

The history of ergot of rye (*Claviceps purpurea*) I: From antiquity to 1900

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ABSTRACT This article outlines the history of ergot of rye up to 1900. Ergot is a fungal disease that affects many grasses but is particularly damaging to rye. It occurs as the result of an infection by the parasitic organism *Claviceps purpurea*, which produces characteristic black spurs on the grass. When incorporated into grain, the ergot fungus can cause severe outbreaks of poisoning in humans called ergotism. There are two main clinical forms of toxicity, gangrenous and convulsive, where coma and death often supervene: the death rate for ergotism has been reported to be between 10 and 20 per cent in major outbreaks. Historical accounts note that ergot could accelerate labour, stop postpartum haemorrhage and inhibit lactation. At the end of the nineteenth century ergot was still regarded as a 'glorious chemical mess', but help would arrive in the early 1900s and the complex jigsaw would be solved.

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INTRODUCTION

The story of ergot is a long, complex and fascinating one.¹ Indeed, ergot has been variously called by pharmacologists a gold mine, a treasure chest or even Pandora's Box. These descriptions have been attached to the fungus for two main reasons: firstly, because of the large number of active compounds that it contains and, secondly, because of the catalytic effect that the discovery of these substances would have on the development of the medical sciences in general and pharmacology in particular.¹

A number of grasses are subject to attack by the fungi of the *Claviceps* family (Figure 1), but whereas rye (*Lolium perenne*) is particularly susceptible, others, such as wheat, barley and oats, are much more resistant to the purple attacker (*C. purpurea*). As a result, the history of ergot (and ergotism, the clinical syndromes it produces) are inextricably linked to the history and distribution of rye.

Rye grass was, in the first instance, the bread grain of the Teutonic nations, whereas in Britain it was somewhat despised and regarded as food fit only for the poor. The chief rye-growing area of Europe, where millions of acres were grown, was a long belt extending from Holland and the Low Countries through Germany to Czechoslovakia and Austria. Use of rye then moved into Poland and Russia, spreading as far east as the Ural Mountains. By contrast, in 1925 only 50,000 acres of rye grass were cultivated in England, chiefly in Lancashire, Yorkshire and the Cheshire Plain.² Some 30,000 acres of the grass were allowed to ripen and the remaining 20,000 were ploughed in to act as a green manure. This

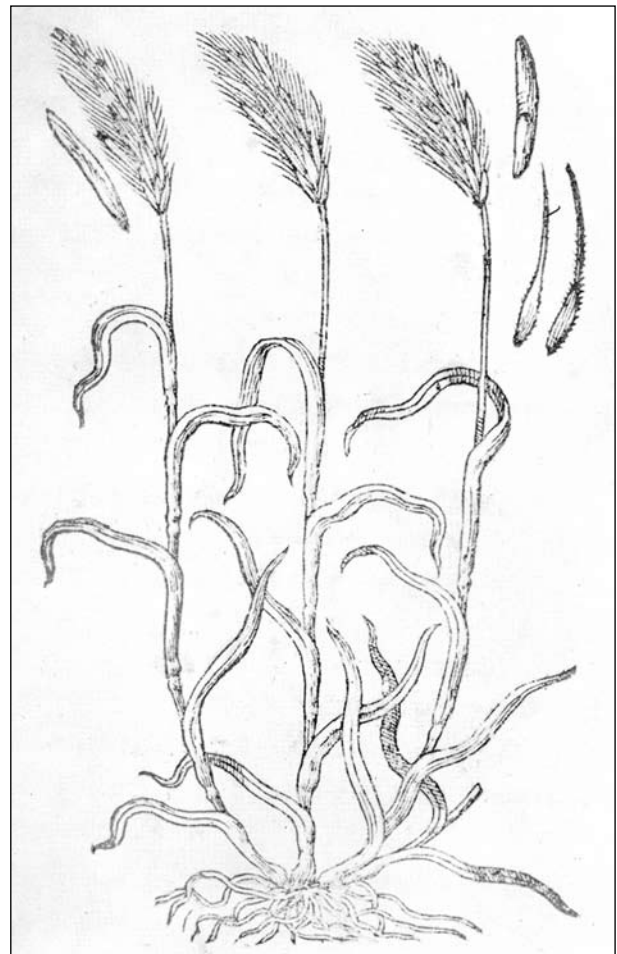


FIGURE 1 The first known illustration of ergot, from Bauhin's treatise of 1658; reproduced from Barger, *Ergot and Ergotism*.¹

explains why ergotism was a common disease in Germany and Russia, but relatively rare in the UK. The contrast is emphasised by the rye to wheat ratio in millions of bushels in 1930 – 4:1 in Poland but only 1:100 in England and Wales.³ Moreover, the climate in Eastern Europe appeared to be much more favourable for the cultivation of rye grass.

The appearance of the black ears of ergot on rye had some mythological significance. In Germany, ergot (*Mutterkorn*, literally ‘mother grain’) was associated with a spirit called *Kornmutter* (grain mother) which ‘lived’ in the ears of corn or rye. The ergot growths were regarded as her children. At first it was thought that *Mutterkorn* referred to the action of ergot on the uterus, but this does not seem to be the case. The word ‘ergot’ probably derives from the Latin word *articulum* (articulation or joint) via the Old French *argot* (cockspur, suggesting the shape of the sclerotium of the fungus; see Figure 2).

DESCRIPTION OF THE FUNGUS

The first unequivocal description of the fungus and its action was that of Adam Lonitzer in his *Kräuterbuch* of 1582 where, in an appendix on rye, he wrote: ‘There are long, black, hard, narrow pegs on the ears, internally white, often protruding like long nails from between the grains in the ear.’⁴ Lonitzer also mentions that they were foul smelling and that these hard pegs had been used to induce pains in the womb.⁴ He gave the usual dose as three sclerotia (pegs; i.e. about 0.5 g) which could be repeated if necessary.

The first illustration of the sclerotium of the fungus appears to be that described by Gaspard Bauhin in his *Theatrum Botanicum* of 1658 (Figure 1). The disease does not appear in an English language text until 1677, when the botanist John Ray referred to it in the second edition of his treatise *Catalogus Plantarum Angliae*.⁵ The word ‘ergot’ is seen for the first time a few years later, in a 1683 publication called *The Weekly Memorials for the Ingenious*, where it is described as ‘that malignity breeding in the ears of corn [sic] which contains certain black grains called, in Sologne, Ergots and in Gastinoise Bled Cornue’. Sologne is a region and Gastinoise a *commune* in France where the cultivation of rye grass was widespread. In 1791 the physician, natural philosopher and poet Erasmus Darwin referred to ergot in his long poem *The Botanic Garden*:

Shield the young harvest from devouring blight,
The smut’s dark poison and the mildew white,
Deep-rooted mould and ergot’s horn uncouth,
And break the canker’s desolating tooth.
– Part I Canto IV (lines 511–4)

In a footnote, Darwin still found it necessary to explain ergot to his readers, saying that it is a disease affecting the rye in France (commonly) and in England (occasionally).⁶



FIGURE 2 Stages in the development of ergot of rye. Left: honeydew; right: the sclerotium (cockspur). From Bové FJ. *The story of ergot*. Basel: S Karger; 1970. (With kind permission by S Karger.)

For a considerable period the nature of the black horns on rye remained a mystery. From 1700 onwards it began to be suggested that it was a parasitic infection, but what was the parasite? Eventually, matters began to move forward: Claude Joseph Geoffroy⁷ in 1711 and Baron Otto von Münchhausen⁸ in 1764 suggested that the parasitic infection was in fact a fungus. The advent of the compound microscope and the development of germination techniques at the beginning of the nineteenth century enabled the nature and behaviour of this fungus to be established. First, sclerotia were allowed to germinate, producing what were clearly fructifications (fruiting bodies). In the 1850s Louis René Tulasne described the full life cycle of ergot.⁹

The first obvious effect of the parasite attacking the grass is the so-called ‘honeydew’ (Figure 2), a sticky yellow sugar solution, which when secreted by the infected plant ovary exudes as drops between the affected glumes (sterile bracts) of the rye. The next stage in the cycle is the development of the black sclerotium (the cockspur). Under normal conditions, the sclerotia fall to the ground at the time of harvesting the grain, lying dormant until the following spring when they are activated by warmer temperatures. They can then undergo either sexual or asexual processes of reproductive propagation. Eventually, structures called asci are formed, releasing ascospores into the air. Clouds of these spores are shot away from the fungus body in an explosive manner (to a height of 7–15 cm) and distributed randomly by the wind or by insects.

In 1856 the French botanist Durien was able to infect rye flowers with *Claviceps* ascospores in the laboratory for the first time.¹ This settled a mystery that had baffled botanists for 100 years.

THE GROWTH OF ERGOT

A serious infestation with *Claviceps*, such as might cause an epidemic of clinical ergotism, is produced by an unusual conjunction of climatic circumstances. The two important factors are a wet season, which favours germination of the sclerotia, followed by a dry and windy spell, which favours the dissemination of the ascospores. Why is rye grain more susceptible to *Claviceps purpurea* infestation than other cereals such as corn, wheat or oats? The answer seems to be that rye grass depends largely on cross-fertilisation for propagation compared with the other grasses. It therefore opens its glumes to accept airborne or insect-borne pollen and as a consequence is also open to fungal ascospores. Ergot damages rye grass very considerably. As much as 50 per cent of the grain may be lost. In areas such as Russia, where rye was a staple food, this could result in famine. The elimination of ergot from parasitised rye can be achieved only with considerable difficulty and expense.

At the end of the nineteenth century ergot began to be used as an important therapeutic agent, and it became necessary to facilitate its growth artificially. Two methods were adopted: shaking the stems of the rye or pulling the ears of the grass between the fingers. These manoeuvres were repeated daily for a week and proved to be extremely labour-intensive. A further procedure was to spray the flowers with a dilute solution of the fungal spores of *Claviceps*. Eventually, yields of ergot as high as 500 kg per hectare (490 lbs per acre) were obtained. Unsurprisingly, in the period before the First World War the price of ergot per kg was 20 times that of rye.¹

ERGOTISM

There is a reference to ergot on an ancient Assyrian cuneiform tablet, and another in a sacred Parsi book,¹⁰ but it was only in the Middle Ages that several authors suggested that there were two forms of clinical ergotism: the gangrenous and the convulsive.¹ The gangrenous tended to occur west of the Rhine, the convulsive to the east. There was some minor overlap when the two forms occurred at the same time in the same individual, but generally this was not so.

At first it was thought that the two forms were caused by different chemical agents in different types of the fungus, but this hypothesis has proved incorrect. Sir Edward Mellanby and his colleagues¹¹ suggested that concomitant lack of vitamin A was the cause of the convulsive form, but this has never been confirmed. Clinical cases of ergotism have reduced remarkably over recent years. As a result, it is unlikely we shall ever find an answer to this medieval puzzle. It may be that some individuals are more sensitive to the neurotoxic compounds in ergot, such as the lysergic acid and ergokryptine derivatives.

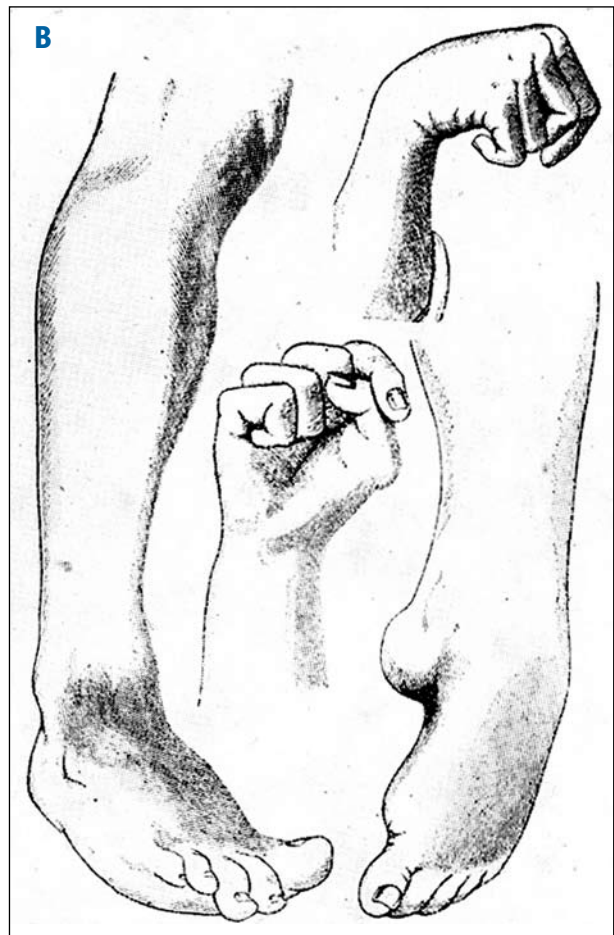


FIGURE 3 Forms of ergotism, both produced by eating contaminated rye grass or by ergotamine orally:
A: Gangrenous ergotism of the feet;¹
B: Convulsive ergotism.¹

By 1800 it was widely accepted that ergotised rye was responsible for all forms of ergotism. Some attempt was made to separate the healthy from the mouldy grain, but technically this is difficult; unscrupulous farmers and millers would often not take the necessary steps to exclude the mould.

The clinical syndrome of gangrenous ergotism

This form of ergotism runs a definite course. Initially, the patient complains of general lassitude accompanied by pains in one of the limbs, usually in the calf of the leg. Over the course of several weeks, the foot or sometimes the hand becomes swollen and inflamed. Then, characteristically, violent burning pains shoot through the affected limbs (presumably neuropathic). These pains were so common and specific in the Middle Ages that they were given special names, such as Saint Anthony's and Saint Martial's fire. Educated Latin speakers knew this pain as *sacer ignis* (sacred fire). Sensations of heat and cold alternated in the limb. The next phase was often signalled by the limb becoming numb and the pains disappearing. The skin turned cold and livid, and red or violet vesicles appeared. The diseased part became black (gangrenous) and the toes and feet could fall off without pain.

In severe cases the whole process was greatly speeded up and the limb would separate at the knee or ankle with only minor haemorrhage, often after a trivial knock. The patient would arrive at the hospice or hospital carrying the limb! In some instances all four limbs were lost and these patients succumbed rapidly. Figure 3A shows a photograph of a modern case (known to the author), in which the patient developed bilateral lower limb gangrene after an overdose of ergotamine.¹² Fortunately, the individual survived after bilateral below knee amputation.

Convulsive, spasmodic or nervous ergotism

The first symptoms of this form of ergotism, the *Kribbelkrankheit*, were described as a heaviness in the head and limbs accompanied by mild diarrhoea (without vomiting). The next manifestations were numbness in the hands and feet, accompanied by a tingling sensation in the limbs which was likened to 'ants running about under the skin' – hence formication. Other sensations described include 'pins and needles' in the extremities (paraesthesiae suggesting peripheral nerve involvement).¹³

Later on in the illness, twitching of small muscle fibres is observed (myokymia or fasciculations), particularly in the muscles around the mouth and eye. In mild cases of the disease the disorder abates at this stage. In more severe poisoning the syndrome takes a violent turn in entering the convulsive stage (Figure 3B). This presents as tonic/clonic spasms of the limbs associated sometimes with contractions of the facial muscles, vocal cords and diaphragm. The tongue was commonly bitten and in some cases severed. Painful whole body spasms could occur (opisthotonus). The subject often cried out, sweated profusely and was prone to violent retching. In the severe form the patient did not sleep, developed multiple convulsions (status epilepticus) and progressed towards coma and death.

Some patients, however, recovered even from this serious state; in them the eyes were particularly affected showing, for example, dilated pupils followed by glaucoma



FIGURE 4 St Anthony, from a medieval woodcut. The sufferer is shown with an amputated foot and the sacred fire coming from his hand. The saint is accompanied by his symbol, a pig.

and, more remotely, cataract. Dementia, delirium and mania were also described in severe forms of the poisoning. Post-mortem examinations showed a degeneration localised to the posterior columns of the spinal cord but also patchy damage in the cerebral hemispheres and mid-brain. The overall mortality in the convulsive form of ergotism ranged between 10 and 20 per cent, surprisingly low in an era when intensive care support and anticonvulsant drugs were not available.¹

St Anthony's fire

In about 1093 the French nobleman Gaston of Valloire founded the Hospital Brothers of St Anthony. He built a hospital near the church of St Anthony at La-Motte-Saint-Didier, near Vienne, to accommodate patients with ergotism who came from all over Western Europe (but particularly from France). Relics of St Anthony's body were brought from Constantinople. Pope Urban II recognised the order in 1095 and in 1297 Pope Boniface VIII raised the priory to the dignity of an abbey. During the twelfth century the *sacer ignis* became strongly associated with St Anthony. Woodcuts of that time (see Figure 4) show the saint accompanied by his faithful pig (identified by the illiterate peasantry as a symbol for Anthony), with sufferers carrying crutches.

Between the twelfth and fourteenth centuries many thousands of patients made pilgrimages to the abbey or one of its satellite churches. The experience of the suffering pilgrims usually followed one of two possible outcomes: many died within seven days of reaching the abbey but, if they survived this critical period, they often experienced a 'miracle cure'. Limbs were still lost, separating, however, without putrefaction. The chief virtues of the hospital at St Antoine-L'Abbaye seem to have been, on the one hand, the wholesome food that the patients received and, on the other, the careful dressing of the auto-amputated stumps of the limbs.¹

The ecboic or oxytocic action of ergot

When ergotism occurred in a lactating woman, the flow of milk often stopped completely and did not return. The ergot alkaloids, particularly ergocryptine, can inhibit prolactin production and release from the anterior pituitary gland, which almost certainly explains the effect of ergot on lactation.¹²

Ergot also seemed to have effects on parturition. Midwives and 'wise women' had used powdered ergot for many years to accelerate labour and prevent uterine haemorrhage, but the evidence was largely anecdotal.⁴ In 1787 Paulitzky reported that a powdered preparation of ergot had come into widespread use in the previous 20 years.¹⁴ It was being used by both midwives and physicians and was called *pulvis ad partum* (literally the powder of birth). It had a powerful effect on the uterus, causing it to contract, and was more effective than anything hitherto described. It did not store well, however, and lost virtually all its activity in two to three months. If too large a dose were given, obstructed labour and signs of ergot toxicity could occur. It could also be used to induce abortion in the early months of pregnancy, but this too could be dangerous.

Major advances in the field took place in the United States during the nineteenth century. In 1808 John Stearns, a New York physician, published an article in the *Medical Repository of New York* entitled 'An account of the *pulvis parturiens*, a remedy for quickening childbirth'.¹⁵ Stearns claimed that this preparation 'expedited lingering parturition and saved the accoucheur a considerable amount of time',¹⁶ without producing any bad effects on either the mother or the infant. His advice was 'to boil half a drachm of the powder in half a pint of water and give one third of this volume every twenty minutes until the uterus begins to contract'. He also stated that ergot was a vegetable and appeared to be a spurious growth on rye. He opined that a practitioner, on examining a granary where rye grains are stored, would be able to obtain a sufficient quantity. Samuel Akerley, a physician at New York's City Dispensary, mentioned in 1809 that extract of ergot had been used to treat amenorrhoea and in attempted abortions.¹⁷

A further stimulus to the development of ergot was given by the physician Oliver Prescott in 1813, when he published a pamphlet entitled *On the natural history and medicinal effects of the *Secale cornutum* or ergot*.¹⁸ This essay proved so popular that it was translated into several European languages. As a result, the use of powder of ergot spread rapidly throughout France (and later Germany).

However, the more regular use of powder of ergot did not come without problems. In 1822 the physician David Hosack commented that the number of stillborn children delivered in New York had risen very rapidly.¹⁹ This resulted in a public enquiry, and Hosack stated that *pulvis ad partum* had become *pulvis ad mortem* (the death powder). He suggested that the powder should not be used, in general, to accelerate labour but only to staunch postpartum haemorrhage, for which it had proved very effective.

In spite of Hosack's strictures the use of ergot spread rapidly throughout North America and Western Europe. The first pharmacopoeia to include ergot was that of the United States in 1820, followed by Italy, Greece, England and France. Many of these preparations were not standardised, and only that of the United States had its total alkaloid content measured. As a result the effects of the American ergot were reasonably reproducible. Ergot contains many alkaloids and only one of them, ergometrine, has a pronounced effect on the uterus. It is no surprise, therefore, that some preparations of ergot were all but useless. Controversy in regard to the efficacy of ergot was to rage throughout the whole of the nineteenth century and would only be settled by Henry Hallett Dale and his colleagues in the early years of the twentieth century.¹²

A GLORIOUS CHEMICAL MESS

The history of ergot between 1820, its date of entry to the United States Pharmacopoeia, and 1905, when Dale joined the Burroughs Wellcome Research Laboratories in England, was to prove extremely frustrating. Ergot is a chemical factory containing everything from the simplest of compounds such as amines and aminoacids to the most complex polycyclic alkaloids. At the last count, there were more than 200 clearly identified chemical compounds in a simple extract of the fungus. Although it was widely recognised that the pharmacological activity largely resided in the alkaloid fraction of ergot, it was not fully appreciated that water (or saline) extracts could also contain powerful vasodilators, for example acetylcholine and histamine, and/or powerful vasoconstrictors such as tyramine.

The situation as far as the alkaloids were concerned was no less complicated. In any preparation of ergot there are as many as 12 different alkaloids (major and minor)

based on the fundamental structure of lysergic acid and its amides, including ergotamine, ergometrine and ergokryptine. Other 'false' alkaloids were identified including ergotoxine,²⁰ ergotinine and ergosterene.²¹ The French pharmaceutical chemist Charles Tanret spent 20 years of his life isolating ergot alkaloids, which in the end proved not to be 'pure' compounds.²¹

The chemical techniques of the nineteenth century were, to put it bluntly, simply not good enough to isolate the active substances reproducibly. Moreover, when the 'substance' was obtained and crystallised, the analytical techniques were not specific enough to determine the side chain substituents of the closely related polycyclic compounds, for example 'ergotoxine'. This was a

formidable impasse which would take another 40 years of sustained effort to overcome. The ground-breaking work would be carried out mainly by two groups: Henry Dale, George Barger and Arthur Ewins in London and Arthur Stoll and Albert Hofmann in Basle in Switzerland.¹²

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REFERENCES

- 1 Barger G. *Ergot and Ergotism*. London: Gurney and Jackson; 1931.
- 2 Barger G. History and distribution of rye. In: *Ergot and Ergotism*. p. 1–3
- 3 Table of relative distribution of rye and wheat. In: *Year book of agriculture of the United States Department of Agriculture*. Washington DC: USDA; 1930. p. 198
- 4 Lonitzer A (Lonicerus). *Kräuterbuch*. Frankfurt am Main: Christian Egenolff; 1582. p. 285a
- 5 Ray J. *Catalogus plantarum Angliae et insularum adjacentium*. 2nd ed. London: J Murray; 1677. p. 269.
- 6 Darwin E. *The Botanic Garden*. London: J Johnson; 1791.
- 7 Geoffroy CJ (le jeune). Observations sur la structure et l'usage des principales parties des fleurs. *Mémoire Academie Royale des Sciences* 1711:207–30.
- 8 Von Münchhausen O. *Der Hausvater. Part 1*. Hannover: N Försters und Sohns Erben; 1764. p. 322
- 9 Tulasne LR. Mémoire sur l'ergot des glumacées. *Annales de Science Naturelle Botanique* 1853; 3:5–56.
- 10 De Costa C. St Anthony's fire and living ligatures: a short history of ergometrine. *Lancet* 2002; 359:1768–70.
- 11 Mellanby E, Surie E, Harrison DC. Vitamin D in ergot. *Biochem J* 1929; 23:710–6.
- 12 Lee MR. The history of ergot of rye (*Claviceps purpurea*) II: from 1900 to 1940. In submission.
- 13 Wichmann JE. *Beytrag zur Geschichte der Kribelkrankheit in Jahre 1770*. Leipzig and Zelle: Gsellius; 1771. p. 78–86. (Kribeln in modern German means to itch, to tingle or to prick.)
- 14 Paulitzky F. *Pulvis ad partum* aus dem Mutterkorn. *Neues Magazin für Ärzte* 1787; 9:44–8.
- 15 Stearns J. Account of the *pulvis parturiens*, a remedy for quickening childbirth. *Medical Repository of New York* 1808; 5:308–9.
- 16 Thoms H. John Stearns and *pulvis parturiens*. *Am J Obstet Gynecol* 1931; 22:418–23.
- 17 Akerley S. Letter: Account of the ergot or spurred rye as employed in certain cases of difficult parturition. *Medical Repository of New York* 1809; 6:341–7.
- 18 Prescott O. *A dissertation on the natural history and medicinal effects of the Secale cornutum or ergot*. Boston: Cummings and Hilliard; 1813.
- 19 Hosack D. Observations on ergot, No. 19. In: *Essays on various subjects of medical science*. New York: J Seymour; 1824. p. 295–301.
- 20 Barger G, Dale HH. Ergotoxine and some other constituents of ergot. *Biochem J* 1907; 2:240–99.
- 21 Tanret C. Cornutine et ergotinine. *J de Pharm et de Chemie* 1885; 11:309–13 and 1888; 17:393–8.

We congratulate Professor Lee on being elected a Fellow of the Linnean Society of London, an honour partly attributable to the 15 outstanding papers he has had published in The Journal of the Royal College of Physicians of Edinburgh – papers on the history of medicinal and poisonous plants and the substances they produce.