

THE CAUSE OF CONVULSIVE ERGOTISM

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(With Plate IV, containing Figs. 1-13)

FROM early times epidemics of ergotism have occurred in Europe on a large scale, especially in France and Germany, and have been very fully described by a host of writers. There are two distinct types, entirely different in their symptoms, the *gangrenous*, and the *convulsive, spasmodic, or nervous*, and, broadly speaking, while the former has been observed almost exclusively in France, the latter has been mostly confined to Germany. This sharp geographical distribution west and east of the Rhine has been the subject of frequent comment and much speculation, but hitherto no conclusive explanation has been forthcoming. It was recognised towards the end of the seventeenth century that the epidemic outbreaks resulted from the consumption of ergotised rye, and that they followed on bad seasons with poor harvests, a general scarcity of other foods, and consequent extreme poverty and hardship. Also, it is now definitely determined that gangrenous ergotism is due to the action chiefly of ergotoxine, an alkaloid elaborated in the rye grain by a fungus, the *Claviceps purpurea*, and which among its other actions brings about such vigorous and prolonged constriction of the arterioles that clotting and thrombosis take place. The consequent blocking of the blood stream leads to dry gangrene of the extremities and of other parts where the collateral circulation is not sufficient to maintain nutrition. Gangrenous ergotism can be very readily produced in the barn-door fowl and pig by feeding on ergotised rye, but other laboratory animals, such as the dog, cat, rabbit and guinea-pig, are extremely insusceptible. Trousseau¹ states that very large quantities of ergotised rye have to be consumed before the disease develops in man, and I failed to produce it in monkeys.

Exp. 1. A bonnet monkey was fed for one month on cakes made of 75 per cent. oatmeal and 25 per cent. ergot lightly baked on a girdle. The monkey received no other food except fresh fruit daily, and the ergot was proved to be of normal physiological activity. At the end of a month the ergot was increased to 50 per cent., and it lived on this for three months longer in good health.

Exp. 2. Two bonnet monkeys were similarly fed for two months on cakes made entirely with ergotised rye (Ergot B.P.). As no symptoms of any kind developed, the experiment was stopped.

The cause of convulsive ergotism has, however, remained unexplained. By some investigators it has been attributed to specific poisons formed in the rye grain by *Claviceps*, by some to the absence of vitamins, and by others to differ-

¹ *Traité de Thérapeutique*, 1841.

ences in the soils of France and Germany leading to the production of different poisons, but all these explanations lack substantial evidence in their support. The curious theory has also been advanced that the two types are merely developments in the action of the same poison.

In any attempt to clear up the etiology, the important points to be considered and explained are: (1) Whether the disease is due to a poison formed in rye grain by the *Claviceps purpurea* or whether it is due to a poison normally present in the grain itself; (2) Whether it is a "deficiency" disease; and (3) Why outbreaks of convulsive ergotism should have been mostly confined to Germany, and those of gangrenous ergotism to France.

These questions can, I think, be satisfactorily settled by a critical examination of the numerous records of outbreaks and by experiments on animals with rye feeding and toxic products isolated from healthy rye grain. It is, fortunately, unnecessary to make use of the whole mass of records except in a very general way, and out of them I have selected three as containing most of the data required to show that convulsive ergotism is not ergot poisoning but rye poisoning. The three contributions are those of Vleminckx¹, Heusinger², and Thieme³. The first of these is an exhaustive account of an epidemic which broke out simultaneously in the government prisons at Brussels, Ghent and Namur. It is important and decisive because it occurred in three widely separated and strictly isolated communities in which the dietary was identical, carefully controlled, and different from that of the general population, and where the inmates could obtain no other or additional food. Further, it was the subject of careful reports by the prison surgeons and of an official inquiry, the cases were examined by leading Belgian physicians and the whole matter was fully discussed in the Royal Academy of Medicine.

Owing to the potato blight which spread through Europe in the fourth decade of last century potatoes had been entirely eliminated from the prison dietaries and cereals substituted in their place. The cereals were preponderatingly rye and wheat with inconsiderable quantities of oats, barley and buckwheat, and it is definitely stated in the reports that these were all of good quality and contained no ergot or foreign seeds. The outbreaks in all three prisons began shortly after the change was made. Each prisoner received 1 kg. of bread per day, and the soup which constituted the remainder of their food was thickened with cereals. No further details of the dietary are given, but presumably the soup contained cabbage and other cheap vegetables and a little boiled meat. Certain prisoners were served with rye bread only and others with wheaten bread only, and the latter were affected as severely and in the same proportion as the former. Here, then, is a large epidemic of convulsive "ergotism" in which it is certain that those affected consumed no ergot, and hence the cause must lie either in a "deficiency" or in an actual poison present

¹ Vleminckx (1846), *Bull. Acad. roy. de Méd. de Belgique*, **5**, 409.

² Heusinger (1856), *Studien über den Ergotismus*. Marburg.

³ Thieme (1930), *Veröffentl. a. d. Geb. d. Medicinalverw.* **32**, 5.

in the cereals and becoming deadly in its effects owing to the abnormally large amount of cereal food consumed.

In the St Bernard prison at Brussels single cases were noted in March, 1844, and by October they had increased to such an extent that 100–160 was the daily hospital quota. None of the staff who lived outside and fed themselves at home were affected. Clinically the cases varied from mild to others of dreadful severity, and out of 288 persons affected 33 died, but many of those who survived suffered permanent damage to the nervous system manifested by dullness of intellect, dementia, epilepsy and insanity, while spinal cord lesions were common of both spastic and ataxic types.

As any or many parts of the nervous system may be affected in convulsive "ergotism" the symptoms vary greatly in detail but are always either irritative or paralytic in character. It is unnecessary to describe them here as this has been so often and so well done at first hand, but I draw attention to the spasmodic jerkings of groups of muscles, the flexure of fingers and toes and of joints generally (Pl. IV, Figs. 1, 2, 3, 6), to the clonic-tonic convulsions, the temporary paralyses, and to the often sudden onset and almost as rapid subsidence of these symptoms, my reason being that they can all be readily and exactly reproduced in monkeys by the hypodermic or stomach administration of small amounts of active substances extracted from healthy rye and other cereals and from beans and peas.

There are other noteworthy symptoms recorded in this epidemic which I have never seen commented on or referred to in other accounts of convulsive ergotism. The prison surgeons report that oedema of the lower limbs was present in many cases, frequently with fluid in the pleural and abdominal cavities also, and that there might be oedema unaccompanied by any nervous symptoms. They say it occurred only in cases where the illness had been of long duration. Death is described as being often unexpected, sudden or instantaneous. All these clinical characteristics establish links with the symptomatology of wet beri-beri and epidemic dropsy, two diseases which are also associated with an excessive consumption of cereals.

With regard to vitamin deficiency as the cause of convulsive ergotism, the old burr-stone mills universally in use in 1844 left abundance of vitamin B (the antineuritic factor) in the meal, more than enough to preserve health¹. Further, in the ergot literature numerous instances are narrated where acute convulsive poisoning occurred after eating large quantities of rye bread for a few days only, and Hussa records two deaths after a single meal of rye dumplings². Here there can be no question of a slow cumulative dietetic deficiency.

The most prominent and characteristic symptoms of convulsive ergotism can be reproduced in monkeys *gradually* by feeding them on rye and many other grains, and *acutely* by administering per os or hypodermically or intravenously toxic substances extracted from the grains. These toxic substances

¹ Voegtlin, Lake and Myers (1928), *U.S.A. Public Health Reports*, 33, No. 18.

² Quoted by Barger (1931), *Ergot and Ergotism*.

are salts of phytic acid (inositehexaphosphoric acid) and decomposition products from it, and they are obtainable in a pure state as white powders of very unequal toxicity.

In a recent communication¹ I have described the actions of a number of these compounds, and in previous papers² the similar results got from the investigation of numerous cereals, peas and beans. The chemistry of phytic acid has been fairly well worked up, but there are no exact data available regarding the amounts present in different cereals or in the same cereal grown in different countries or districts or under different seasonal conditions, or whether the compounds present in all the seeds are always the same. I found, for instance, that different lots of *Lathyrus* peas varied greatly in toxicity when fed to the same monkey³, and further that one of the substances obtained from maize was more poisonous than those from any of the other grains. In addition some of the acid salts, even when neutralised with NaOH to neutral sodium salts, were intensely irritating when injected hypodermically, while others had no such local action. It is evident therefore that more than one substance is accountable for the poisoning and that further chemical and botanical research is urgently needed. Hitherto it has been assumed that phytin (an acid CaMg salt of phytic acid) is the compound invariably present in these seeds.

I have reproduced from Heusinger and Thieme some of the illustrations which they give of cases of convulsive ergotism in man in order that they may be compared with the effects on monkeys of feeding with rye and other grains and the administration of phytates and other phosphorus compounds obtained from these grains. The resemblances are very striking. As regards subjective symptoms the monkeys often scratched a great deal early in the poisoning as if the skin were irritated, and this may correspond to the highly characteristic formication in man.

Exp. 3. A monkey fed on rye porridge (with some milk, butter and fresh fruit) developed after 65 days paresis of all its limbs with flexures of the joints so that it was unable to use its hands and progressed by hobbling along with its hips on the ground. Its toes were sometimes so flexed that it walked on the dorsal aspect of its feet and it was unable to jump or climb. There were tremors and twitching of muscles. These symptoms came and went erratically, one day it would seem to be fairly well and the next much affected. Suddenly, on the 93rd day, it became distinctly paralysed, and next day was much worse (Fig. 4) with flexures, muscular twitchings and tremors—a mixture of irritative and paralytic symptoms. Two days later it had recovered to a considerable extent (Fig. 5) but was still very paretic, with flexures of its joints and muscular twitchings. It had relapses, became very thin, and as it showed no tendency to recover, was chloroformed on the 102nd day. Figs. 4 and 12 are comparable with the photograph given by Thieme (Fig. 6) of a human case of convulsive ergotism.

Exp. 4. A monkey was given hypodermically 3 g. and later 2.5 g. of an organic (phosphorus-containing) salt obtained from the acetate of lead precipitate of a water extract of rye. It soon became very paretic with flexures of its fingers and toes (Fig. 7). The paralytic symptoms deepened and it took three days to recover. There was severe local irritation at the points of injection.

¹ *J. Hygiene* (1934), **34**, 144.

² *J. Hygiene* (1931), **31**, 550; (1933), **33**, 204.

³ *Edinb. Med. J.* (1917), Nov.

Exp. 5. A monkey was fed for 30 days on whole wheat porridge with a little milk, butter and fruit. It was affected by the 12th day and during the ensuing time showed paresis with contractures of the hands, wrists and other joints. Some days it seemed quite well and on others considerably affected. Photographs could not be taken owing to its restlessness and suspicion of the camera, but the description may be compared with Fig. 1 which represents a mild case of convulsive ergotism in a lad of 15 years.

Exp. 6. A monkey fed for 10 days on the same diet as the preceding, was given per os a cold-water extract of 400 g. ground wheat. It became very depressed and died suddenly 6 hours later, when microscopic examination of the nervous system revealed widespread destructive changes in the nerve cells. This corresponds to those cases reported in the literature of convulsive ergotism in which death occurred after one large meal of rye.

Exp. 7. A monkey was given hypodermically 2 g. of an acid phytic acid salt isolated from wheat and neutralised with NaOH to slight alkalinity. In an hour it had become so parietic that it mostly lay down (Fig. 8). The hands and wrists became fully flexed and its other joints less so. When roused it moved about on all fours, but its wrists were so flexed that it walked on the back of them. It recovered gradually in 3 days.

Fig. 10 shows the effects of feeding with *Lathyrus* peas, and Fig. 11 (contractures and clonic-tonic convulsions) those following the hypodermic injection of a phytic acid salt isolated from lentils.

Phosphoric acid, which is the end-result of the decomposition in the bowel of phytic acid, when given as a sodium salt has an action similar to that of phytates and their intermediate products, but larger doses are required and locally it is non-irritant.

In Fig. 9 the action of sodium phosphate (4 g.) obtained from rice is shown, and in Figs. 12, 13, that of 4 g. sodium phosphate (B.P.), both having been administered hypodermically. In both the contractures and paresis are very marked, but they passed off in about 10 days, leaving no evident sequelae.

In the monkeys when examined after death the cerebro-spinal and sympathetic nervous systems showed widely scattered degenerative changes similar to those described in cases of convulsive ergotism¹.

Both in man and monkeys the variability in the severity of the symptoms from day to day is a striking feature of the poisoning. The explanation seems to lie in the extent to which phytic acid is broken down in the bowel by phytase and bacteria. Phytic acid is more poisonous than its immediate organic decomposition products and they in turn much more than inorganic phosphates, which, moreover, are absorbable from the bowel in very small amount. If the phytates are only partially broken up and become absorbed in sufficient quantity the symptoms may be very severe, whereas if they are fully decomposed there may be an almost complete remission, and of course there are many stages between these extremes. Individuals who escape entirely, and there are many in all epidemics, are those capable of completely breaking down the phytates just as occurs in the digestion of normal quantities of cereals and peas. It is owing to the ability of the bowel to decompose pure phytates that these are so much less poisonous when given per os than when given hypodermically, and

¹ *J. Hygiene* (1933), **33**, 204.

enormously less poisonous than when injected directly into the blood stream through a vein.

The prevalence of the gangrenous type in France and the convulsive type in Germany is explainable by the differences in the dietetic habits and the relative comfort and social condition of the poorer agricultural populations west and east of the Rhine. Even in Germany families supplied with eggs, milk and bacon—the well-to-do farmers—did not suffer, the victims were the labouring classes and the very poor. Rye was practically their only cereal, and in famine time they got scarcely any other food as they were miserably poor in money. From the rye grain bread, porridge, soups, dumplings and cakes were made, and with the addition of coarse vegetables and inferior substitutes for them the poor were reduced to the same dietetic conditions as the inmates of the Belgian prisons and with similar results. It is evident from some of the records that the amount of ergot in the grain was sometimes not large. Further, it is a possibility, but there are no exact data on which it may be definitely affirmed, that rye poisoning requires a much shorter time for its development than ergot poisoning, and the occurrence of the gangrenous affection was forestalled under treatment by a change of diet.

In France, on the other hand, all accounts agree that milk and other country foods were available and consumed in reasonable quantities, sufficient at least to prevent the consumption of excessive quantities of rye. In that case the phytase and the bowel bacteria would be able to cope with and break down the highly poisonous phytates of the grain into the comparatively innocuous inorganic phosphates, and hence, as no convulsive symptoms developed, the people continued to consume the ergotised rye until its ergotoxine action became fully developed and gangrene resulted.

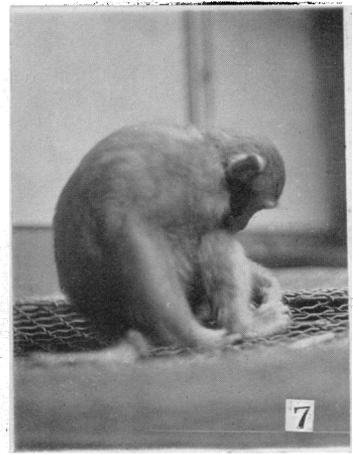
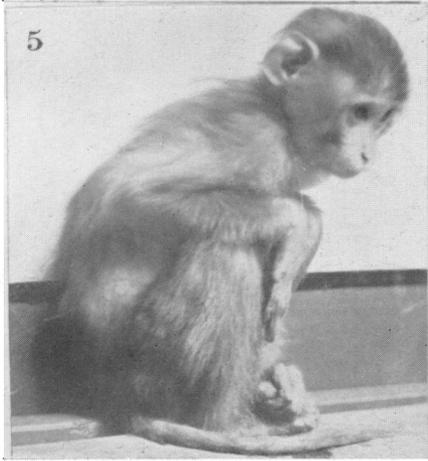
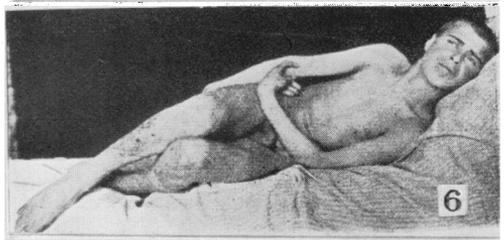
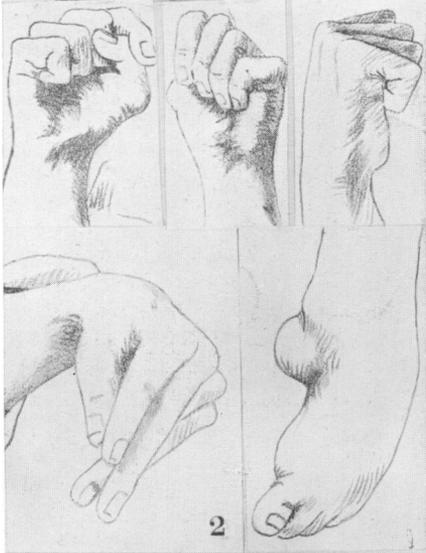
Convulsive ergotism was common in Germany in the seventeenth and eighteenth centuries, but diminished notably after 1770 owing to the extensive cultivation of the potato which supplied a valuable supplement to the formerly almost exclusive use of rye as the carbohydrate element of the rural dietary. The last serious outbreak was in Ober Hesse in 1881, when about 500 persons were affected with twenty-five deaths and many cases of nervous sequelae. In Manchester in 1928 a very mild epidemic occurred among foreign Jews who ate rye bread. There were about 200 cases, but the symptoms cleared up as soon as the cause was recognised and the bread changed¹.

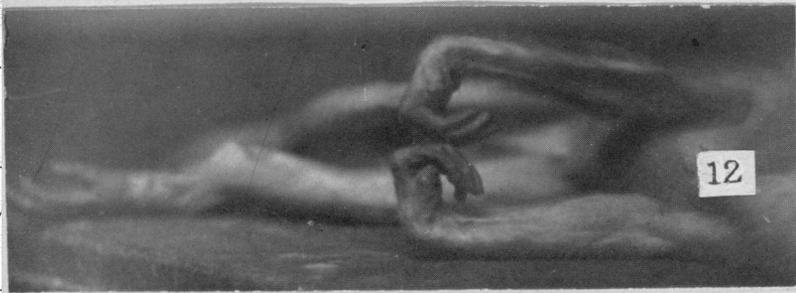
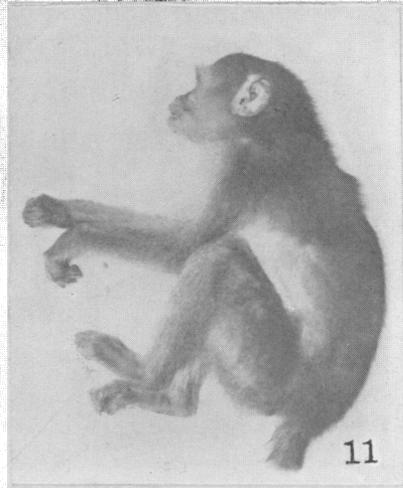
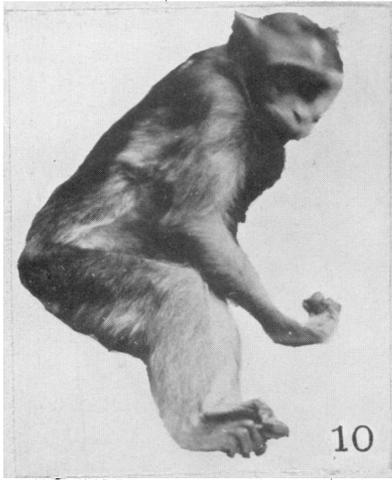
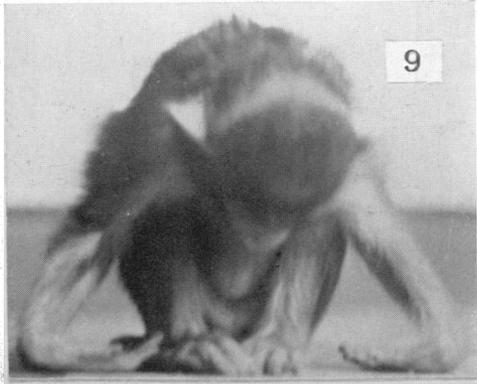
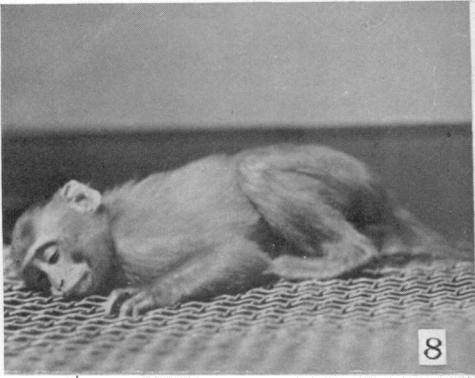
SUMMARY

By feeding monkeys on healthy rye, wheat and other cereal and leguminous seeds convulsive and paralytic symptoms similar to those of convulsive ergotism in man can be produced.

Large amounts of cold-water extracts of the grains given to monkeys per os

¹ Robertson and Ashby (1928), *Brit. Med. J.* i, 302. Morgan (1929), *J. Hygiene*, 29, 51.





may cause the symptoms acutely, just as large meals of rye bread have occasionally been reported to do in man.

Salts of phytic acid and decomposition products from it, isolated from all these grains and given to monkeys by the stomach or hypodermically, occasion symptoms exactly similar to those caused by feeding the grains.

The occurrence of poisoning when these grains are consumed as food is partly a question of the quantity consumed and partly a question of the ability of the consumer to break down in the bowel the poisonous phytates and so render them innocuous. If they are not fully broken down they are absorbed and act as poisons to the nervous system.

The pathological lesions in the nervous system of monkeys are the same as those which are described as occurring in convulsive ergotism in man.

Convulsive ergotism is not a "deficiency" disease, nor is it an ergot disease, but is caused by poisons normally present in rye and other grains.

EXPLANATION OF PLATE IV

- Fig. 1. Lad, 15, contractures of hands, feet and diaphragm, spasmodic seizures, sometimes double vision and other nervous symptoms. Recovered on change of food. (Heusinger.)
- Fig. 2. Contractures of hands and feet. In one of the hands only the first phalanges are flexed, the others being fully extended. (Heusinger.) Compare with monkeys (Figs. 9-13).
- Fig. 3. Woman, 40, spasm of hands and feet and muscles of face and body, flexed joints, spasmodic attacks, each lasting a few days. Recovered on change of food. (Heusinger.)
- Fig. 4. Rye: feeding, 94 days. Compare with Fig. 6.
- Fig. 5. Rye: feeding, partial recovery (same as Fig. 4).
- Fig. 6. Lad, 16, contractures of joints, paresis, spasm of face muscles and spasmodic seizures, dullness of intellect. Death after 3 years from exhaustion. (Thieme.)
- Fig. 7. Rye: phytate hypodermically.
- Fig. 8. Wheat: phytate hypodermically.
- Fig. 9. Rice: sodium phosphate hypodermically.
- Fig. 10. *Lathyrus* peas: feeding.
- Fig. 11. Lentils: phytate hypodermically.
- Fig. 12. Sodium phosphate (B.P.) hypodermically.
- Fig. 13. Sodium phosphate (B.P.) hypodermically.

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