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St Anthony's gift

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Numerous outbreaks of a disease whose most prominent effects were gangrene and loss of limbs occurred in Europe in the Middle Ages. Sufferers sought relief at the shrine of St Anthony at Vienne in France. Quite early, it was recognized that the disease was a poisoning due to the consumption of bread prepared from rye contaminated with the fungus ergot. Many interesting substances have been isolated from ergot, some of which are used in medicine in migraine and in childbirth, but the most dramatic substance derived from ergot is LSD. The circumstance of some of these discoveries is recounted.

In the Middle Ages, in many parts of Europe – but especially in France, Germany, The Netherlands and Poland – there were quite common outbreaks of what was called the Holy Fire, the *ignis sacer*. There were two forms of the condition: in the first, limbs became gangrenous, while in the second there were convulsions accompanied by intense pain, sometimes with blindness or deafness. The symptoms of the gangrenous form were, at first, a feeling of heat in the limbs, later alternating with cold, numbness and sometimes with red or violet vesicles. The limb then became black, often quite suddenly, then shrank, became mummified, dry and gangrenous; it affected the feet more often than the arms. It is recorded that a woman who was riding to the hospital on an ass pushed against a shrub and her leg became detached at the knee without bleeding; she carried it into the hospital in her arms! The condition occurred in whole communities, most commonly in late summer and, in both forms of the condition, the mortality was high, often carrying off a fifth of those affected.

It was regarded as a visitation of evil that could be cured by prayer at a suitable shrine. In 994, there was a violent outbreak in the Aquitaine, whereupon the local Bishop exhibited the bones of St Martial to the populace and later buried them in a shrine; many who came to the shrine were cured and there were no new cases. The bones of St Anthony the Hermit – who had originally lived in Alexandria but became a hermit living in the desert – were taken to St Sophia in Constantinople when the Saracens seized Alexandria. In 1070 they were brought

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back from Constantinople by the Crusader, Geslin II, to France and became associated with the Order of St Anthony near Vienne in the Dauphiné. During the 12th century, this became the favourite place where sufferers from the condition went and cures were reported. St Hugh, Bishop of Lincoln who visited Vienne in 1119, said 'From all parts of the world, those who are struck by this disease come to this place … And are cured in the space of seven days. If they are not, they die. This is an extraordinary miracle after the skin, flesh and limbs are destroyed.' The treatment offered included a beverage called St Vinage, a liquor that on Ascension Day was exposed to the bones of the saint. At the beginning of the 12th century, a large hospital had been built to deal with the pilgrims. On the doors and on the walls of the church desiccated limbs were displayed. St Anthony was regarded as having absolute power over the 'fire' and, in consequence, the condition acquired the name of 'St Anthony's Fire' (Figure 1).

It was noted quite early that the outbreaks were connected with bread prepared from flour that was rather grey and sometimes sticky. It was most often associated with rye, although wheat could also be affected; the spoiled rye had a 'honeydew' on it or was discoloured by little hard, blackish objects, called sclerotiae (Figure 2). The material on the rye was usually termed *Mutterkorn* in Germany or *ergot* in France, although many other names were recorded. The material and its use in childbirth were clearly described in 1582 in Lonicer's *Kreuterbuch* as 'long narrow corn pegs … which are a proved means of inducing pains of the womb'.

The first suggestion that ergot was a fungus came from Geoffroy in 1711. The description was of sclerotiae, hard seed-like bodies about 15 mm long and 6 mm across, which germinated under damp climatic conditions, grew hyphae and released ascospores, which were spread by the wind and also by insects; this is how an epidemic was set up. Tulasne gave the fungus the systematic name, *Claviceps purpurea* in 1853.

In some locations, epidemics occurred repeatedly and could be extensive; for instance, in the Sologne district, near Orléans in one epidemic in 1777, 8,000 people died! The cures at the shrines of St Anthony and St Martial were presumably due to these being in areas where the infected rye was not found and, in consequence, the patients were eating uninfected bread. After a major outbreak in France in 1855, the regular inspection of grain largely eliminated further incidents; however, there was even an outbreak in 1951, at Pont-Saint-Esprit in Burgundy (not far from the Sologne!) due to the use of mouldy grain in flour. An American journalist, John Fuller has recorded this outbreak in detail. It was dominated by diarrhoea, convulsions and vivid hallucinations. On the 5 August, bakers in the region received flour that was greyish and somewhat sticky, but it was mixed with the more usual flour and baked satisfactorily. Early complaints were of diarrhoea, colic and, in some cases, a rash and the extremities

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Figure 1. St Anthony and the sacrifice of St Anthony's fire. A woodcut from the end of the 15th century (Schreiber no. 1215. Staatlich-Graphische Sammlungen, Munich). The detached limbs displayed around the figure are the result of the disease.

were cold or burning. A dog died in convulsions after eating the bread.. One person described feeling weak, the room would spin and enlarge to enormous proportions and then shrink and squeeze him; he had visions of enormous flowers, in blinding brilliant colours, then felt ill and dizzy and later had feelings of ecstasy. Another woman started shaking convulsively and saw visions of tigers about to eat her. Another had great pain and suddenly saw a doctor dressed in black, but he had no face only a skull. It is interesting that, according to George Barger (see later), this convulsive type of ergot poisoning had not been recorded in France in the Middle Ages, although it was a common form in Germany.

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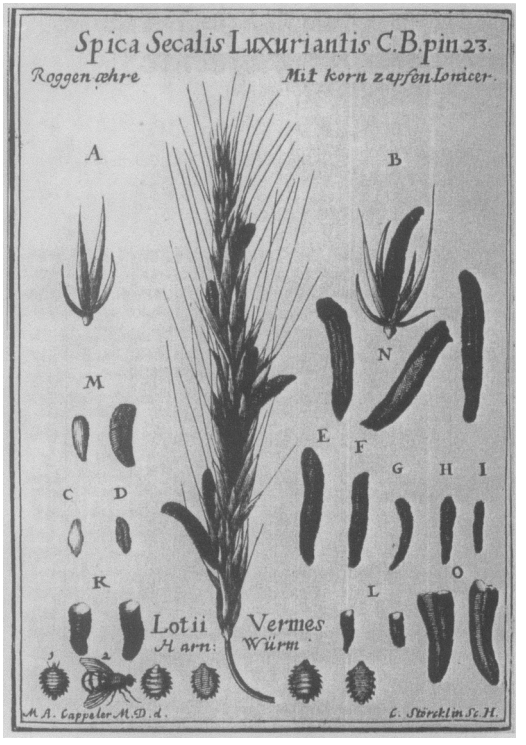

Figure 2. Rye with ergot. Engraving in Carl Nicolaus Lang (1717) *Der Korn Zapfen* (Luzern). This shows the sclerotia and the other forms of the fungus.

Apart from the reports of poisoning, such a potent material attracted the interest of pharmacists. We have already observed that Lonicer had noted the use of ergot in midwifery and there are a number of other references to that use in the older literature. However, ergot came into regular medical use due to the publication of an American obstetrician, John Stearns of Saratoga, who wrote a full account of its use in 1808 in the *New York Medical Repository*. This was followed by an extended thesis by another American, George Oliver, in his 1813, 'Dissertation on the natural history and medicinal effects of the Secate cornutum or ergot'. It was then mentioned in 1817 in Chapman's 'Compendious system of midwifery' and shortly thereafter entered the official pharmacopoeias. It was still the case that the dose was very casual, usually given as two or three sclerotia, although powdered ergot was also used (it is recorded as being used in Marburg back in 1787) and the first full official preparations appeared in about 1883. By this time it was not only being used in obstetrics but also in the treatment of migraine. Although the 'official' preparations described in the pharmacopoeias were partly purified, they were by no means reliable and, for such a potent substance, this represented a hazardous situation.

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At the end of the 19th century, pharmacy was becoming industrialized and the preparation of medicines by the local pharmacy was gradually being replaced by preparations coming from pharmaceutical manufacturers. Up to this time, no pure active substance had been obtained from ergot, but a number of actions of ergot in animals had been studied and could provide the means of biological standardization. Some of the reputable manufacturers now developed such methods, amongst whom was Henry Wellcome who, with his fellow American, Silas Burroughs had set up a manufactory in London. Wellcome had engaged an excellent chemist, George Barger, to purify the drugs that he marketed and one of the tasks that he had been set was the isolation of materials from ergot. In 1905, Wellcome appointed the young Henry Dale to supervise the physiological work in the factory, which also involved the biological testing of products of the factory. One of these products was adrenaline, a hormone extracted from the adrenal glands of cattle. Both ergot and adrenaline raised the blood pressure of cats and this was used as the assay method for them. One day Dale received a sample of adrenal extract from the factory, injected it in a cat and, to his surprise, found no rise in blood pressure, so he condemned the sample; however, the following week the same thing occurred. His suspicions were aroused and he tested a sample of pure adrenaline and this was also without effect. He realized that this must be because the animal had previously received ergot. He was then able to proceed logically and show that ergot was an antagonist of some of the effects of adrenaline on blood pressure. Ergot was the first substance known to antagonize some of the effects of both adrenaline and the sympathetic nervous system.

An apparently pure form of the substance was prepared by Barger in 1906 and named ergotoxin; later it was found to be a mixture of three closely related alkaloids but they had very similar actions. A few years later, the Swiss chemist, Arthur Stoll, isolated another related but somewhat more powerful alkaloid, ergotamine. Both ergotoxine and ergotamine found medical use in the treatment of severe migraine; however, in sensitive individuals they were liable to produce the effects on blood vessels that gave rise to St Anthony's fire. For this reason they have largely been replaced by a different kind of ergot alkaloid, methysergide and non-ergot substances such as sumatriptan, which do not have the undesirable effects on blood vessels in the limbs.

Despite their obvious complexity and variable potency, the pharmacopoeial ergot extracts continued to be used by obstetricians in preference to ergotoxine or ergotamine. In 1931, the London obstetrician, Chasser Moir, started an experimental study of ergot in pregnant women; he placed a small balloon filled with water in the cervix of the uterus and connected it to a manometer, so that he could record the contractions of the uterus. When he gave ergotamine or ergotoxine by injection he saw increased contractions of the uterus, but he was surprised how long it took for them to develop. After all, John Stearns in his

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account of the action of ergot when given *by mouth* had said, 'in most cases you will be surprised by the suddenness of its operation; it is therefore necessary to be completely ready before you give the medicine, as the urgency of the pains will allow you but a short time'. Moir found that an extract of ergot given by mouth was much quicker, the contractions sometimes coming on after as little as four minutes. His account reads as follows 'The first recording with this old preparation was indeed memorable. As I watched the pressure rise higher and higher, my first reaction was that there was a fault in the recording apparatus. My next was that the patient must be behaving in some unprecedented manner – but no, a quick inspection of the woman as she lay in the adjacent room showed that she was in fact calmly eating her lunch. My third and lasting impression was one of sheer astonishment … There flashed on me the true meaning of Dr John Stearns's words.' In his paper in 1932, Moir said 'thus there was reason to believe that the characteristic and traditional effect of ergot is due to a substance as yet unidentified'.

Moir then collaborated with an experienced natural product chemist, Harold Dudley, and in 1935 they were able to announce that they had obtained this substance pure. It was distinct in structure from either of the other alkaloids and they called it ergometrine. Almost simultaneously, two other groups also isolated it using a purely chemical approach (and gave it different names, ergonovine and ergobasine; confusingly, the multiple names have persisted). Ergometrine was far more active on the uterus than the other ergot alkaloids, had few other actions and was also exceptional in being very well absorbed when given by mouth; it has completely replaced ergot extracts in obstetrics.

Why had this substance not been discovered earlier? One possible explanation is that what is called ergot is not the same everywhere, different strains exist. For instance, ergotamine is found in Hungarian ergot but not in that from Spain or Russia. The concentration of ergometrine also varies but not so radically that this is likely to be the full explanation. However, there is another reason. In 1907, Dale saw a demonstration of the rapid action of an aqueous extract of ergot on the isolated rat uterus at the Physiological Congress in Heidelberg. He assumed that it was due to one of the amines in ergot and, when he returned to London, he and Laidlaw then isolated *histamine* from ergot, which indeed has a rapid and powerful action on the uterus. He did not search further and so missed finding ergometrine.

Arthur Stoll, who we have mentioned in connection with ergotamine, spent his life studying the chemistry of the main characteristic compounds in ergot. The chemistry was complex, but he could show that all the main alkaloids were derived from an acid, *lysergic acid*, which was either combined with rather simple amines as was the case with ergometrine or with more complex peptides as in ergotamine and the ergotoxines. Stoll and his colleagues, notably Albert Hoffmann, synthesized a wide range of derivatives of lysergic acid looking for

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more effective drugs. In 1938, Hoffman prepared the diethylamide of lysergic acid, hoping to find a cardiac stimulant, basing this on the structure of a well-established stimulant, coramine. Testing in animals showed a strong effect on the uterus and the only other feature noticed was that the animals became restless. The results were not of particular interest.

However, something about the diethylamide nagged at Hoffmann and on Friday 16 April 1943, Hoffmann prepared another sample for further pharmacology. He immediately entered into a dream world. His surroundings had changed in a strange way and had become more luminous. He felt uneasy so he went home and rested. Lying on a couch with eyes closed, because he found daylight unpleasantly glaring, he perceived an uninterrupted stream of fantastic pictures, with an intense kaleidoscopic play of colours. After some hours this strange but not unpleasant condition faded.

He presumed that intoxication by one of the materials he had been working with was responsible for this strange, bizarre experience. He guessed that it might be due to dichloroethylene, one of the solvents that he been using, but a test of this was negative, so he was led to the supposition that it might have been due to the lysergic diethylamide itself.

He then deliberately took 0.25 mg of the substance by mouth; this was a modest dose by the standard of other ergot alkaloids, such as ergometrine. The result was a repeat of the previous sensations, although it was even more dramatic (this was actually a large dose)! He says:

> … After 40 minutes I had the beginning of dizziness, feeling of anxiety, visual distortion, desire to laugh. I asked my laboratory assistant to escort me home. Having no car, we went by bicycle. On the way home, everything in my field of vision wavered and was distorted as if seen in a curved mirror. I lost the feeling of time, so felt that we had not moved very rapidly. At home, the dizziness and sensation of fainting became so strong that I had to lie down on a sofa. My surroundings had transformed in a terrifying way, everything in the room spun around and familiar objects such as the furniture assumed grotesque, threatening forms. They were in continuous motion as if driven by some inner restlessness. When a neighbour brought some milk, she was no longer Mrs Ruch, but rather a malevolent witch with a coloured mask. Every exertion to try and end this disintegration of the outer world seemed a wasted effort. I was seized by a dreadful fear of having become insane. I was taken to another world, another place, another time. My body seemed to be without sensation, lifeless and strange … slowly I came back to a reassuring everyday reality. The horror softened and gave way to a feeling of good fortune… I could begin to enjoy the unprecedented colours and plays of shapes … it was remarkable how every sound became transformed into visions.

This was the first experience of LSD (Lysergsäure-diäthylamid) the most spectacular of the substances to be derived from ergot! At first it seemed that this

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new substance might have great potential in medicine, but experience has emphasized its dangers rather than its benefits and it remains as a hallucinogen, like mescaline and others used experimentally by youth, and has been popularized in literature, such as Aldous Huxley's *Doors of Perception.*. All these hallucinogens seem to work through the receptors for a normal brain transmitter, serotonin (5HT).

It was subsequently found that the Mexican hallucinogen *oloiuqui*, derived from a plant of the morning-glory group contained a mixture of two related lysergic amides that are hallucinogenic. These same compounds were found in an ergot variety, *Claviceps paspali*, which grows in Greece in the region of Eleusis and may have been concerned in the Eleusinian Mysteries. Harking back to the accounts of convulsive ergotism that we mentioned earlier, it seems not unlikely that this might have been caused by a similar strain of ergot.

I have only touched upon the astonishing variety of fascinating and important biologically active substances that this extraordinary fungus produces. Acetylcholine, which is the 'chemical transmitter' in many parts of the nervous system, was first discovered in ergot, as was histamine, which is responsible for sneezing and wheezing in hay-fever and asthma, and wheeling in allergy. Vitamin D, *calciferol* was also first isolated from ergot and was first named *ergosterol* because of it origin.

Ergot has truly been a gift of St Anthony.

Further reading

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