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J R Soc Med 2013 106: 150
DOI: 10.1177/0141076813482256

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Four early clinical studies to assess the effects of Peruvian bark

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DECLARATIONS

Competing interests

None declared

Funding

Wellcome Trust

Ethical approval

Not applicable

Contributorship

A-HM

Acknowledgements

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

From the late 17th 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 18th century: in a hospital, the army, the navy and finally in private practice.

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.^{1–3} In words reminiscent of John Aikin's *Thoughts on Hospitals*,⁴ 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 with 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 (see Ref.², pp. v–vi; Ref.⁴, pp. 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'² (pp. 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 (see Ref.², p. vi; Ref.⁴, pp. 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'⁴ (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'² (pp. 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-17th 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 (see Ref.², pp. 2–6; Ref.⁵).

In 14 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 crossover 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 vomiting² (pp. 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 system² (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'² (pp. 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'² (pp. 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 inflammation² (pp. 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 time² (pp. 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.⁶ 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.⁶

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'⁶ (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'⁶ (p. 257).

McCausland was similarly careful in his judgments 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.⁷ 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'⁶ (pp. 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 observations⁶ (pp. 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, while the virtues of every truly

valuable remedy would be publicly known, and established upon the most incontestable footing⁶ (pp. 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 15 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.^{8–12} 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.¹⁰ 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 comparison¹² (vol. ii, pp. 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)¹² (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 been¹² (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’).¹⁰ 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 lighted¹⁰ (pp. 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 treatment⁴ (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.¹³ 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 Peruvian 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 bark¹³ (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'¹⁴ (pp. 221–3).

Collectively, the examples of Home, McCausland, Robertson and Colingwood show the methodical range used by these late 18th 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 Ref.^{15,16}), 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 (pp. 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/cli/1999/00000053/00000001/art00005>

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