aikin's *Thoughts on hospitals*;[35] Thomas Kirkland's *Inseparability of the different branches of medicine*;[36] an anonymous author's contribution to *Medical Observations and Inquiries*;[37] Gilbert Blane's *Observations on the diseases incident to seamen*;[38] and George Fordyce's *An attempt to improve the evidence of medicine*,[39] which was published in the *Transactions of a Society for the Improvement of Medical and Chirurgical Knowledge.*

Of course, there is a difference between calls for numerical methods to be applied and actually applying them. However, the principles enunciated by Clifton and others were applied widely in civilian practice in Britain, as well as in the British armed forces.

The application of numerical approaches to documenting diseases and assessing medical interventions in 18th-century Britain

The British medical literature contained many discussions of the need to document diseases and their treatments using numerical data derived from patients seen in civilian and military practice. Beginning in the 1720s, numerical methods were used to compare mortality after smallpox inoculation (variolation) with mortality after natural smallpox, in Britain, and in other parts of Europe, and in America.[18,19] Throughout the 18th century, writers prepared detailed numerical reports of their work and experience, and emphasized the need to use this type of information (see, for example, John Millar,[40–45] John Coakley Lettsom,[46,47] John Clark,[48,49] William Black,[50–52] Edward Alanson,[53] Gilbert Blane,[38] William Withering,[54] William Falconer,[55] and John Rowley[56]). They insisted on the need not only for regularly kept summaries of patient records and for mass observation, but also for numerical analysis of these data. Other authors simply got on with doing it. While the first group clearly thought about what they were doing, the others may just have fallen in line with what was becoming the empirical tradition, or, later in the 18th century, may have used numerical data simply because, by then, this was 'what was done'. Numerical data were sometimes reported only in

texts.[21,22,25,53,54,57–69] From early in the 18th century, however, data were increasingly also being presented in tables, beginning with results of smallpox inoculation.[2–5,70,71] The smallpox inoculation issue was probably the key to the use of what was later called the numerical method, that is, counting and comparing, as this appealed not only in Britain but was also used on the continent and in America.[72,73] In clinical medicine, the results of a new technique for amputating limbs were presented in a table.[74]

In his *Medical Memoirs of the General Dispensary* in London, John Coakley Lettsom[46] published detailed information about his treatments in tables arranged by disease categories. John Millar[41] did likewise with data from cases seen at the Westminster General Dispensary, as did John Clark[48] after founding a dispensary in Newcastle–upon-Tyne. Clark's tables were further subdivided according to age, sex and the calendar month of the onset of the health problem.[23] Alexander Gordon[75] tabulated data gathered at the Aberdeen dispensary, modelling his reports on the tables of Lettsom and Millar.

James Currie[76,77] tabulated data from patients admitted to the fever wards in the Liverpool Infirmary. Similar numerical analyses were published by other exponents of what has been called the late 18th century British 'fever hospital movement', for example, John Haygarth[78] in Chester. Rice Charleton[79] tabulated data by diagnosis when recording the progress of 1053 patients treated with the warm waters of Bath. Thomas Fowler[80] used tabulated data to report the progress of 400 patients to whom he had administered tobacco, and others to whom he had administered arsenic for treating the ague.[81] In 1795, a table of 78 cases backed up his conclusion that bleeding was only an auxiliary remedy in acute cases of rheumatism, and even less so in chronic cases.[82]

In the Royal Navy, Robert Robertson[83,84] and Gilbert Blane[38,85] tabulated the diseases experienced by British sailors in Africa, the West Indies, North America and the English Channel, always indicating the number of deaths following given treatments, sometimes in comparative tables.[83,84] John Clark,[48] when working as a naval surgeon for the East India Company, published very detailed tables of the diseases and fates of the sailors under his care.[23]

In the Army, John Rollo[86] may have been the first to use tables to give a detailed account of all the cases he had treated in a military hospital in Barbados. When he became chief of the Hospital of the Ordnance (artillery) at Woolwich, he published a hospital report based on the same principles.[87] Richard McCausland[88] published his comparative studies of various treatments for intermittent fevers in statistical tables.[89] Thomas Dickson Reide's[90] *View of the diseases of the Army* was full of tabular compilations and arithmetical calculations, as were James McGrigor's reports.[91,92]

Numerical data were quite often used to calculate simple ratios. For example, William Falconer[55] compared the results of his practice in Bath with that of Rice Charleton,[79] published earlier, by calculating success:failure ratios. Some analyses were quite sophisticated. For example, John Haygarth, with the help "of an ingenious friend, Mr Dawson, a truly mathematical genius", calculated that if two people living together escaped continuous fever and/or smallpox, the probability that they had never been exposed to 'an infectious quantity of the poison' was about 400 to 1; and if three persons in a family had escaped, this probability rose to above 8000 to 1. These probabilities 'computed arithmetically by the doctrine of chances, according to the data' led him to advocate the immediate isolation of smallpox and fever patients in specific wards in Chester.[78]

These and other hospital reports can be termed institutional investigations. They certainly had practical consequences. However, some writers also used institutional data explicitly to assess the effects of treatment.

Causal inferences about the effects of treatments based on numerical comparisons

Numerical data were used to make causal inferences about the effects of treatments from early in the 18th century. Discussions about variolation were informed by comparisons of mortality following variolation with mortality following naturally acquired smallpox.[2–5,71] Some of the observers engaged in these discussions recognised that it was important to ensure that these comparisons were based on comparing like with like. For example, in challenging inferences about the effects of variolation, Isaac Massey, an apothecary

at Christ's Hospital, London, insisted that "to form a just Comparison… the Circumstances of the Patients, must and ought to be as near as may be on a Par".[93] James Lind,[59] and later Alexander Hamilton[94] and Charles MacLean,[95] insisted on this point.[24,96]

Application of this principle in practice can be illustrated using William Cheselden's observation that it was necessary to take the ages of patients into account when comparing case series reporting mortality associated with different methods of lithotomy. As early as 1740 he noted that '… what is of most consequence to be known is the ages of those who recovered, and those who died'.[97] He grouped 213 patients in 10-year age groups and reported the number of deaths for each group, thus showing the substantially lower mortality among children than in adults, as shown in Table 1 derived from Cheselden's text.

In 1779, John Millar presented a tabulated account of 'the comparative success of bleeding and cooling medicines, and of opium and the Peruvian bark' on 'contagious fever' in Senegal. In 1783 he insisted that 'the stubborn evidence of arithmetical demonstration could not be shaken by argument', and used yet another comparative table to show the supremacy of Peruvian bark (cinchona) over conventional bleeding and purging.[45] Edward Alanson, a surgeon working in Liverpool, used 'historical controls' to assess the effects of using skin flaps to achieve primary closure of wounds after amputations.[20,53] Robert Robertson compared Peruvian bark (cinchona), bleeding and antimonials in treating fevers,[84] and John Ferriar tabulated a comparison of different treatments (mainly digitalis and cream of tartar [potassium bitartrate]) for different forms of dropsy.[98] John Clark[49] used the surgeons' day-books of the East India Company to compare the results of various treatments of 'fevers', as did John Millar.[42]

In addition to these and other causal inferences about the effects of treatment comparisons based on retrospective analyses of numerical data, there are also examples based on prospective experiments. James Lind's account of his comparison of six treatments for scurvy is probably the best known of these;[59] less well known is Thomas Trotter's demonstration that unripe guavas were more effective anti-scorbutics than ripe guavas.[99] Some 18th century experiments were very sophisicated:[100] William Watson used a beautifully designed prospective comparison to assess alternative ways of reducing the side effects associated with variolation.[101] Besides the smallpox work, a trial of delayed versus immediate amputation,[63] and the refutation of mesmerism by Benjamin Franklin and the other members of a commission of the Académie Royale des Sciences in Paris[102] make clear that methodologically refined studies were also being done outside Britain.[103] Towards the end of the century, again in England, Caleb Hilliar Parry[104] did a cross-over trial to evaluate the effects of various types of rhubarb[105] and, at the turn of the centuary, John Haygarth conducted a single blind cross-over trial on seven patients to assess whether Perkins' metal 'tractors' had any more effect on symptoms than placebo tractors made of wood.[68] In prospective studies done during the Peninsular War, George Guthrie compared immediate versus delayed amputation of shattered limbs of wounded soldiers,[106] and Alexander Hamilton assessed the effects of bloodletting by alternating 366 sick soldiers to treatment with or without venesection.[94]

Were these numerical approaches recognized as important?

How were these numerical approaches to the assessment of medical interventions received in

Table 1
The substantially lower mortality among children than in adults, derived from Cheselden's text

	Age (years)								
	10 or under	*11–20*	*21–30*	*31–40*	*41–50*	*51–60*	*61–70*	*71–80*	*Total*
Operated	105	62	12	10	10	7	5	2	213
Died	3	4	3	2	2	4	1	1	20

contemporary Britain? This question can be addressed by looking at the evidence presented during the first three decades of the 19th century. Some prominent contemporary British medical writers appear to have ignored these numerical approaches. For example, Tröhler[8] was unable to find direct reference to numerical approaches in the lectures of Cullen or Gregory in Edinburgh, or those of John Hunter in London. Important figures of the London medical establishment around 1800, such as William Heberden and his son, though interested in vital statistics, did not mention or use numerical approaches when they wrote about treating diseases.[107,108] On the other hand, the revival of bloodletting in the first decade of the 19th century was launched by a book in which the mortality of three regimens (no bleeding, moderate bleeding, and copious bleeding) were compared in the same disease in the same hospital.[109] These analyses suggested that the more the lancet was used, the better were the results. As noted many years ago by Peter Niebyl, this comparison was made 'long before the famous work of Pierre Louis in France'.[110] The effectiveness of bloodletting was claimed, in the year after Sutton's book, by another book written entirely without numerical data,[111] and in 1812 by one comparing mortalities.[112]

What did the medical journals of the time have to say about numerical assessments of medical interventions? The most important review journal of British medical literature was *Medical and Philosophical Commentaries* (published between 1774 and 1795, and then continued first as *Annals of Medicine*, then as the *Edinburgh Medical and Surgical Journal* until 1855). It was published simultaneously in London, Edinburgh and Dublin, and had a wide circulation.[113,114] The journal published reviews of many of the books referred to above. John Clark's books were included twice, the second time with some very flattering remarks.[115,116] The journal reviewed favourably several works which had employed numerical approaches, although it made no specific remarks on methodology. These included, for example, Thomas Percival's numerical analyses of mortality in and around Manchester, John Coakley Lettsom's work at the Aldersgate Dispensary, and William Black's work on smallpox. By contrast, Thomas Fowler's and William Withering's works were the subject of repeated methodological comments concerning the use of numbers. The review of Gilbert Blane's *Observations* was 70 pages long, and commented very favourably on his methodological programme using mass observation.[117] Haygarth was praised for calculating the probability of the contagiousness of typhus.[118]

From 1805, the *Edinburgh Medical and Surgical Journal* began to publish critical book reviews, not mere analyses. One such review described James Currie's *Medical Reports* (which had made extensive use of numerical data) as 'one of the most valuable [books] which has ever been published… the style and manner should be imitated'.[119] Haygarth's *Clinical Histories of Diseases*[120] was seen as a good example of a doctor taking the trouble to record his observations and, having accumulated a sufficient number, to arrange and then reduce them to a tabular state, intelligible to others.[121] When reviewing William Black's Dissertation on insanity,[122] the editor of the *Edinburgh Medical and Surgical Journal*[123] emphasized the need to subject assessment of remedies and modes of cure and prevention to 'arithmetical proof'.

On the other hand, failure to provide numerical evidence sometimes prompted questions about the author's claims of therapeutic success stated only in 'general and equivocal terms'. For example, the reviewer of a book by Jackson[124] observed:

> *we are altogether at a loss to discover the comparative advantages of the practice of his own hands… we doubt whether he has made the comparative experiment so often, as to ascertain the effect [of his method of cure].*[125]

Another review journal – the *London Medical Review* – included an analysis of the third edition of Blane's *Observations on the diseases incident to seamen*. Blane's methods were seen as having set an example worthy of imitation, and its principles were again fully reprinted. The journal deemed John Rollo's account of the arrangements made for collecting patient data in the Artillery Hospital at Woolwich so valuable that it 'might be read with advantage by all persons concerned in the establishment or regulation of an infirmary'. It was fully reprinted, including the tabular hospital report.[126]

From about 1820, a few doctors reacted to such feelings of perplexity and to outspoken criticisms of numerical methods made by men who had never actually used them. For instance, in the debate about bloodletting, simple comparisons were now considered inadequate if they did not compare similar groups of patients.[127] In 1820 Guthrie found it easy to defend his views against an influential civilian surgeon, John Bell, who 'had no practice of his own and little opportunity of enquiry into that of others [… and] reasoned from theory, probably on an individual case, and not from actual observation made on many'.[128]

Alexander Copland Hutchinson refined Guthrie's examination of the timing of amputations by sending a circular letter to the surgeons of all 11 ships engaged in the Battle of Algiers, in 1816. He required not only precise anatomical locations but precise timing of amputations and cure rates and summaries of the results a year later.[129] Among others, Rutherford Alcock, a pupil of Guthrie, went on to criticize his teacher's recommendations. He asserted that comparisons of conservative with operative treatment were required which used more data and analyses that took account of a number of external circumstances. Alcock furnished these in a series of detailed statistical reports compiled from returns he had required as medical head of a British expeditionary force in the Carlist War in Spain (1835–1836), using the reporting approaches initiated decades earlier, by his chief, the still active James McGrigor.[130–132]

It seems reasonable to conclude from the evidence presented so far that many British doctors around 1800 must have been aware of numerical approaches. As noted in the *Edinburgh Medical and Surgical Journal* in 1809, it seemed to have become unacceptable to defend a treatment method as 'generally successful without any discrimination of circumstances'.[133] For example, Ferriar's *Medical Histories*[134,135] were criticized for lacking the additional evidence that the first editions had seemed to promise.[136,137] That the principle of numerical approaches was accepted in some influential circles is further illustrated by the fact that complaints about the absence of accurate hospital record-keeping which Blane, Robertson and many others had made in the 18th century continued to be endorsed by 19th-century authors (see, for example, Marcet[138] and Phillips[139]) and by the *Edinburgh Medical and Surgical Journal* in the 1810s and 1820s. This deplorable state of affairs was even noted by a Select Committee appointed by the House of Commons in 1818, the censure of which was published by the journal.[140] The *Lancet* also led a vigorous campaign for the publication of results as part of its original policy (see, for example, Wakley,[141] Sprigge[142] and Gibbon[143]).

In 1831, in the spirit of Clifton and those following him over the previous century, Tweedy John Todd, a fellow of the Royal College of Physicians of London, published a methodological book entitled *The book of analysis, or a new method of experience whereby the induction of the Novum Organon is made easy of application to medicine… .*[144] Two years later, William Poulteney Alison, a celebrated Edinburgh professor of medicine, published his *Dissertation on the state of medical science, from the termination of the 18th century to the present time*.[145] Alison noted the contributions of the numerical methods which were being used by his early 19th-century contemporaries – mentioning Johnson[146,147] and Hawkins[148] in particular. However, he also pointed out that they were not the originators of a new method of enquiry; rather, they continued a long line of development of comparative numerical inquiries to assess therapy, to which Robertson, Percival, Clark, Blane and McGrigor had all contributed.[145] Furthermore, in the same sentence in which he mentioned the numerical nosography of Louis and others in France, he also noted earlier comparable work by John Cheyne[149] in Dublin and Thomas Bateman[127] in London (he might also have mentioned Haygarth's much praised *Clinical Histories of Diseases* in this context). Alison's and Hawkins' overviews around 1830, as well as the specific reports of contemporary army, navy and civilian hospital doctors,[8] rather than being innovative, were the products of a steady development which had its roots in British military medicine and specific aspects of British hospital and dispensary medicine of the 18th century.

In summary, it had begun to be quite widely accepted among opinion-formers in British medicine that treatment claims should no longer be accepted on the basis of reports of single cases by medical 'authorities', as previously. A 'numerical culture' had become established during the

18th century in British medicine and surgery.[150] This process was nurtured by the specific intellectual climate of the Age of Enlightenment in Britain, which opened the door for the acceptance of meritocracy in medicine.[16,151] This new medical culture did not dominate the research activities of British doctors; it competed with normal and pathological anatomy, animal experimentation, and clinical case studies. Yet, as far as the evaluation of therapies was concerned, there was now an expectation that treatment claims would be supported by numerical statements based on the results of numerous, comparative observations – an approach characterized by the term 'rational empiricism'. John Bostock, a well-known physician, physiologist and medical historian, wrote in 1833:

> *rational empiricism… has produced a most beneficial influence on the general state of medical practice. If it has, on some occasions, produced fluctuation of opinion, and in others indecision of inertness, it has tended to sweep away much error, and to purify the science from many of the antiquated doctrines and practices that still maintain their ground among our continental brethren.*[152]

Disputes about the interpretation of numerical data

In 1813, Thomas Mills had re-introduced copious bloodletting and purging during a temporary appointment at the Dublin Fever Hospital. The statistics comparing his mortality rates with those of the regular physicians who had hardly used bloodletting were reprinted in the review of his *Essay on the utility of blood-letting in fever*,[112] and elicited the following comment:

> *presuming… .these are candid and correct statements, we may deem them potent arguments in favour of the advantages of the anti-phlogistic [bloodletting and purging] treatment of fever.*[153]

With this method, Mills was judged to have adduced 'very strong proof' of the superiority of bloodletting.[153] Guthrie's answer to the question of the timing of amputation, and the works of McGrigor and Blane drew forth similar praise.[154]

With the availability of more and more numerical data, numbers began to be pitted against numbers. Thus, for example, during the debates about bloodletting for the treatment of fever, statistics were widely used on both sides.

This reiterated the debate about the interpretation of the statistics used, which had gone on in the 18th century about the statistics of inoculation.[155] For instance the *Monthly Review* wrote that Mills' work left 'a rather painful impression on our minds'[156] and noted that these impressive results might be explained by the type of patients treated by Mills rather than by the therapy he had applied.[155] But a writer in the *Edinburgh Medical and Surgical Journal* in 1813 stressed that, if one could assume the data to have been honestly assembled and presented by both sides, the only way out of the maze would be through 'extensive comparative experiments'.[153]

In contrast to the evidence of national acceptance of numerical methods in Britain early in the 19th century, numerical analyses published in Paris by Pierre-Charles-Alexandre Louis,[157] which called into question the value of bloodletting,[158] caused controversy that lasted for several decades.[159–164] Among others, Louis was criticized by his mathematically inclined contemporary, Jules Gavarret, who pointed out that the size of Louis' samples had been too small to be reliable,[165] a problem that had been recognized 20 years earlier by British authors discussing paradoxical statistics in the bloodletting controversy around 1810.[153] The controversies in France must have played a useful role in prompting reflection on causal inferences in medicine, at least in Paris. There were lively academic discussions in the 1830s and again at the end 1840s, both in the Académie Royale de Médecine and the Académie Royale des Sciences.[163] Later in the 19th century, the discussions in Paris ended with the compromise that 'medical statistics' needed to be distinguished from 'the numerical method': while the former was applicable, even indispensable, to epidemiological studies, the latter procedure was rarely convincing in the clinical evaluation of therapies, mostly 'because therapeutics was so much in need of appropriate remedies'.[163] Although interest in the methodology of treatment evaluation never actually died out (see 19th-century entries in www.jameslindlibrary.org), it was no longer in the forefront of discussions after 1850. However, it was at about that time that medical researchers began to give serious attention to the design of prospective comparative clinical experiments.[166,167]

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