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Ipecacuanha: the South American vomiting root

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ABSTRACT The story of ipecacuanha, derived from the plant *Cephaelis*, is a fascinating one. It was discovered in Brazil in the 1600s and then transported to Paris in the latter part of the same century. It was used there by the physician Helvetius on various members of the French royal court to treat the flux (dysentery) with some success. Later, in the eighteenth century, it was taken up by the physician and privateer Thomas Dover and became, with opium, a fundamental constituent of his celebrated powder, which was used widely to treat fevers and agues for the next 200 years. Progress was then delayed until the early 1800s when the School of Chemistry at Paris established that the dried root of ipecac contained two powerful alkaloids, emetine and cephaeline, that consistently caused vomiting and diarrhoea. The discovery of the pathogenic amoeba, *Entamoeba histolytica*, in the latter part of the nineteenth century, allowed a distinction to be made between the two main forms of dysentery (amoebic and bacillary). Emetine was shown to be active against the amoebic form of dysentery but ineffective against that caused by bacteria. Ipecacuanha, its root and the pure alkaloid emetine have now been abandoned on the grounds of toxicity. They have been replaced by safer, more effective compounds. Nevertheless, they deserve an honoured place in the history of medicine, especially in the search for an effective treatment for amoebic dysentery.

KEYWORDS Amoebic dysentery, cephaeline, emetine, ipecacuanha, South America, vomiting

DECLARATION OF INTERESTS No conflict of interests declared.

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Author's note: The shortened colloquial form 'ipecac' has been used in place of ipecacuanha in many instances, for ease of reading.

INTRODUCTION

The history of ipecacuanha is a long and fascinating one. In a manner similar to that of *Cinchona* (quinine) and *Chondrodendron* (tubocurarine) it emerged from the forests of South America.[1,2] Then, by devious means, it was transferred to the capital cities of Europe, in particular Paris and Lisbon. In contrast to these other two substances, ipecac may have done more harm than good. Nevertheless, from the sixteenth to the nineteenth centuries it was widely used for the induction of therapeutic vomiting and as part of the treatment of the 'flux', whether bloody or watery (these were forms of dysentery). In the nineteenth and twentieth centuries, the pure alkaloid emetine, derived from the powdered root of ipecac, was used to treat amoebic dysentery (the bloody flux). The alkaloid was also used to locate one of the centres for the control of vomiting in the mammalian medulla oblongata, the chemoreceptor trigger zone.

THE PLANT

The French Pharmacopoeia defines ipecac as follows: 'The root consists of the subterranean part of either *Cephaelis ipecacuanha* (*Rubiaceae*), known also as Rio (or Brazilian ipecac) or that of *Cephaelis acuminata* (the so-called Cartagena or Nicaraguan root).'[3]

The name *ipe-cac-uanha* is of traditional native American origin and can be loosely translated from its Portuguese derivative as the 'roadside vomiting plant'. Other South American plants that cause emesis have also been called 'ipecac'. These include the genera *Psychotria*, *Richardsonia*, *Asclepias* and *Tylophora*, but this is not acceptable to the pharmacopoeias.

The *Cephaelis* genus is a group of small perennial shrubs growing to a height of 20–40 cm (Figure 1). They have opposite decussate leaves and white flowers. The flowers are grouped into compact cymes (*cephaelis* means grouped at the head; see Figure 1). The roots consist of twisted fragments, like small beads on a necklace, ranging from 6–15 cm in diameter. When the shrubs were harvested, the roots were cut to size and dried slowly. Some of the roots were replanted, to conserve the shrub, and a further harvest could be taken three to five years later. The plant was sold either as the dried root or in powder form.

TRANSPORTATION TO EUROPE

How ipecac reached Europe is something of a mystery. In this way its story resembles that of *Cinchona*.[1] There was a great deal of commercial traffic between South

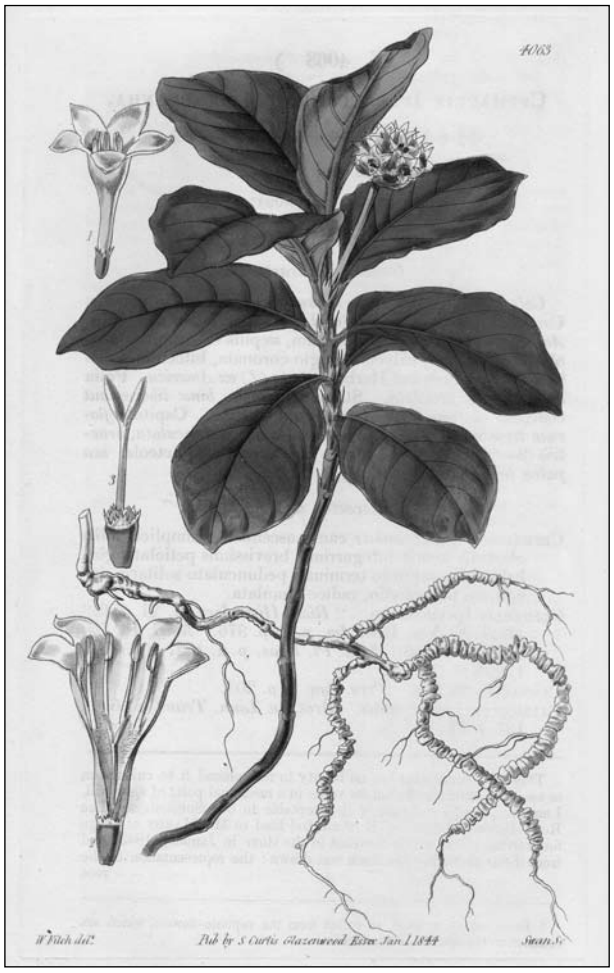

FIGURE 1 A nineteenth-century illustration of *Cephaelis ipecacuanha*, which appeared in *The Botanical Magazine* (vol. 70), published in London in 1844.

America and Portugal, Spain and, latterly, France. In fact, merchants, priests and doctors regularly made the journey across the Atlantic. After the discovery of the Peruvian bark (*Cinchona*) by the Jesuits, they were also on the lookout for further powerful medicinal herbs. The first mention of ipecac was in a 1648 collection of papers and notes by the naturalist Georg Marggraf and the physician Willem Pison, who travelled to Brazil in 1638 and published their observations a decade later. In 1672 another physician, Le Gras, transported a substantial amount of ipecacuanha from South America to Paris.[4] Subsequently it was used sporadically in France for the treatment of the flux (dysentery) and the ague (fever). For a time, supplies were very limited. In 1680, however, a Parisian merchant imported a substantial quantity, approximately 150 lb.

As a result of the root's wider availability, it was taken up by a number of physicians, most notably by Jean-Adrien Helvetius, the grandfather of the philosopher Claude-Adrien Helvetius.[4] At one stage Helvetius was given the sinecure of chamberlain to the queen's household. He used ipecac on a number of individuals in this group who were suffering from dysentery with, in some cases, considerable effect. One notable success was his treatment of the dauphin, the heir to the throne, who made a complete recovery. Consequently, Helvetius's reputation was enhanced, and King Louis XIV granted him a sole licence to sell ipecac root. As a result Helvetius became a very rich man. Later on the French Government decided to buy the licence back for the princely sum of 1,000 Louis d'Or.

When the root and powder became widely available in Europe in the eighteenth century, the indications for its use were studied intensively. It was established that, in small doses, ipecac was a diaphoretic (a sweating drug) and an expectorant (encouraging the coughing of sputum). In larger doses, the actions became emetic and cathartic (purging). At this time, disease was still regarded as an imbalance of the humours. If some of the 'bad' humours could be expelled by vomiting or purging, this would be all to the good. As a result, ipecac became a popular supplement to traditional methods of restoring the balance of the humours, such as bleeding and cupping. Moreover, during this period in Paris, poisoning was commonplace and the favoured substances included arsenic, antimony and henbane (hyoscine).[5] Ipecac was a valuable antidote.

THOMAS DOVER AND IPECACUANHA

Thomas Dover lived through a turbulent period in English history: born in 1660 at the time of the restoration of Charles II, he survived the Glorious Revolution of 1688–89 and lived on into the Hanoverian period, dying in 1742 at the ripe old age of 82.[7] He started out as a sea captain and privateer but went on to be a distinguished if controversial physician. While at sea, Dover made enough money from captured prize ships to secure his future. In 1709, as second master of the sailing ship *Duke*, he helped rescue Alexander Selkirk from Más a Tierra island in the South Pacific archipelago of Juan Fernandez (Figure 2). The story was later immortalised in *Robinson Crusoe* by Daniel Defoe.[6]

On his return from the South Seas, Dover practised as a physician in London and Bristol. Opinionated and quarrelsome, he fell out with both the Royal College of Physicians in London and the Society of Apothecaries. He also became known as 'the quicksilver doctor' for his advocacy and use of mercury in the treatment of syphilis and in other vague complaints that he thought 'could be due' to cryptic venereal disease. In later life, Dover wrote a famous textbook of medicine entitled the *Ancient Physician's Legacy to his Country*.

This treatise was groundbreaking in two respects: firstly, it marked a watershed between the old Galenical certainties and the rational enquiry of the Enlightenment.

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FIGURE 2 Thomas Dover greets Alexander Selkirk on the South Pacific island of Más a Tierra. Illustration by an anonymous artist in Strong LAG, *Doctor Quicksilver*.[6] (Unsuccessful efforts have been made to trace copyright)

Facts were sacrosanct, and clinical experiments must be carried out on patients to provide new evidence. Secondly, Dover illustrated this approach by giving patients varying doses of mercury and trying to achieve a dose/response relationship to treatment. In this endeavour he was well ahead of his time.

Dover's work on mercury is now largely forgotten, but one of his preparations, Dover's powder (*Pulvis Ipecacuanha*), would survive for nearly 200 years (Figure 3). It was the standard treatment for gout until *Colchicum* arrived from the East. The major ingredients of Dover's powder were ipecacuanha, opium, saltpeter and cream of tartar. In small doses it was employed for fevers and agues; in larger doses for gout and dysentery (podagra and the bloody flux). Dover often used heroic doses of the powder (60–80 g), and remarked acerbically that some apothecaries would advise patients 'to settle their affairs by making a last will and testament before venturing to take such a large dose'.[6] (For an extensive and interesting account of Dover's life the reader is referred to Strong's biography.[6])

As the eighteenth century ended, two difficult problems surfaced with regard to the ipecac root: the nature of the plant source and the identity of the active principles contained therein. The first was solved by the advent of

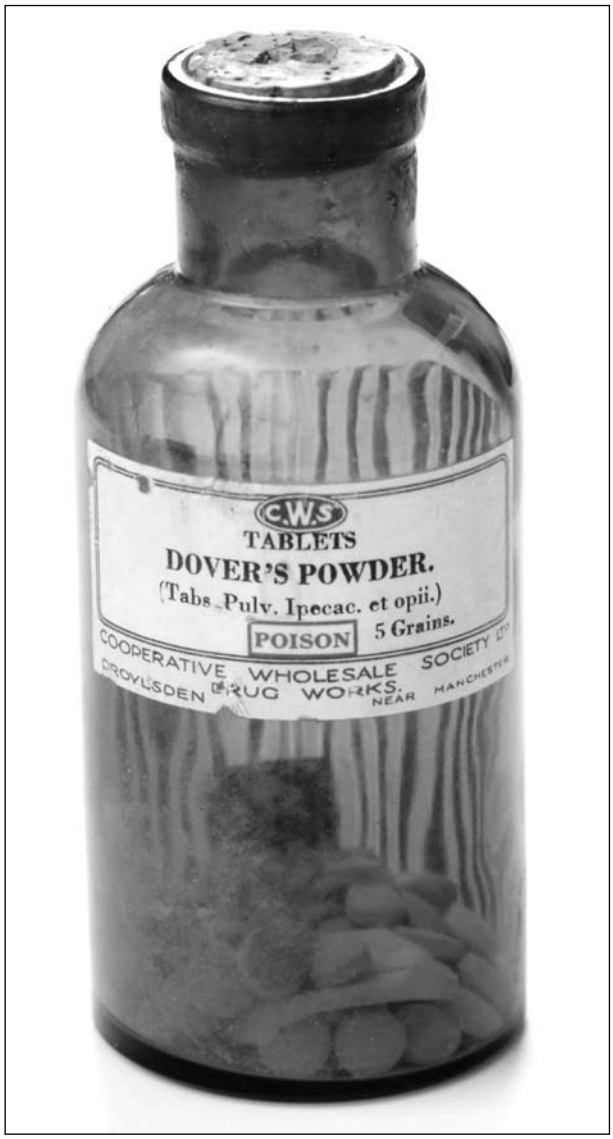

FIGURE 3 A bottle of Dover's powder. (Image courtesy of the Royal Pharmaceutical Society of Great Britain)

the Linnaean binomial system for the identification and classification of plants. This allocated ipecac fairly and squarely to the genus *Cephaelis*, and to the species *ipecacuanha* or *acuminata*. The second problem, which was intrinsically much more difficult, would await the rise of the modern discipline of chemistry from 1780 onwards.

PLANT ALKALOIDS IN IPECACUANHA

Modern chemical knowledge began to emerge as a specific discipline in the late eighteenth century. There were several important developments in this period:

- The rejection of the phlogiston theory;
- The development of the gravimetric and volumetric systems of measurement and analysis;
- The work of Joseph Priestley, Laurent Lavoisier, Carl Scheele, John Dalton and Humphry Davy;
- The adoption of the metric system in post-revolutionary France.

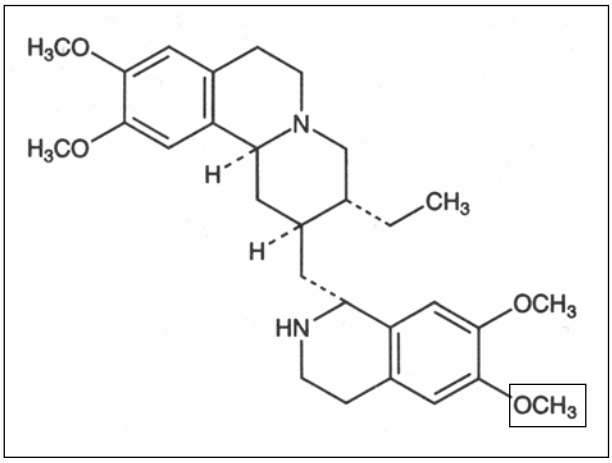

FIGURE 4 The chemical structures of emetine and cephaeline. Cephaeline is desmethylemetine (radicle CH_3 – shown in box – is removed).

As a result, at the end of the Napoleonic wars, a great chemical enterprise became concentrated in Paris, both at its University and School of Pharmacy.

The three principal protagonists were Francois Magendie, Pierre-Joseph Pelletier and Joseph-Bienaimé Caventou. This brilliant group, in a sustained period of excellent work, isolated the alkaloids emetine, brucine, strychnine and quinine.[7] They also extracted and named the important plant pigment chlorophyll. Moreover, together with Mathieu Joseph Bonaventure Orfila, the father of modern toxicology, they studied the pathological effects of these alkaloids in animals.

Emetine hydrochloride

The main alkaloids found in the root of ipecac are emetine[8] (methylcephaeline) and cephaeline. The detailed chemical structures are shown in Figure 4. Both emetine and cephaeline are complex polycyclic molecules, and the details of their structure were only established in the twentieth century. Emetine is obtained either by direct extraction of ipecac root or by methylation of cephaeline (also obtained from the plant). It has many biochemical and pharmacological actions. In vivo in eukaryocytes, emetine inhibits protein synthesis by blocking the elongation of polypeptide chains. It also blocks oxidative phosphorylation in the mammalian mitochondrion. In addition, it has important systemic effects in mammals, inhibiting both the adrenergic and cholinergic components of the autonomic nervous system and blocking the direct reuptake of noradrenaline in the heart.

In therapeutic doses, emetine also has a direct lethal action on the trophozooites of *Entamoeba histolytica*, the causative protozoan of amoebic dysentery. Pure emetine proved to be a toxic drug when used clinically, as its therapeutic ratio is narrow. Adverse reactions include those on the gastrointestinal tract (vomiting and diarrhoea), the nervous system (polyneuritis) and on the heart (arrhythmia, hypotension and sudden death).

AMOEBIC DYSENTERY[9]

In the period between 1850 and 1900, the 'golden age' of microbiology (and pathology) revolutionised the approach to many of the diagnostic dilemmas that had faced the physician and surgeon. Several important developments contributed to this explosion of knowledge:

- The production of the compound microscope (reducing chromatic and spherical aberration);
- The development of dye stuffs that would stain microbes and tissues specifically (e.g. Gram's stain);
- The ability to cultivate bacteria in vitro in pure culture, using methods such as the Petri dish and the test tube.

As far as dysentery was concerned, one of the first major steps came in 1875 when the Russian pathologist Fedor Lösch examined the stool of a patient called Markoff, who was suffering from this complaint, and on microscopy discovered a suspicious amoeba.[10] Lösch called the presumed parasite *Amoeba coli*, but it was subsequently renamed *Entamoeba histolytica*. Some ten years later, Stephanos Kartulis,[11] working in Alexandria in Egypt, identified the same *Entamoeba* in pus derived from a hepatic abscess. It was not until 1961, after much difficulty in the intervening period, that Louis Diamond was able to culture the pathogenic amoeba in vitro.[12] During the same decade that *E. histolytica* was identified, it proved possible to identify the bacterial genera that were responsible for the other forms of dysentery. These proved to be largely *Salmonella* or *Shigella* species. It then transpired that neither the pure emetine alkaloid nor the complex mixture obtained from ipecac root had any effect on these bacterial organisms in vitro or in vivo.

IPECACUANHA AND AMOEBIASIS

In the twentieth century, when pure emetine became available, large-scale trials were undertaken by Sir Leonard Rogers and others.[13,14] There was no doubt that emetine was extremely effective in eradicating amoebae, but there were considerable practical difficulties in its use: the patient had to be kept on bed rest for the duration of treatment, the drug was best given by injection and close observation had to be maintained to detect potentially fatal cardiovascular complications, including hypotension and tachycardia. If either of these two problems occurred, treatment had to be stopped immediately. In spite of these rigorous precautions, sudden death occasionally occurred.[9]

As a result, from 1950 onwards, alternative treatments were sought that would prove effective by mouth and be free from potentially lethal cardiac effects. Success was eventually achieved with diloxanide for intestinal amoebiasis and metronidazole, a nitroimidazole, for the hepatic form. Emetine is now rarely, if ever, used.

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IPECACUANHA AND EMESIS

The powdered root of ipecac achieved lasting fame until pure emetine became available. The dried root contains many other compounds apart from emetine and cephaeline. These include psychotrine, methylpsychotrine, ipecacuanhic acid and the glycoside of ipecacuanha.[3] It is thought that the small amounts of these compounds present in the root do not contribute materially to its pharmacological and emetic actions. The powder was therefore standardised as containing 2% of emetine by weight.

Cephaeline proved to be twice as potent an emetic as emetine. The powder has a dual action effect on the mechanisms of vomiting:

1. It directly irritates the stomach and upper gut;
2. It acts indirectly, after absorption into the bloodstream, on the chemoreceptor trigger zone in the area postrema of the medulla oblongata of the brain, an area that is important in the control of vomiting in mammals.[8]

Small doses of the powder produce reflex coughing with expectoration, often accompanied by stimulation of the nasal mucosa and sneezing. Larger doses stimulate the whole of the gastrointestinal tract, producing copious vomiting and diarrhoea after a latent interval of approximately 20 minutes. Generally speaking, ipecac powder was an effective, safe inducer of emesis (90% success rate). In the UK it was generally used in accident and emergency departments, whereas in the US and Australia there was much greater emphasis on its employment in the home as a first aid measure. Although it had a good safety record, ipecac occasionally produced severe complications. These included rupture of the oesophagus or stomach, Mallory-Weiss tear of the oesophagus, pneumomediastinum, pneumoperitoneum and aspiration pneumonia.[8]

As time went on, doubts arose as to the amount of poison removed from the body by therapeutic emesis with ipecac. This resulted in a consensus view, which emerged in the 1990s, that the use of ipecac should be abandoned. Moreover, it must not be combined with instillation of activated charcoal, the preferred treatment, as it may induce vomiting of the absorbent, reducing its effect.

Finally, it should be noted that ipecac has been used as a drug of self-abuse in patients with anorexia nervosa and/or bulimia. A clinical syndrome can result that includes myopathy, neuropathy, convulsions and sudden death. Although ipecac is not widely available at the present time, if in doubt the urine should be checked at the same time as for other laxatives. Children have been poisoned with ipecac by their relatives (Munchausen's syndrome by proxy), and this can be extremely difficult to detect.

CONCLUSIONS

> Be not the first by whom the new are tried,
> Nor yet the last to lay the old aside.
> – Alexander Pope, *Essay on Criticism*

From the time of Columbus, Pizarro and Cortes, Europe was fascinated by South and Central America, as a potential passage to the East Indies and as a source of precious metals and gems, in particular gold and silver. As time passed, Spanish, Portuguese and, later, British explorers became aware that there might be value in some of the continent's indigenous plants as medicines or foods. These included the drugs *Cinchona* (quinine), *Nicotiana* (tobacco), *Chondrodendron* (tubocurarine), *Erythroxylon* (coca and cocaine) and the foods *Theobroma cacao* (chocolate) and *Solanum tuberosum* (the potato). These plants have influenced medicine and economies for the past 400 years. The great German explorer and naturalist Alexander von Humboldt, who spent a prolonged period in South and Central America, wrote in the 1840s that this vast, and as then largely unexplored, continent had given mankind both the good and the bad; the good in *Cinchona* and the potato, the bad in tobacco and coca.

Compared with quinine, which has saved the lives of millions of malaria sufferers, it would appear that ipecacuanha is but a minor player in tropical medicine. Nevertheless, emetine was the first effective and relatively safe emetic. More importantly, perhaps, it was the first efficient amoebicide and, for 200 years, the only one available. It also enabled, with other evidence, the differentiation between amoebic and bacillary dysentery. Eventually, however, it was replaced in poisoning by activated charcoal, and by diloxanide/metronidazole for the different forms of amoebic dysentery.

The path from plants to the bedside is a difficult and devious one, involving as it does pharmacognosy, chemistry, toxicology and therapeutics. In the case of ipecac, there were also contributions from bacteriology, protozoology and parasitology. Quinine and emetine encouraged later investigators to believe that if protozoal diseases such as malaria and amoebic dysentery could be defeated by specific chemical substances, then it was only a matter of time (and luck) before other 'magic bullets' could be found against microbes such as the treponemes, streptococci and staphylococci. Paul Ehrlich, Gerhard Domagk, Alexander Fleming, Howard Florey and Ernst Chain would prove the point for syphilis, meningitis and pneumonia.[15] Ipecacuanha from the forests of Brazil had, like quinine, shown convincing proof of concept for the action of a natural product (chemical agent) on a specific form of dysentery. In due course, the antimicrobial drugs would work the same magic against many of the common infections.

In summary, ipecacuanha and its active alkaloids emetine and cephaeline deserve an honoured place in the history of tropical medicine.

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