

Durham Research Online

Deposited in DRO:

07 January 2014

Version of attached file:

Accepted Version

Peer-review status of attached file:

Peer-reviewed

Citation for published item:

Maehle, Andreas-Holger (2013) 'Four early clinical studies to assess the effects of Peruvian bark.', *Journal of the Royal Society of Medicine.*, 106 (4). pp. 150-155.

Further information on publisher's website:

<http://dx.doi.org/10.1177/0141076813482256>

Publisher's copyright statement:

The final definitive version of this article has been published in the *Journal of the Royal Society of Medicine* 106/4, 2013 © The Royal Society of Medicine by SAGE Publications Ltd at the *Journal of the Royal Society of Medicine* page: <http://jrs.sagepub.com/> on SAGE Journals Online: <http://online.sagepub.com/>

Additional information:

The full-text of the deposited file is made available under a Creative Commons Attribution 3.0 Unported License.

Use policy

The full-text may be used and/or reproduced, and given to third parties in any format or medium, without prior permission or charge, for personal research or study, educational, or not-for-profit purposes provided that:

- a full bibliographic reference is made to the original source
- a [link](#) is made to the metadata record in DRO
- the full-text is not changed in any way

The full-text must not be sold in any format or medium without the formal permission of the copyright holders.

Please consult the [full DRO policy](#) for further details.

Maehle A-H (2011). Four early clinical studies to assess the effects of Peruvian bark.



© Andreas-Holger Maehle, Department of Philosophy, University of Durham, 50 Old Elvet, Durham DH1 3HN. Email: a.h.maehle@durham.ac.uk

Introduction

From the late seventeenth century onwards, *in vitro* and animal experimentation, chemical tests and microscopical observation, and the analysis of single case histories were used to understand the pharmacology and therapeutic properties of the Peruvian bark. Four examples illustrate how “clinical experiments” with the bark were made during the last third of the eighteenth century: in a hospital, the army, the navy, and finally in private practice.

Cite as:

Maehle A-H (2011). Four early clinical studies to assess the effects of Peruvian bark. JLL Bulletin: Commentaries on the history of treatment evaluation (www.jameslindlibrary.org).

Francis Home

The first example is that of the Edinburgh professor of *materia medica*, Francis Home (1719-1813), who tested various medicines on patients in the Royal Infirmary ([Home 1780](#); Home 1782; Risse 2005). In words reminiscent of John Aikin’s *Thoughts on Hospitals* ([Aikin 1771](#)), Home explained why he regarded patients in this charitable institution as particularly suitable: their complaints originated from the body rather than the mind or habits; compared to patients in “higher life”, their “theories and caprices” were less troublesome; they usually had no long history of previous treatments; and their diet was under absolute control (Home 1782, p v-vi; Aikin 1771, p 79-80). Furthermore, since simple medicines were prescribed in hospital practice, the effects of single drugs could be observed in rather pure form. More specifically, in the teaching ward of the Edinburgh Royal Infirmary, studies were witnessed and discussed by other doctors and students; and the cases were carefully documented, both in the Infirmary’s records and the students’ ‘report-books’ (Home 1782, p vi-ix).

Home was aware of the ethical implications of his therapeutic experiments. The physician, he stated, was ‘responsible to his own conscience alone’ and could try new treatments, provided he had ‘a probability of success’ and proceeded with caution (Home 1782, p vi; Aikin 1771, p 80-1). Indeed clinical experimentation was criticized by Home’s colleague James Gregory (1753-1821), who described it as ‘*corio humano ludere*’, that is, ‘playing with human hide’. Like Home, he demanded that the patients themselves should benefit from the studies to which they had contributed, and that they must not be put in danger for the sake of scientific curiosity. Aikin, in contrast, in defending studies on hospital patients, observed ‘I am aware that the very name *experiment* occasions great outcries and prejudices among the vulgar; and that it is apt to startle some well disposed persons of a superior class’ ([Aikin 1771](#), p 76).

In such a climate of ethical awareness it was certainly important for Home to be clear about his intentions. These were, as he declared in the summary of his studies, ‘to ascertain the effects and value of several remedies in general use, and to discover new relations in others’ (Home 1782, p vii-viii). Both aspects played a role in his studies of Peruvian bark. Home’s main study of the bark was concerned with whether it should be given shortly before or just after a fit in intermittent fevers. The former method was traditional, going back to the *Schedula Romana*, i.e. the common form of prescribing Peruvian bark since the mid-seventeenth century; yet, it was also the most up-to-date, being taught by his colleague Cullen, because the drug’s supposed nervous action was thought not to last very long. The second method, on the other hand, had been advocated by authorities on fevers, such as Sydenham in England and Torti in Italy (Home 1782, p 2-6; Jarcho 1993).

In fourteen patients with various intermittent fevers (tertian, ‘double tertian’, and quotidian) treated in the Royal Infirmary at different times between 1769 and 1779, Home compared the two methods. In eight patients to whom the bark was administered shortly before the next expected fit, the fit could not be stopped, and only in three patients was the succeeding fit prevented. By contrast, in six patients to whom the drug was given after a paroxysm, there were no further febrile attacks. Being aware that his patients were not entirely comparable, Home tried both methods at different times in the course of treating three patients, in what we would term cross-over trials today. The outcome of these experiments also indicated that giving bark after a fit stopped further fits, whereas administration just before a paroxysm failed to do so. Moreover, in two cases the latter approach had made patients worse by provoking vomiting (Home 1782, p 8-11).

Home’s inferences from these studies were not limited to conclusions about therapy. Without naming Cullen, he also

modified the latter's theory of the bark's action. In Home's view, the rather long period of time taken by the drug to have its effect showed that it did not act solely through the stomach and nervous system, but that its chief effect depended on its absorption into the circulating blood. In addition, he pointed out that Peruvian bark preparations applied to the skin were effective, which demonstrated that action on the stomach was not necessary. Though Home explicitly conceded that the bark probably did act on the nerves, he thus concluded that it would find 'a much greater field' and 'greater sensibility' in the vascular system (Home 1782, p 12).

Home's remaining experiments explored the efficacy of Peruvian bark in other diseases, without the comparative method used in his first trial. In four patients the drug was given in *typhus nervosus*, or low fever, with varying results. While bark appeared inappropriate when the disease was linked with respiratory problems, it seemed recommendable if there was 'general symptomatic sweating', tremor, or 'little or no drought' (Home 1782, p 15-20). In two cases of *phthisis pulmonalis* (one of whom was from Home's private practice) the bark seemed to make symptoms worse through its property 'to bind the breast' (Home 1782, p 119-20). Finally, in eight patients to whom Peruvian bark was given as an antispasmodic (in epilepsy, hysteria, St Vitus' chorea, catalepsy, and hiccup), most were 'much relieved' or 'cured' (except in hiccup). Home concluded that the bark was an excellent remedy in 'pure spasmodic diseases', but since it was generally known that it was harmful in inflammatory states, care had to be taken to avoid using it in spasms accompanying inflammation (Home 1782, p 206-8).

The reason why Home had experimented with the bark was not only to find the best form of treatment in a given clinical condition. Economic considerations played a role as well. As he explained with reference to his first trial:

It is often necessary to save the bark, as much as possible, in the army and navy. It may become scarce during war, or fail us from other accidents. Less will do, when given in the proper time; more will be required in a less proper time (Home 1782, p 1-2).

This was precisely the background to the next two examples of clinical studies to assess the effects of Peruvian bark. These were performed by two surgeons in the British army and navy, respectively, during the American War of Independence.

Richard McCausland

Richard McCausland (dates not known) had been stationed at Niagara since 1774 with the King's 8th Regiment of Foot. The frequency of intermittent fevers among the troops, seamen, and 'persons dependent on the post' had led to a shortage of Peruvian bark, making it necessary for him to try other remedies. Between 1775 and 1781, McCausland treated these patients with tartar emetic (antimony potassium tartrate) in the form of pills or solutions ([McCausland 1783](#)). In his report, published in Andrew Duncan's *Medical Commentaries*, he claimed to have had a success rate of two in three cases with this medicine, and to have 'removed' on the whole three hundred 'agues' in this way (McCausland 1783).

He gave details of some of these cases in statistical tables, which indicated that the pills were more successful than the solutions. Overall, McCausland recorded that, among all his fever patients treated with tartar emetic (in either form), 84 had been 'cured', 19 had 'relapsed', and 49 had not been 'cured'. He compared these results with those following the use of Peruvian bark: 60 fever patients were registered as 'cured' and 34 as 'relapsed'. In other words, the ratio of cures to relapses was about 4:1 for tartar emetic, and about 2:1 for Peruvian bark, and McCausland commented that there had been 'much fewer relapses after the tartar emetic than after the Peruvian bark' (McCausland 1783, p 256). However, he interpreted and weighed his evidence very carefully. He noted that, because of vomiting, tartar emetic had been 'inadmissible' in 15 of the patients treated with bark, and that bark had been previously given without success in a further 15 patients. On the other hand, tartar emetic treatments had been conducted in the summer, when the rate of relapses was usually high, while the bark had been used later in the year, when cold weather put a natural end to the epidemic of intermittent fevers. Moreover, a 'considerable number' of those treated with the bark left Niagara immediately afterwards, so that possible relapses could not be noted. These circumstances spoke indirectly for the tartar emetic. All in all, McCausland concluded that 'the arguments on both sides seem so nearly balanced, that we may venture to take the table as it stands' (McCausland 1783, p 257).

McCausland was similarly careful in his judgements on other comparative studies that he did while at Niagara. For intermittent fevers, these included tartar emetic combined with liquid laudanum (opium in wine) and *sal ammoniac* (ammonium chloride), and tartar emetic together with crude opium; in syphilis, various mercury sublimate preparations, with and without 'decoction of the woods' (probably guaiac and sassafras wood) and warm baths, mercurial ointments plus warm baths, and Plummer's Pills (sulphides of antimony, sublimated sulphur, calomel, and gentian) together with 'decoction of the woods'; and in dysentery, various combinations of emetic and cathartic salts, astringents, ipecacuanha, rhubarb and calomel, and *vitrum ceratum antimonii* (glass of antimony with beeswax).

The comparative design of McCausland's studies – as well as that of Home's studies on the bark in intermittent fevers – are reminiscent of James Lind's 1747 comparisons of treatments for scurvy ([Lind 1753](#)). Yet, there was an important difference. Lind's report indicates that his study was carefully planned prospectively, and performed on a selected

group of comparable patients treated concurrently under similar conditions. McCausland's and Home's studies, by contrast, were retrospective comparisons of patients treated over a period of many years during which various treatments had been tried on a rather *ad hoc* basis – sometimes deliberately, sometimes out of necessity.

Even so, the evidence of methodological awareness, especially in McCausland (a figure unknown in the historiography of medicine), is remarkable. The army surgeon, who asked his readers for forbearance, since he had been cut off from the literary world 'for these last thirteen years, and ever since he left the schools of medicine', discussed in detail 'the fallacy of observation'. Errors arose, he argued, when 'decisive conclusions' were drawn from a very limited number of experiments. Individual factors could influence single cases. The patient might hide the cause of his complaints from his physician (for example, in venereal diseases), or, disgusted with a nauseous remedy, he might unjustly ascribe bad effects to it. Diet, air, and other diseases could determine the outcome. Or the 'effort of nature' and 'lucky circumstances' might bring success, leading the practitioner to the false belief that this was due to the remedy. Moreover, medical practice could be influenced by motives of 'prejudice', 'obstinacy', and 'caprice' (McCausland 1783, p 280-3). McCausland concluded that, to avoid errors through such individual influences, large numbers of observations were necessary, and these had to be documented and published:

As long as there is no public repository of facts, nor any channel by which they might be conveyed to the world, so long will medicine probably labour under the imperfections we have been endeavouring to describe; for I believe it will readily be acknowledged, that in the proportion that experiments increase in number, in the same proportion are they set out of the reach and influence of the above mentioned casualties. It follows, therefore, that solid and invariable conclusions upon any subject, can only be drawn from a very large number of experiments and observations (McCausland 1783, p 281-2).

Obviously unaware of the work of Home and others, McCausland therefore suggested that tabulated registers of cases were kept in military and public hospitals and dispensaries, and that private practitioners did the same. The colleges of physicians, he imagined, could organize clinical studies in the hospitals, and as a result, the pharmacopoeias would quickly be 'weeded of their useless articles, whilst the virtues of every truly valuable remedy would be publicly known, and established upon the most incontestable footing' (McCausland 1783, p 285-6).

Robert Robertson

As for McCausland, it was the scarcity of the Peruvian bark during the American War – not doubts about its efficacy – which prompted the 'arithmetic observations' on this medicine made by Robert Robertson (1742-1829) in the Royal Navy. In 1776, when his observations began, Robertson had served for over fifteen years with the navy and was surgeon on His Majesty's Ship *Juno*. From his long experience he had been convinced that the bark was the 'only' reliable cure of fever in hot climates (Robertson 1773; 1783; 1789; 1790; 1807) Accordingly he had used the drug also for the treatment of ship fever (the equivalent to 'typhus' or hospital fever) when it broke out on board the *Juno* in America (Robertson 1789). Towards the end of 1776, however, he was running out of stock. When the ship arrived at New York, Robertson later recalled that 'Peruvian bark was sold a guinea per pound: a price sufficient to tempt the sellers of that valuable drug to adulterate it; and to prevent surgeons of his majesty's ships from purchasing it'. He could therefore only use the bark 'in particular cases', a fact, which became the basis of a therapeutic comparison (Robertson 1807, vol. ii, p 176-177).

Because of the shortages, most of Robertson's fever patients had to be treated with antimony preparations, camphor, and blisters. Robertson recorded six deaths among the 296 patients of this group, and contrasted this mortality of 1:49 (2.03%) with only one death in 216 fever patients (0.46%) who had been given Peruvian bark. These figures referred to cases treated on board the *Juno*. A number of the ship's fever patients were sent to the New York Hospital and Rhode Island Hospital, where they were treated with camphor and antimonials. In both these institutions the death rate for these patients was about 1:7 (5 of 36, and 4 of 26, respectively) (Robertson 1807, vol ii, p 233). In Robertson's view these results – which he presented in tables – demonstrated how justified his preference for the cinchona treatment had been (Robertson 1807, vol. ii, p 177). In fact he became later known as a staunch advocate of a generous and early administration of the bark in any kind of fever (except those originating from 'actual inflammation, or topical affection') (Robertson 1789). Or as Robertson put it full of confidence in 1789, now being physician to the Royal Hospital in Greenwich:

The danger which theorists threaten us with, from an early and liberal use of bark in fever, strikes me with the same idea as if they told me, I should possibly fall, if they saw me running out of a magazine of powder, which I knew was immediately to blow up by a train leading to it being lighted. (Robertson 1789, p 371-372)

T Colingwood

As mentioned above, Home had seen the 'theories' and 'caprices' of patients in 'higher life', that is, of private patients, as an obstacle to therapeutic experimentation. And John Aikin had stressed in the same context that, outside the hospital, practitioners had to be too much concerned about their reputation and were therefore reluctant to try new methods of treatment (Aikin 1771, p 80). Yet the enthusiasm both for Peruvian bark and for arithmetic observations of

its effects also reached private practice.

In 1785, Duncan's *Medical Commentaries* published a report from T Colingwood (dates not known), an otherwise unknown surgeon in Alnwick, Northumberland. This included quantitative information about his various therapeutic experiences with the bark (Colingwood 1785). Colingwood's observations were less organized and less coherently presented than those of Home or of the military surgeons McCausland and Robertson; they were also based on the results of retrospective analysis of cases. But Colingwood had clearly followed two approaches. First he explored the therapeutic spectrum of Peruvian bark. He reported having 'cured' 22 out of 25 cases of intermittent fever with bark in 1778, and, in the same year, of 80 smallpox patients given the bark, five died, compared with two out of six patients who had not been treated with it. The following year, 21 of 25 cases of confluent smallpox had recovered after the bark therapy, and, of nine dysentery patients who had previously been treated with ipecacuanha, *vitrum antimonii ceratum*, and bloodletting, five recovered after treatment with bark. Colingwood further mentioned that he had used the bark successfully in whooping cough, remittent fevers, mortification in cachectic patients, slow and nervous fevers, and periodic pain in the face and temples, which he regarded as 'a species of rheumatism'. On the other hand, Peruvian bark had proved 'hurtful', if a 'topical inflammation' or an 'obstruction of the viscera' existed, and it had increased the 'hectic fever' of *phthisis pulmonalis*. In other words: Colingwood's (more or less) quantitative observations largely supported the therapeutic indications for the bark which had been suggested by more prominent authors of his time, such as Pringle, Cullen, and Home.

Colingwood's second approach concerned the therapeutic efficacy of different 'species' of Peruvian bark then on the British market. The experiences described above had been made with the commonly used 'quill bark'. In 1779, however, so-called 'red Peruvian bark' had become available. Colingwood, who regarded 'experiments tried on human bodies preferable to pharmaceutical investigation', reported his observations with the new kind of bark: of eight patients with intermittent fever in 1782 he had 'cured' four with 'red' and two with 'quilled' bark. Moreover, he reported successful use of the new red bark in nervous fevers, in two cases each of 'chronic rheumatism' and 'obstructed menses', and 'without any failure' in dysentery. On the whole he thought the new, red bark was more reliable, and curative in smaller doses, than the conventional sort; and it rarely caused gripes, which had been a common problem with the quill bark (Colingwood 1785, pp 273-5). In fact in the mid-1760s, the young Thomas Percival, then practising in Warrington, had made numerous pharmaceutical studies to find a preparation of the bark that was not only 'elegant' and 'sufficiently efficacious', but also 'palatable' (Percival 1767, p 221-3).

Collectively, the examples of Home, McCausland, Robertson and Colingwood show the methodical range used by these late eighteenth century medical practitioners in their attempts to justify and refine therapeutic methods by providing comparative, quantitative information on their successes and/or failures with different forms of treatment. The quantitative, retrospective analysis of their therapeutic experiences during a given time, sometimes with a few, sometimes with hundreds of cases arranged in tables, helped practitioners to shape their preferred methods of treatment (see also Maehle 2008; [Tröhler 2010](#)), although they were aware that the outcomes of their therapies could have been influenced by many factors beyond the remedy itself.

There was also an ethical awareness about the risks for patients posed by novel treatments, as well as concern about a practitioner's reputation if his patients felt that they were experimented upon. However, charitable hospital practice and shortages of medical supplies in the army and navy during wartime provided opportunities to investigate the efficacy of an established but expensive remedy such as Peruvian bark for new indications or different manners of application, and to compare it with other, cheaper treatments.

Note: This article is based on a section (p 268-275) of Maehle A-H (1999). 'Peruvian Bark: from specific febrifuge to universal remedy'. In Maehle A-H. *Drugs on Trial: Experimental Pharmacology and Therapeutic Innovation in the Eighteenth Century*. Clio Medica/The Wellcome Institute Series in the History of Medicine. Amsterdam: Rodopi, the full text of which is available here:

<http://www.ingentaconnect.com/content/rodopi/clio/1999/00000053/00000001/art00005>

Acknowledgement

The author thanks Sir Iain Chalmers for his friendly encouragement and the Wellcome Trust for its generous support.

This James Lind Library commentary has been republished in the *Journal of the Royal Society of Medicine* 2013;106:150-155.

References

Aikin J (1771). Thoughts on hospitals. London: Joseph Johnson.

Colingwood T (1785). Observations on the Peruvian Bark. *Medical Commentaries*, x, 265-275.

Home F (1780). Clinical experiments, histories and dissections. Edinburgh: Creech; London: Murray.

Home F (1782). Clinical experiments, histories, and dissections. 2nd edition, London: Murray.

Jarcho S (1993): Quinine's predecessor: Francesco Torti and the early history of Cinchona. Baltimore: Johns Hopkins University Press.

Lind J (1753). A treatise of the scurvy. In three parts. Containing 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. Edinburgh: Kincaid and Donaldson.

Maehle, A-H (2008). Experience, experiment and theory: justifications and criticisms of pharmacotherapeutic practices in the eighteenth century. In: Helm J and Wilson R, eds., Medical theory and therapeutic practice in the eighteenth century. Stuttgart: Steiner, p 61-76.

McCausland R (1783). Facts and observations on different medical subjects. Medical Commentaries, viii (1781/82), 247-96.

Percival T (1767). Experiments on the Peruvian Bark. Philosophical Transactions, lvii, p 221-3.

Risse G B (2005): New medical challenges during the Scottish Enlightenment. Amsterdam: Rodopi.

Robertson R (1777). A physical journal kept on board His Majesty's Ship Rainbow. London: Dilly.

Robertson R (1783). Observations on the jail, hospital, or ship fever. London: Murray.

Robertson R (1789). Observations on jail, hospital, or ship fever. 2nd edition, London: for the Author.

Robertson R (1790). An essay on fevers. London: For the Author.

Robertson, R (1807). Observations on fevers, 4 vols. London: Cadell and Davies.

Tröhler U (2010). The introduction of numerical methods to assess the effects of medical interventions during the 18th century: a brief history. JLL Bulletin: Commentaries on the history of treatment evaluation (www.jameslindlibrary.org).

[Home](#)

[Contents](#)