

History of ergot alkaloids from ergotism to ergometrine

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Abstract

Epidemics of ergotism occurred frequently in the Middle Ages. They were a source of inspiration for artists and were popularly known as 'St. Anthony's Fire', resulting in gangrene, neurological diseases and death. It was caused by eating rye bread contaminated with the fungus *Claviceps purpurea*. In 1582 it was described that a delivery could be hastened by administering a few spurs of the *secale cornutum*. The dosage was, however, very inaccurate resulting in frequent uterine ruptures. The nickname of the preparation of 'pulvis ad partum' was changed to 'pulvis ad mortem'. Therefore, after 1828 the ergot alkaloids were no longer used during delivery but only as a measure to prevent postpartum haemorrhage. From 1875 onwards many derivatives of ergot alkaloids were found. Dudley and Moir isolated ergometrine in 1932. It proved to have a very specific uterotonic action. However, because of severe and unpredictable side effects and the instability of the drug, ergometrine is not the drug of choice for either the prevention or the treatment of postpartum haemorrhage.

Keywords: St. Anthony's fire; *Claviceps purpurea*; Ergot alkaloids; Uterotonic activity; Postpartum haemorrhage

1. Early history

The very fertile crescent of Mesopotamia between the Euphrates and Tigris produced the first agricultural settlements around 9000 BC. The wild grasses were cultivated and yielded good harvests of grain from wheat and rye. Assyria and Babylonia could develop because of the stable supply of this staple food. However, grasses and especially rye can be contaminated by the fungus *Claviceps (C) purpurea* during wet seasons, producing the typical ergot, i.e. the sclerotium, in the ears of grain (Fig. 1).

Ergot is probably first mentioned around 600 BC on an Assyrian cuneiform tablet as a 'noxious pustule in the ear of grain'. The Roman historian Lucretius (98–55 BC) called erysipelas 'Ignis sacer', i.e. Holy Fire, which name was given in the Middle Ages to ergotism. In one of the holy books of the Parsees in the 7th century ergotism was described as 'noxious grasses that cause pregnant women to drop the womb and die in childbed' [1,2].

2. Ergotism

Epidemics of ergotism occurred frequently in the Middle Ages. It was caused by eating rye bread contaminated with *C. purpurea*, resulting in gangrene of limbs, disturbances in the function of the central nervous system and ultimately death.

Ergot is derived from the old French word *argot*, meaning the cock's spur. The violet or black sclerotia consist of hyphae and are at least three times longer than the grains. Before or at harvest time the sclerotia fall on the ground and remain inactive till they germinate in the next warm and moist spring by developing 15–60 white spherical heads on stalks (hence the name *claviceps*; Fig. 2). Ascospores are set free by rupture of the head and propelled into the air by several cm. Within 8 days the infection of the flowering rye causes a secretion, the so-called honey-dew, in which the conidia (asexual spores) develop. This secondary infection leads to the production of the mycelium and then to the solid sclerotium, closing the lifecycle of *C. purpurea* [3–5].

If bread was prepared without removing the black spurs, epidemics of ergotism sprang up. Rye was mainly

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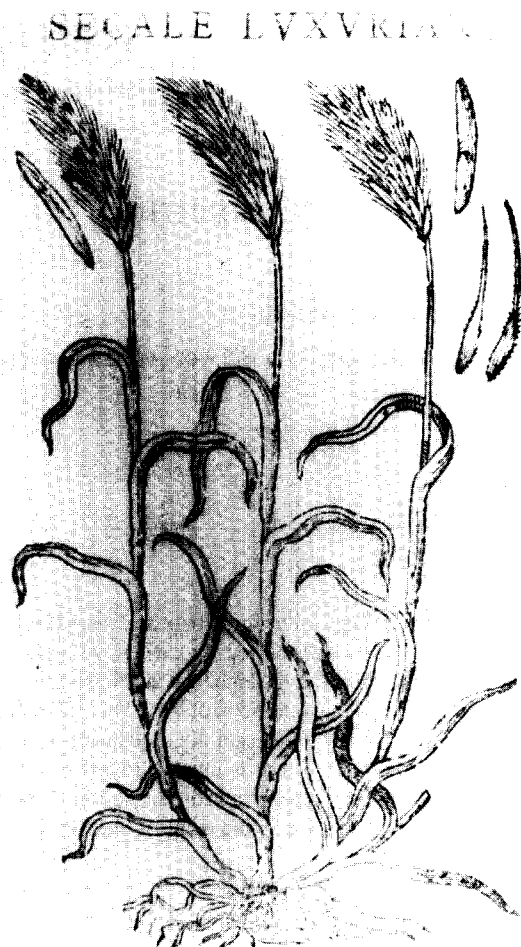


Fig. 1. The first illustration of ergot. Woodcut in Caspar Bauhin's *Theatrum Botanicum* (1685)

eaten by the poor people, especially during famines. The suffering from ergotism was then doubled, because the spurs were also collected because of hunger. The Russians in the late Middle Ages considered the spurs as a

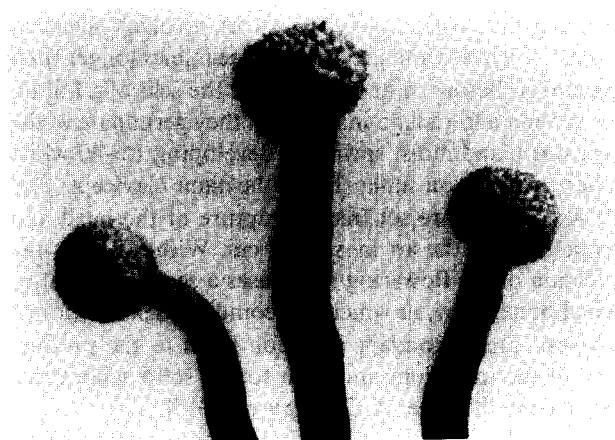


Fig. 2. Fully developed heads of the *claviceps purpurea*.

necessity to produce good quality bread. The German mythology explained the 'sudden' appearance of ergot by transgression of the 'Kornmutter' (mother-grain) through fields during foggy weather [1].

The first mentioning of gangrenous ergotism can be found in the 'Annales Xantenses' (Germany) in 857 AD: 'A great plague of swollen blisters consumed the people by a loathsome rot so that their limbs were loosened and fell off before death' [6]. The first epidemic of convulsive ergotism is described in 945 in Paris, France [1]. It was accompanied by erythema, diarrhoea, vomiting, formication and agonizing burning sensations as if the limbs were burning, often preceded by convulsions, catalepsy, dullness or maniacal excitement, hence the mentioning of 'dancing epidemics'. Most victims died, but some who fled to the church of St. Mary or Martial survived, most probably because they got non-contaminated food as was seen in the epidemic of Aquitaine, France (994 AD) in which 40 000 people perished [1].

The gangrenous type was mostly seen in France and the convulsive one in Germany. The two distinct types of ergotism (gangrenous and convulsive) may be considered as acute and chronic varieties of ergotism. The different symptoms described are given in Table 1. As the formication is typical in the convulsive type, it was called 'Kriebelkrankheit' in Germany. Mixed types were described as well, especially in other European countries [2].

3. Holy fire

In 1095 the order of St. Anthony was founded in Vienne, France. Especially in the 12th and 13th centuries, people flocked during epidemics to the hospitals

Table 1
Symptoms of ergotism

Gangrenous ergotism	Convulsive ergotism
Abortion	Fatigue
Amenorrhoea	Giddiness
Failure to lactate	Paraesthesia
Lassitude	Formications
Lumbar pain	Nausea/vomiting
Calf pain	Burning sensation
Feet/hands	Clonic/tonic spasms
Swollen	Flexion of arms/hands
Vesicles	Paralysis, hemi(para)plegia
Inflammation	Maniacal excitement
Alternating hot or cold	Hallucinations
Livid, black	Visual disturbances
Analgesia	Delusional insanity
Gangrene	Psychosis
Amputation	Convulsions
Jaundice	Dullness
Severe diarrhoea	Cataract
Death	Death

of the Antonines. The bones of the Egyptian hermit St. Antony (251–356 AD) were sprinkled with holy water and wine and given to the sufferers of ergotism. Soon the hospitals were called the 'h^opitaux des d^emembre's' because at its entrance the spontaneously amputated limbs were exhibited as kinds of ex votos. Due to the good treatment by providing non-contaminated bread, the popular hospitals spread all over Europe to a zenith of 390 settlements [3].

The frequent epidemics were called St. Anthony's Fire, 'Holy Fire' or Ignis Sacer because of the burning sensations in the limbs, as is depicted in the art of the time [7–10]. Victims of ergotism could identify themselves easily with the lifelong tortured St. Anthony. In the woodcut from 1517 (Fig. 3) a farmer who lost his right foot, extends his left arm engulfed in symbolic flames towards St. Anthony for help and protection. Medieval medicines were thought to restore the balance between hot and cold, wet and dry ailments. The Holy Fire was of course considered as a very hot disease, treatable with cooling elixirs, holy vintage with rare and

costly ingredients, fish and water, thistle and mandrake, mandragora apple and root. The juice of the mandragora apple was also used for analgesia but overdoses caused often untimely death, hence the nickname 'devil's apple'. It contains the two belladonna alkaloids hyoscyamine and hyoscine with the parasympatholytic properties mydriasis, bradycardia and reduced glandular secretions, but also visual hallucinations, especially sensations of flying. The famous St. Anthony Tryptich (Lisbon, Museu Nacional de Arte Antiga) shows not only the temptations of St. Anthony, all 'cold' treatments for ergotism including the mandragora apple and roots and suffering ergotants, but also strange flying aircrafts. Jeroen Bosch (1452–1516) painted all three interior panels with outrageously strange and diabolic scenes, as if seen by a hallucinating brain. Ergot, when baked with dough, may be transformed into lysergic acid diethylamine (LSD), a known hallucinogen. Ergotants were therefore twice afflicted by hallucinations: first by the transformed ergot alkaloids and then from the belladonna alkaloids from the mandragora [3,7,8,10].

O heylghehen Antony groß / Abt.ß der sünd/gots huld of gunst /
Erwurd uns gnad on vnderloß / Behüt uns vor dem schwarze bruff.



Fig. 3. Woodcut by Hans Wächtlin, Straßburg. 'Von der kalten Brandt' in: Feldtbuch der Wundartzney, Hanns von Gersdorff (1517).

4. Use of ergot as an oxytocic drug

The European Renaissance may be defined as the transition from the medieval, mythical religious society to the modern world. For ergotism, the Middle Ages ended in 1582 when Adam Lonicer in Germany mentioned for the first time the use of ergot to stimulate uterine contractions of labour ('pains of the womb') by administering three sclerotia (containing 0.5 mg ergot). The first accurate description of the ergot is also from his *Kreuter-buch*: 'long black hard narrow corn pegs, internally white, often protruding like long nails from between the grains in the ear' [2].

The honour of the first description in a medical journal is given to Paulizky in 1787. Ergot as 'pulvis ad partum' was prescribed by midwives and physicians alike. It showed an action which was 'more rapid and powerful than any other known drug' [11]. John Stearns from New York (1807) wrote in a famous letter to Mr. S. Akerly about the properties, dosage and side effects of ergot [12]. The crude ergot was given in a dosage of 5–10 g to parturients resulting in a rapid and sudden termination of labour with an induction delivery time of not more than 3 h. However, this 'pulvis parturiens' was not suitable for accurate therapeutic administration because of the large variation of active ingredients and the severe adverse events like violent nausea and vomiting. Its use in labour induction ended in 1822 when Hosack from New York stated that many stillbirths were due to uterine rupture with resulting maternal death. The 'pulvis ad partum' was renamed 'pulvis ad mortem' [13]. By the end of the 19th century its use as an oxytocic was virtually abandoned.

5. Cause and prophylaxis of ergotism

The first suggestion that ergotism was caused by blighted grains was already mentioned in 1125. Caspar Schwenkfeldt (Poland, 1600) thought that the honeydew of the rye was the cause of the ergot epidemics [3].

During an epidemic of gangrenous ergotism in Sologne (France, 1630), Tullier Sr. did animal research by giving 'cornicula nigra' to chickens, geese and pigs: they all died. Unfortunately, he did not publish his results. Only in 1676, did Dodart with help from the son of Tullier, solve the problems of the epidemiology and cause of the gangrenous ergotism. Likewise, Johann Brunner, described the cause of the convulsive type in 1695 in Leipzig, Germany [3].

Although the cause of ergotism was known, it took more than a century to specify the first prophylactic measures by L'Abbé Tessier in 1778. A vast epidemic of gangrenous ergotism with more than 8000 victims in Sologne, France, was caused because the grains were not cleansed from ergot. He proposed drainage, cultivation of potatoes in stead of rye and the enforced cleaning of grains [14]. A second description of preventing ergotism by controlling the quality of bread in hospitals was elucidated by Johann Taube in his magnificent book 'Die Geschichte der Kriebelkrankheit' (Göttingen, Germany, 1782). Moreover, his clinical pictures of the neurologic and psychiatric disorders are still valuable today. His recommended treatments of ergotism were waterbaths at 20°C, electrotherapy and anthelmintic drugs [3].

The last epidemic of convulsive ergotism in Germany (Oberhessen) was eloquently depicted by Siemens in 1879 [15]. He noted that neurological symptoms, like painful tonic contractions of the flexors, ataxy of the limbs, instability and epilepsy, always preceded psychiatric disturbances like decreased awareness, delirium and hallucinations. Moreover, the damage proved to be irreversible (Table 1).

6. Analysis and mode of action of ergot alkaloids

Although the word alkaloid is a misnomer, it is still used widely. Originally, alkaloids were described in 1913 as 'basic substances occurring in plants' [16]. Nowadays, nitrogenic constituents are included as well. One may say that ergot is a 'treasure chest of valuable pharmaceuticals' (Table 2, [2]).

The honour of the first person trying to analyse and isolate the active constituents of ergot goes to the pharmacist Heinrich Wiggers (1835) in Göttingen, Germany [17]. However, after numerous systematic botanical and chemical investigations no fundamental discovery was made.

The first pure alkaloid was described in 1875 by Tanret in France [18]. The crystallized ergotinine was,

Table 2

A choice of pharmaceutical constituents found in ergot alkaloids^a

Acetylcholine	Ergotocin
Agmatine	Ergotoxine
Amino-sulphonic acid	Guanosine
Betaine	Histamine
Cadaverine	Histidine
Choline	Iso-amylamine
Ergobasine	Iso-leucine
Ergochrysin	Leucine
Ergoclavine	Putrescine
Ergocornine	Sclerocrystallin (secalonic acid)
Ergocristine	Secale cornutum
Ergokryptine	Sensibamine
Ergoflavin	Trimethylamine
Ergometrine (ergonovine)	Tyramine
Ergosterol	Tyrosine
Ergotamine	Uracil
Ergotaminine	Valine
Ergothioneine	X-alkaloid (ergostetrin)
Ergotinine	

^aThe four alkaloids ergometrine, ergobasine, X-alkaloid and ergotocin are identical (see text).

however, almost inert. Sollmann and Brown [19] studied in 1905 the circulatory effects in mammals after both intravenous and intramuscular injections of crude ergot. The results varied considerably because of differences in the preparations and hence the dosages of ergot. Even after destruction of the spinal cord the same pattern of a rapid drop of blood pressure followed by a prompt recovery of the blood pressure was noted, but only after intravenous injection of ergot and not after oral administration. The response to adrenalin (hypertension) was decreased by ergot. The adrenergic blockade by ergot is therefore first described by Sollmann [19] and not by Barger as stated in his extensive monograph [1]. Barger and Carr [20] obtained two impure fractions from ergotinine. The uterotonic activity was attributed to a single alkaloid, the so-called ergotoxine.

Ergotamine was developed as a new physiologically active agent in 1920 [21,22]. Its uterotonic properties are easily lost during storing [23]. At present, ergotamine is only used in the treatment of migraine and other vascular headaches. When inadvertently given during pregnancy it may cause fetal stress. A review of all side effects of ergot alkaloids during pregnancy has been published elsewhere [24].

Uterine action after oral administration of extract of ergot (according to the British Pharmacopoeia) was monitored externally in 1927. It was found to be wholly inert, as was the extract according to the U.S. Pharmacopoeia [25]. Ergotamine or ergotoxine exerted a prolonged action and were therefore considered to be ideal agents for use after delivery. However, it took 4–10 min after intravenous injection before any uterotonic action was noted, 20 min after intramuscular

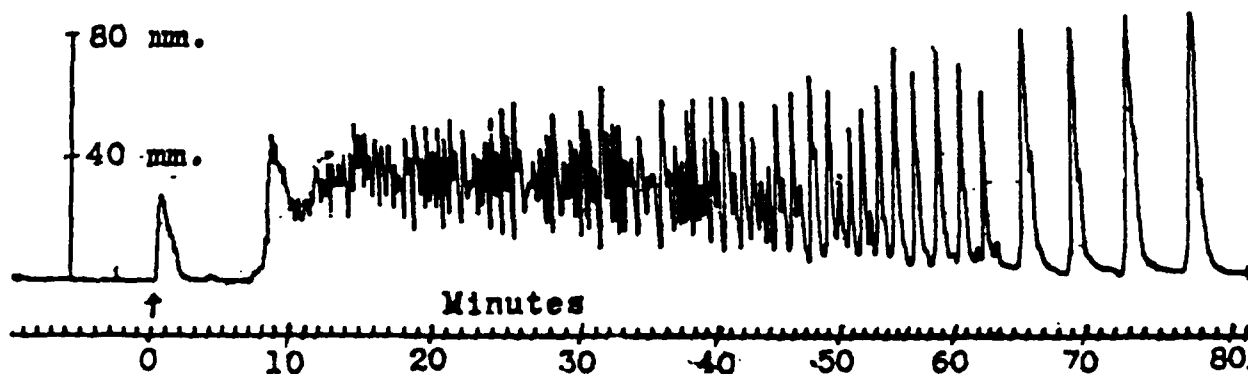


Fig. 4. Tracing of uterine contractions made on sixth day of puerperium by intra-uterine bag method, showing the effect of oral 0.5 mg ergometrine. The arrow shows moment of administration. (Fig. 1 from Dudley and Moir [29] 1935. Reproduced with permission of British Medical Journal).

injection, and even 35 min or longer after oral administration.

In their classic paper of 1932, Moir and Dale used the same technique for intra-uterine pressure recording as Schatz in 1872 [26] and Bourne and Burn in 1927 [25]: a sterilized bag was inserted in the puerperal uterus, connected by tubing to a mercury manometer and to a rotating drum with a recording device [27–28]. When an aqueous extract of ergot was given orally to a postpartum woman, the effect appeared not only in a remarkably short time of 4 min, but also strikingly different to that seen after administration of ergotamine or ergotoxine. The contractions were more frequent (2–3/min), more regular, with greater amplitude and rise of the basal intra-uterine pressure than observed after administration of any other drug. Therefore, it was concluded that another and more powerful uterotonic agent must be present. Indeed, a water-soluble alkaloid was isolated in 1935 by the same group and henceforth called ergometrine [29]. The properties were described as follows: 'the onset is sudden, and accompanied by pronounced uterine spasm, which appears to be caused by a succession of contractions so rapid that the organ as a whole has no time to relax. This stage lasts for about 1 h, and is followed by a second stage, during which the uterus shows regular, vigorous, isolated contractions,

continuing for 1 h or more'. Oral administration of 0.5 mg ergometrine provoked, after an interval of 6.5–8 min, contractions identical with those produced by the aqueous extracts of ergot as described in 1932 [27] (Fig. 4). Therefore, the active substance of ergot extract must be ergometrine. After intramuscular or intravenous administration of ergometrine the sudden action was recorded after 4 and 2 min, respectively.

Within a month, three other groups — two in the USA [23,30,31] and one in Switzerland [32] — described the same alkaloid, although by different names: ergotocin [30,31], ergostetrin [23] and ergobasine [32]. The four alkaloids proved to be the same substance. In the United Kingdom it adopted the name ergometrine; a fifth name ergonovine was selected for use in the USA.

7. Chemistry of ergometrine, its derivatives and bromocriptine

All naturally occurring alkaloids are derived from lysergic acid and contain a substituent at position 8 (Fig. 5; [33]). Two groups are described with different target organs, pharmacological properties and side effects. Ergometrine is the simplest compound with a single amine group as substituent (Fig. 5). Upon hydrolysis, ergometrine yields lysergic acid and an amine; conse-

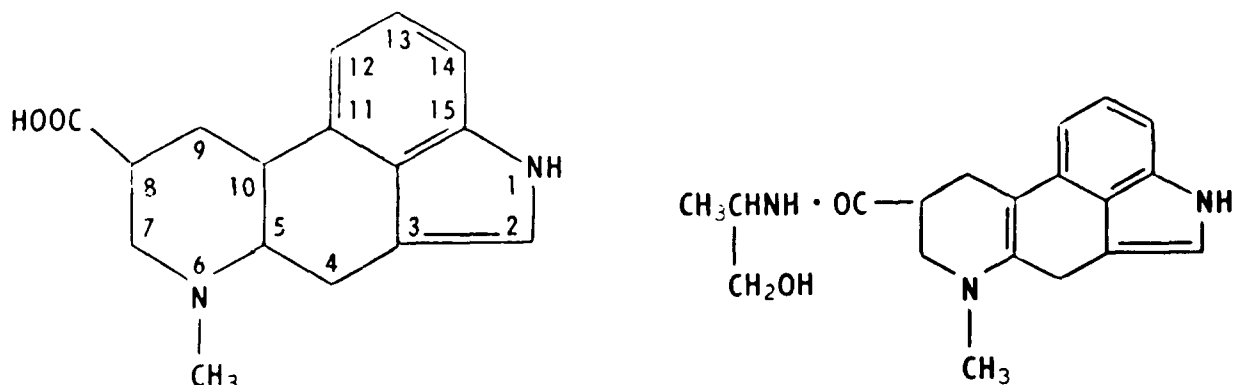


Fig. 5. Structural formulae of lysergic acid (left) and ergometrine (right) (Reproduced with permission from C.V. Mosby Company, Goth 1964, Medical Pharmacology).

quently it is designated as amine alkaloid. Methylergometrine is a semi-synthetic amide derivative of d-lysergic acid. It contains an extra methyl group in the substituent at position 8. (Methyl-)ergometrine has greater uterotonic than vasoconstrictive abilities [24].

The partial synthesis of ergometrine by Stoll and Hofmann in 1938 [34] was followed by the synthesis of lysergic acid diethylamide (LSD) in 1943 by Hofmann. It proved to be more toxic and less uterotonic than ergometrine. Within 40 min after swallowing an overdose, Hofmann himself experienced dizziness, unrest, difficulty in concentration, visual disturbances and 'delusional insanity', as was described in the old epidemics of ergotism (Table 1). It was shown that the hallucinogenic activity resulted from serotonin (5-hydroxy-tryptamine)-antagonism [35].

The amino acid alkaloids comprise the naturally occurring ergotamine and ergotoxine and the semi-synthetic bromocriptine. Prolactin secretion inhibition is caused by the α -ergokryptine compound. The synthesis of bromocriptine (2-bromo- α -ergokryptine) in 1965 heralded the new era of dopamine receptor stimulation. Interestingly, it is known that during epidemics of ergotism the milk production of nursing mothers and cows stopped. Ergot extracts were also used in the 19th century to treat amenorrhoea [33]!

8. Management of the third stage of labour with ergot alkaloids

The World Health Organization (WHO) estimates that each year at least 500 000 women die from causes related to pregnancy and childbirth [36]. Postpartum haemorrhage (PPH) is one of the most common causes of maternal death, amounting to 13% of all maternal deaths in developed and 33% in developing countries [37]. The calculated maternal mortality rate (MMR) in the British Isles in the 18th century was about 2000 per 100 000 live births. William Smellie described PPH in 1751 as follows: 'all women, when the placenta separates, and after it is delivered, lose more or less red blood from the quantity of 1/2 lb to that of 1 lb or even 2; but should it exceed this proportion and continue to flow without diminution, the patient is in great danger of her life' [38]. The MMR in the United Kingdom in 1930 was still 300/100 000 live births. Nowadays, in Western Europe and North America this figure is about 8/100 000 live births [36].

The tremendous decrease in MMR is due to improved social-economic factors and introduction of antibiotics, blood transfusion facilities and oxytocic drugs. The active management in the third stage of labour and treatment of excessive blood loss in the so-called 4th stage of labour (after expulsion of the placenta) by administering oxytocics has been described as 'one of the enduring achievements of modern science' [36]. After administering 'secale luxurians' after birth, Schwenkfeldt in 1600

noted for the first time in history that 'sanguinem sistere vulgus credit', i.e. 'one believes it will stop the bleeding' [3]. The 'Guide to midwifery' from 1912 recommends an intramuscular injection of ergotine after the birth of the infant [39].

The first application of ergometrine as a prophylactic drug is attributed to Browne in 1935, but it was published in 1947 [40]. Ergometrine (0.5 mg) was given intramuscularly to 500 consecutive normal cases as soon as the head was delivered. However, results of blood loss are not given — it is only stated that no cases were seen with manual removal of the placenta.

Joyce and Lennon studied 156 cases with PPH between 1938 and 1947. They advocated that if PPH occurred before delivery of the placenta, 0.5 mg ergometrine should be given intramuscularly by 'the midwife while awaiting the doctor's arrival' [38]. Shaw (1949) noted that the duration of the third stage was markedly reduced. Moreover, less blood transfusions were needed if a manual placental removal was done after prophylactic intravenous injection of ergometrine (54% vs. 8%) [41].

Daley (1951) is the first to routinely administer 0.5 mg ergometrine intramuscularly in normal parturients (490 vs. 510 controls) as the head was crowned. The blood loss was carefully measured. A significant reduction in the duration of the third stage of 4 min and in blood loss of 70 ml was established. However, the most important finding was that the frequency of PPH — defined as blood loss > 560 ml — was significant less in the ergometrine group (9.2%) compared to the control group (15.7%) [42].

At present, evidence of the effectiveness of active management with oxytocic drugs is based on meta-analysis of randomized controlled trials. Prescribing any oxytocic drug routinely for the prevention of PPH resulted in significantly decreased blood-loss, less blood transfusions, lower incidence of PPH (from 10%–6%), shortened third stage of labour and decreased need for further administration of oxytocics [43–46]. No statistical differences in the incidence of PPH was found after administration of oxytocin, ergometrine or prostaglandins [45–47]. However, it is very clear that ergometrine may provoke unpredictably severe hypertension, nausea, vomiting and many more side effects due to its vasoconstrictive effects [24], sometimes leading to maternal deaths [50]. Moreover, there is ample evidence that both oral and parenteral ergometrine is not stable under humid, warm and light conditions [49–53]. It was therefore concluded that the best choice for use in the third stage of labour is not ergometrine but oxytocine [54].

9. Conclusion

We may have come full circle, from the accidental poisoning with ergot alkaloids (ergotism), acceleration of

labour, prevention and treatment of PPH, to the knowledge of the severe side effects and instability of ergometrine. Perhaps the time has come to abandon ergometrine from obstetrics. Primum est non nocere.

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