Ergot – the Story of a Parasitic Fungus

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<**Opening credits over shots of a field of rye**>

<**Unspecified narrator over shots of heads of rye**>

The black outgrowths on this head of rye are the sclerotia of ergot, *Claviceps purpurea*. The sclerotia (from the Greek skleros – hard) occur on many grain crops and grasses. They contain a group of alkaloids of which ergotamine, specific in the treatment of migraine, and ergometrine, of great value in obstetrics, are now the most widely used.

<**Narrator over various images showing aspects of the history of ergot**>

At least as early as the sixteenth century, midwives in Europe used ergot to speed labour and to control postpartum haemorrhage. Then this knowledge was largely forgotten. It was rediscovered in the new world when John Stearns heard the tale in Massachusetts early in the nineteenth century; he drew the attention of doctors to its medicinal possibilities in obstetrics.

But there are two sides to the ergot story – on the one hand there is its value in therapeutics, on the other, its poisonous nature.

For centuries, the European peasant has used rye in its bread, and rye is particularly susceptible to the fungus. Frugal in habit, ignorant of the dangers, the impoverished peasant often neglected to remove the ergot from the rye. So the fungus, milled with the flour, found its way into the bread. Damp years increase the danger, for it is then that the fungus thrives, the harvest poor and each ear of grain invaluable. In popular tradition, records abound of the suffering of people, especially the poor; of fiery burning pains along the limbs, mutilations from gangrene, delirium, convulsions, hallucinations and in many cases, death.

As long ago as 1095, an order, named after St Anthony of Egypt, was founded to take care of these sufferers, so that the gangrenous condition, particularly with the burning pains which preceded it, became known as St Anthony's Fire. But several centuries were to elapse before ergot became suspect.

A French suggestion by Dodart in 1676 seems to be the first trustworthy reference to this connection; his ideas were not widely circulated and so the outbreaks of ergot poisoning continued. They occurred even in England, a country where rye has never been widely used. One outbreak occurred at Wattisham, near Bury St Edmunds in 1792. In the town of the village church, there is a tablet recording the deaths of the wife and children of a poor agricultural labourer. The parish register gives a vivid description of their sufferings, but it is obvious that ergot was not suspected as the cause <*quote from parish register*>:

> Elizabeth, the next daughter, aged 14 years, was on the next day, namely Monday January 11th, 1762, seized only in one leg and foot, which she could not set on the floor for three weeks, but stood all that time upon the other, leaning against the chimney. After which being taken in the same manner in her other foot, she lay down. One foot mortified and came off at the ankle, the other leg near the knee.

<**Narrator over shots of historical articles relating to ergot poisoning**>

In the London Medical Times of 1847, there is an account of mutilation which occurred to a young Irishman who ate rye bread; he lost fingers and toes through gangrene. Again, as recently as 1928, some Jewish immigrants in Manchester were taken ill with characteristic symptoms after eating bread made from rye which was later proved to have been infected with ergot.

But perhaps the most disquieting outbreak was that which occurred in France in 1951 – disquieting in that it could still occur today. From the small town of Pont-Saint-Esprit came news of the sufferings of the people there. Through the news, the world learned of the hallucinations, convulsions, delusions and deaths which had resulted from ergot poisoning.

<**Narrator over shots of infected cow**>

Unfortunately, the poisoning of farm stock from ergot-infested grasses other than rye is still fairly common. This heifer is typical. It is lame as a result of gangrene developing in the extremities; here it is in the hoof, and also in the tail.

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<**Narrator over shots of fungi**>

Ergot belongs to the group of fungi known as Ascomycetes, it is therefore related to the stag's-horn fungus (*Xylaria hypoxylon*), the devil's bunion (*Daldinia concentrica*), the edible morel (*Morchella crassipes*), the vegetable caterpillar (a species of Cordyceps), the coral spot fungus (*Nectria cinnabarina*), the orange peel fungus (a species of Peziza), and also, here shown growing on a crust of bread, *Penicillium notatum*, the microscopic mould from which penicillin is derived.

<**Narrator over various shots, illustrations and animations showing ergot fungus lifecycle**>

The ergot sclerotium is a tough resting body which, when fully developed, falls from the ear. During the winter it lies on the soil; germination depends on this period of exposure to cold. In the spring a number of little forked bodies grow out from the sclerotium. The tips of these stalks become globular and pitted with little holes; from these holes the spores will eventually be ejected. The holes are the openings of small, flask-shaped cavities, the perithecia. This is how the perithecia appear in a stained section. Each perithecium is lined with fungal threads, the hyphae.

A single, multinucleate hyphal elongates and produces a side branch. After nuclear division, copulation takes place between these branches and the nuclei associate in pairs. Elongation occurs and cell walls are laid down. Small projections, each containing two nuclei grow from the sides of these cells; this process is known as hook formation. After a further synchronous division, fusion takes place, while the nuclei which have not fused proceed to further hook formation. The cell now elongates enormously to form an ascus. The diploid nucleus divides to form eight haploid nuclei, around which he protoplasm aggregates to form eight cylindrical ascospores. Each ascus, when it has matured, ejects its ascospores and they are blown away in the wind.

At this time, the rye is coming into flower. The anthers, three to each flower, burst forth and shed their pollen. Later, the feathery stigmas are exposed. Ascospores, carried by the wind, adhere to them. The ascospores send out hyphae, which grow

down through the fragile tissue of the stigmas and penetrate the ovary. Soon the fungus will have replaced quite a large proportion of the ovary tissue.

This is a longitudinal section through an infected flower. In the central mass of the fungus, pockets are formed from which enormous numbers of little conidiospores are liberated. These conidiospores, or conidia, are ovoid in shape, not long and thin like the ascospores. At the same time, a strong sugar solution, called honeydew, is secreted and slowly wells out between the florets. In these drops of honeydew are numerous conidia. Insects are attracted by the honeydew which sticks to their bodies and they thus carry the spores to other rye flowers. If deposited on the stigmas, the spores will germinate, as they are doing here, and infect the ovaries of more flowers; in this way, an infection spreads throughout the crop. The tissues of infected ovaries, instead of developing into grains of rye, become replaced by fungus. The external hyphae darken in colour, spores and honeydew are no longer produced; a new generation of sclerotia has been formed and the lifecycle is complete.

In August, the sclerotia will be dropping to the ground again. Next spring, each sclerotium will develop ascophores, in the heads of which ascospores will be formed. These will be ejected and infect the rye. Honeydew will be produced; later a new crop of sclerotia will be formed.

<**Narrator over shots of different grasses**>

Ergot will grow on a variety of cereals and other grasses such as wheat, barley, ryegrass (*Lolium perenne*), tussock grass (*Deschampsia cespitosa*), cocksfoot (*Dactylis glomerata*) and Yorkshire fog (*Holcus lanatus*).

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The demand for ergot alkaloids for medicinal uses is increasing and greater quantities are being used annually.

<**Narrator over shots of a globe, then of the harvest and sale of ergot in a Portuguese market, followed by shots relating to its international distribution**>

Supplies can only come from the grasslands and cereal farms of the temperate zone. To the peasants of some of those areas such as North West Spain and Portugal, the fungus which infects their rye has now become an important crop. The peasants pick the ergot by hand from the standing crop and when they feel it will command the highest price, take it to dealers in the local village market.

Such a village is Arcos de Valdevez in Northern Portugal, close to the Spanish border. Here, the dealers set up their stalls – barter is often the vehicle of trade, and a few other dealers who enquire whether the ergot was smuggled across the border. These supplies of ergot are subject to wide variations in quality and price. Because of the constant commercial tug of war between dealer and peasant, regularity of supply can never be guaranteed. At Oporto, the ergot is dried and inspected before being shipped to Britain and other countries.

Twenty sacks of ergot may yield as little as a hundred grams of ergometrine; the yield depending greatly on the strain of ergot. Thus it is not surprising that a great deal of attention has been paid to the possibility of cultivating ergot and developing better strains.

<**Narrator over laboratory manipulation of ergot and dispersal of the product onto a field of rye**>

In the laboratory, it is possible to dispense with part of the normal lifecycle. conidia are produced by a mycelium which is grown under sterile conditions from the sclerotia. A sclerotium is washed, sterilised and rinsed. Now soft enough to cut easily, sections are placed on a nutrient medium in Petri dishes; after suitable incubation a mycelium begins to grow. Numerous sub-cultures are prepared; first on slopes in test tubes, then later in Thompson bottles.

The conidia are dislodged from the final culture by shaking with glass balls in water. A suspension of spores is thus prepared and is removed by suction. Pure cane sugar is added to make a 50% solution; this fluid is maintained at a low temperature to retard germination of the spores. A trial dilution is prepared to determine the concentration of spores; a counting chamber is used for this purpose. Here, through a microscope we see the appearance of the conidia. By counting the spores on a known number of the cells of the counting chamber, the concentration in the original suspension can be counted.

In the field, the stock suspension is diluted according to the calculations made in the laboratory. There are various ways of infecting the ears of rye with the inoculum, but this one gives a high percentage of satisfactory results. Each worker has a felt pad which he dips into his suspension of spores, he claps the ears between the felt pad and a clapper set with needles, the spore suspension is thus forced into the rye tissues through holes made by the needles.

At a later date, the ears missed by the clapping technique are infected with spores obtained from the developing honeydew. Under natural conditions this operation is performed by insects and is therefore unpredictable, and so man aids nature in ensuring the completion of the task. Using brushes with nylon bristles, the worker sweeps the honeydew from plant to plant; his protective clothing is necessary because of the sticky nature of the honeydew.

These techniques achieve two objects: they enable known strains of ergot to be perpetuated and they ensure a heavy and satisfactory crop.

00:16:23:00

<**Narrator over stills of Sir Henry Dale and of his work with ergot alkaloids**>

Sir Henry Dale, at that time Dr HH Dale, initiated the pharmacological study of ergot alkaloids. In a paper in 1906, he drew attention to the remarkable activity of these compounds. His two collaborators, Barger and Kerr, were thereby able to isolate the

first of the ergot alkaloids, ergotoxine. Ergotamine was isolated some fifteen years later. In action, indistinguishable from ergotoxine, ergotamine has the advantage of being easier to prepare and hence is more widely used in medicine. Ergometrine, a more recent discovery, differs in type and action from ergotoxine and ergotamine.

All the known ergot alkaloids are derivatives of lysergic acid. Ergometrine is composed of lysergic acid and D2-aminopropanol, while ergotamine is more complex. These, the two ergot alkaloids most commonly used in medical practice, have to be separated from the many other substances contained in ergot. The methods we are about to see are essentially the same as those used in large-scale manufacture.

<**Narrator over shots of production of ergot-based medicines**>

The ergot is ground and macerated with sodium bicarbonate and water. The mixture is transferred to a percolator and extracted with an organic solvent. This percolate, containing all the alkaloids is chemically and physically assayed. Then an acid solution is added to the percolate, which, on shaking, takes out the alkaloids. The solution is run off and transferred to a vessel where it is treated with alkaline. This precipitates the watery soluble alkaloids comprising ergotamine, ergosine, ergocornine, ergocryptine and ergocristine.

From the filtrate, the water-soluble ergometrine is extracted with chloroform. After concentration, crude ergometrine crystallises out; it is further purified to give ergometrine maleate.

Ergotamine is specific against migraine – the symptoms of which are: unilateral headache, visual disturbances, nausea and vomiting. Unfortunately, ergotamine when given by mouth in adequate doses, increases the nausea and vomiting. Even when potentiated by caffeine, the smaller dose of ergotamine is still liable to induce these side effects. So the potent and rapid acting anti-emetic, cyclizine hydrochloride, is added; this successfully counters nausea and vomiting, whether due to ergotamine

or the migraine. More, it allows the dose of ergotamine to be increased. Migril is a product compounded to meet these requirements.

<**Narrator over shots of the use of ergot in obstetrics**>

The use of ergot to promote contraction of the uterus and to control postpartum haemorrhage, as we have already said, dates from very early times. The midwives of long ago used an aqueous extract of ergot and this type of extract was official in the 1914 *British Pharmacopoeia*. In the 1932 revision it was replaced by an alcoholic extract, on the ground that the active principles known at that date, ergotoxine and ergotamine, were soluble in alcohol but scarcely at all in water. Many practitioners, however, after trying the new preparation expressed a preference for the old watery extract. Their views, and incidentally those of many generations of midwives, were vindicated with the obstetrician Dr Chassar Moir clearly showed by mechanical tracings that the watery extracts caused a powerful contraction of the human uterus after childbirth, and that this action could not be explained by any of the then-known alkaloids.

And here is Professor Chassar Moir to continue the story himself:

<**Chassar Moir tells the story of the use of ergot in obstetrics**>

These were exciting days and I vividly recall the details of the hunt for this new active principle of Ergot. I was working at the time with Professor FJ Brown in University College Hospital, London; and now, at Sir Henry Dale's suggestion, I also collaborated with the chemist, the late Dr HW Dudley; Dudley preparing the ergot fractions and I testing them on the human subject.

After three years of continuous work, Dudley succeeded in 1935 in isolating the illusive principle, which, at Sir Henry Dale's suggestion, we named L-ergometrine; metra being the Greek for uterus. Our paper described ergometrine as an alkaloid, over three times more soluble in water than in alcohol and by far the most potent

oxytocic agent yet isolated from ergot, with the property also of being rapidly absorbed when given by mouth.

Shortly after the publication of our paper, the same alkaloid was described from three other laboratories where the search for it must have been simultaneously, but independently, in progress. In the United States pharmacopoeia, by the way, ergometrine is known as ergonovine.

<**Narrator introduces film of ergometrine in use during childbirth**>

And now let us see ergometrine in routine use at University College Hospital.

<**Further unspecified narrator, over shots of woman giving birth, receiving a shot of ergometrine, then seen cuddling her baby**>

This patient is in the second stage of labour, as the child is born, ergometrine will be administered. Its action is to promote contraction and retraction of the uterus, thus expelling the placenta and minimising the risk of haemorrhage.

<**Original unspecified narrator over shots of ergot being picked and researched**>

The story of ergot is not yet ended. New strains are being propagated, new compounds sought. Who knows what undiscovered secrets may still remain within this extraordinary fungus?

<**End credits**>