

St Anthony's fire and living ligatures: a short history of ergometrine

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Ergometrine, although now declining in use, has been the most important drug for prevention and treatment of postpartum haemorrhage, which is still a major cause of maternal mortality. "Ergot of rye", wrote Francis Ramsbotham, founder of the Obstetrical Society of London, in 1841, "has been known to possess deleterious and poisonous qualities for more than 800 years, and it has been used on the continent by female midwives as a promoter of labour pains for nearly 150 years".¹ Ergotism, or epidemic ergot poisoning, caused by eating affected rye bread, was indeed one of the scourges of the Middle Ages, and use and abuse of ergot as a uterine stimulant by midwives has been frequently documented. The pharmacological properties of ergot were recognised for centuries, although they were not well researched and publicised until the early 20th century.

Ergot is the alkaloid-containing product of a fungus, *Claviceps purpurea*, that grows on grain, especially rye. The fungal spores are carried by the wind to the ovaries of young rye, where they germinate into hyphal filaments. These grow deeply into the rye, forming a dense tissue that gradually takes over the grain and hardens into a purple curved spur or sclerotium ("ergot" is derived from "argot", Old French for the cock's spur). The sclerotium is still the main commercial source of ergot alkaloids.²

There are a couple of very early references to ergot: it was probably the "noxious pustule in the ear of grain" noted on an Assyrian cuneiform tablet of around 600 BC, and in one of the sacred books of the Parsees (400 BC to 300 BC) are mentioned "grasses that cause pregnant women to drop the womb and die in childbirth".³ However rye was not eaten by the early Greeks and Romans, so there are no undisputed references to ergotism in the literature of that period. It was not until the Christian era that rye was introduced into western Europe, and therefore not until the Middle Ages that written accounts of ergot poisoning are found.⁴

Ergotism had two main manifestations: gangrene (referred to as chronic ergotism) and convulsions (acute ergotism). The first, known as Holy Fire or St Anthony's Fire, was characterised by intense burning pain and gangrene of feet, hands, and whole limbs, due to the vasoconstrictive properties of ergot. In severe cases, affected tissues became dry and black, and mummified limbs dropped off without loss of blood. Spontaneous abortion frequently occurred. Convulsive ergotism was often accompanied by manic episodes and

hallucinations, especially a sense that the subject was flying; these symptoms were due to serotonin antagonism by various components of ergot related to lysergic acid diethylamide (LSD). The gangrenous and convulsive forms of ergotism could occur concurrently.^{2,5}

St Anthony himself was a third century Egyptian ascetic, who lived an unblemished life in the desert near the Red Sea, fasting for long periods, which was probably the reason for the visions and temptations he is said to have experienced. He believed them to be the work of the devil, and resisted steadfastly. In his own lifetime, Anthony had no direct connection with ergotism, however his name was taken by an Order of Hospitallers, founded in France about 1100. The Hospitallers, wearing black robes embroidered with blue crosses, travelled widely across medieval Europe, ringing little bells to attract alms, and the hospitals they thus funded became pilgrimage centres for sufferers from ergotism.⁶ The Antonite monks were credited with many cures, and thus Anthony's name and life story became attached to the disease. What were said to be the saint's bones were sprinkled with holy water or wine, which was then drunk by the afflicted; however it seems more likely that cures were related to the Hospitallers providing a diet free from contaminated grain. Amputated limbs were frequently left at the sites of shrines to St Anthony as offerings of thanks and evidence of the saint's success.

The first mention of a plague of gangrenous ergotism in Europe comes from Germany in 857; thereafter there are numerous records of epidemics in France, Germany, and Scandinavia.¹ Wendelin Thelius, a German physician, gave an account of an epidemic that raged in the Kingdom of Hesse in 1596; he was one of the first to attribute the cause of ergotism to grain.¹ In the 17th century many writers confirmed this connection. However; it was not until the late 18th century that measures were suggested to combat ergot poisoning. S Tessier, observing a huge epidemic at Sologne, France, in 1778 in which more than 8000 people died, recommended drainage of fields, compulsory cleaning of grain, and the substitution of potatoes for affected grain.⁷ Epidemics of ergotism continued to occur sporadically in Europe until the end of the 19th century; since then, although outbreaks have occurred in less-developed countries, ergotism in the more-developed world has been confined to individual cases of ergotamine overdose.⁸

The dramatic symptoms and signs of ergotism gained the attention of many artists, particularly in the late Middle Ages. The German painter Matthias Grunewald, a contemporary of Albrecht Dürer and Lucas Cranach, painted for the Antonite friars in the Rhine Valley. He depicted figures with abnormal postures and seizures, probably modelled from patients with ergotism in the monastery.⁹ Hieronymus Bosch, Dutch contemporary of Grunewald and noted painter of religious allegories,

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among many other famous works, drew on the temptations of St Anthony for his triptych, now in Lisbon (figure 1); this picture depicts the saint himself and sufferers from various forms of ergotism with strange flying objects that represent hallucinations.⁷

The first reference to use of ergot in childbirth seems to be from 1582, when A Lonicer in Germany recommended use of three sclerotia of ergot for the flagging contractions of prolonged labour.^{1,7} In 1688, another German physician, R J Camerarius, stated that “in some parts of Germany midwives are in the

of the founders of the city’s Lying-In Hospital. Hosack observed cases of stillbirth associated with prolonged uterine contraction before delivery, and commented dryly: “Ergot has been called . . . *pulvis ad partum*; as it regards the child, it may, with almost equal truth be denominated the *pulvis ad mortem*.”^{9,10} Astutely, though, he recommended use of ergot for cases of postpartum haemorrhage, as indeed had Stearns.

At the time, and indeed for much of the 19th century, postpartum haemorrhage was greatly feared as a killer of young mothers, and recognised as frequently due to

failure of the recently emptied uterus to contract adequately. It was treated with various not very effective remedies, including “a lemon imperfectly quartered” or “a large bull’s bladder distended with water”, both of which were introduced into the uterus, or douches of vinegar or iron perchloride.^{11–13} By the end of the century, however, ergot was recognised by obstetricians as “the most powerful substance to stimulate a uterine contraction” and although the dangers of its use in labour were now recognised, administration of its extract in water was recommended for postpartum haemorrhage.¹⁴ In England “it could be left in a medicine glass with instructions to the nurse to administer a teaspoon if bleeding became excessive” and in France “up to six doses of one gram” could be given orally.^{13,14} In the early years of the 20th century a further idea appeared—prophylactic use of ergot immediately postpartum to prevent haemorrhage, and in addition to oral preparations, intramuscular or subcutaneous injections were used; Edgar’s *Practice of Obstetrics* of 1913 recommends one drachm by mouth or 20 minims hypodermically.¹⁵

Attempts were made from the mid 19th century onwards to isolate the active alkaloids from ergot. All naturally occurring alkaloids of therapeutic interest are derivatives of the tetracyclic compound lysergic acid. Ergotoxine, isolated by

G Barger and H Dale in 1906, was initially thought to be a pure substance, but was later found to be a mixture of four alkaloids; the first pure alkaloid, ergotamine, still used for its vasoconstrictive properties in treatment of migraine, was obtained by A Stoll in 1918.² Pure ergotamine had tonic effects on the uterus, but these were slower to appear than when an aqueous extract of ergot was administered. It was clear that there were more active alkaloids, and in their paper of 1932, Chassar Moir (figure 2) and H Dale described experiments with 2, 3, and 4 drachm doses of extract of ergot.

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Figure 1: Hieronymus Bosch (c1450–1516), *The Temptation of St Anthony*

habit of giving it to accelerate parturition”.¹ In France, A-A Parmentier noted in his *Journal de Physique* of 1774 that ergot was frequently used by midwives as “a childbed remedy”. In 1777, another Frenchman, J Desgranges, met with some midwives of Lyons, who were accustomed to use of ergot, made some trials with it himself, and published his observations in various journals.^{1,2} A detailed description in German of use of ergot was published in 1787 by F Paulizky, who introduced the phrase “*pulvis ad partum*” (a powder [to aid] birth).⁷ All these accounts, however, are confined to use of ergot during labour, rather than for treatment of postpartum bleeding.

Use of ergot during labour became widespread in the USA during the early part of the 19th century, but it was less popular in Europe, possibly because the Old World had long experience of the “deleterious qualities” of the fungus. In 1808, John Stearns published in the *Medical Repository* of New York “An Account of the *Pulvis Parturiens*, a Remedy for Quickening of Childbirth” in which he stated that: “It expedites lingering parturition and saves to the accoucheur a considerable portion of time, without producing any bad effects on the patient . . . Since I have adopted the use of this powder I have seldom found a case that detained me more than three hours”.³

That complications could result from use of the drug in labour was, however, soon recognised, most notably by David Hosack, a prominent New York physician and one

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Figure 2: Chassar Moir

A sterilized rubber bag (was) passed into the puerperal uterus with full antiseptic precautions, and connected by water-filled tubing to a mercury manometer. A light float on the manometer carries an ink point, which records variations of intrauterine pressure on a slowly revolving drum . . . a remarkably short time . . . elapsed between the swallowing of the extract and the onset of powerful uterine contractions . . . there was a rise in the base line to an extent much greater than observed with any other drug.¹⁶

In 1935, Moir and Dudley reported isolation of the active substance, "to which ergot rightly owes its long-established reputation as the *pulvis parturiens*. We propose to name it ergometrine".¹⁷ From 1935 on, pure preparations of ergometrine (known as ergonovine in the USA) were given intravenously or intramuscularly both prophylactically and for treatment of postpartum haemorrhage. The prolonged uterine spasm noted by Moir meant that the smooth muscle fibres of the myometrium could act as "living ligatures" around the vessels of the placental bed.

The maternal mortality rate in England in 1870 has been estimated at one woman in 20 births; in Saxony in 1880, the rate is said to have been one in 66; in New South Wales for 1894–96 a figure of one in 148 has been quoted.¹⁵ By 1935, the maternal death rate in England and Wales was five per 1000, and by 1967, 0.2 per 1000, figures elsewhere in Europe are similar.¹⁸ Admittedly, numerous factors contributed to this remarkable decline. However, it is widely accepted that haemorrhage was and still is the cause of a high proportion of maternal deaths, 25% being the acknowledged figure, and among these haemorrhages most are postpartum and due to uterine atony.^{15,18} Undoubtedly, use, firstly of the aqueous extract of ergot, and later of the pure alkaloid ergometrine, contributed enormously to this most welcome fall in deaths of young mothers in more-developed countries.

Postpartum haemorrhage continues to be a major cause of maternal mortality in less-developed countries. WHO statistics indicate that worldwide around 600 000 women die yearly of pregnancy-related complications. Of these, about 100 000 have a postpartum haemorrhage due to uterine atony; a large proportion die without access to appropriate medical care, including ergometrine or other oxytocics.¹⁹

Use of ergometrine has been criticised in recent years, and side-effects including nausea, vomiting, and hypertension have led to use of synthetic oxytocin, misoprostol, and other prostaglandins for prevention and treatment of postpartum haemorrhage. The literature abounds with details of the search for the perfect

postpartum myometrial stimulant.²⁰ Nevertheless, ergometrine still has a life-saving role in obstetric practice in more-developed countries, and is likely to do so for the foreseeable future. In large parts of the less-developed world, women continue to die, every day, who might be saved by judicious use of a few grams of the extract of ergot of rye.

Conflict of interest statement

None declared.

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