REPORT ON AN OUTBREAK OF ALLEGED ERGOT POISONING BY RYE BREAD IN MANCHESTER.

By M. T. MORGAN, M.C., M.D.

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Ashby and Robertson have recently given an account of an outbreak of illness in Manchester which had come under their notice and which they attributed to the consumption of rye bread made from rye meal contaminated with ergot.

On one or two occasions during the past few years isolated instances of illness which were suspected to have been due to the consumption of ergotised rye have been reported to the Ministry of Health, but on enquiry it has not proved possible to arrive at definite or certain conclusions as to their causation.

In view, however, of the circumstances of the outbreak mentioned above I was instructed by the Ministry of Health to visit Manchester and investigate the matter with the object, if possible, of bringing to light further facts with regard to the nature of the illness and its causation, the likelihood of recurrence of similar outbreaks and the measures which should be taken to prevent such recurrences.

Nature of the illness.

On reference to Robertson's and Ashby's article it appears that the first symptoms observed in the patients (all of whom were Jews) were coldness and numbness in the extremities; tailors, button-makers, etc., noticed their fingers felt numb and they experienced difficulty in keeping up with their work. Sensation was also impaired; they could prick their fingers without feeling anything. Formication was a very typical symptom in all well-defined cases, and many of the patients stated that they experienced a sensation as if an insect was creeping over or under their skin. Itching was also a common symptom. Nervousness, depression, headaches and abdominal pains were frequent, and in the more severe cases ataxia with a staggering gait occurred. In most cases of long standing, the blood pressure was definitely raised, for example, a woman aged 44 had a systolic blood pressure of 174 mm.

During a visit to Manchester I saw both Dr Ashby and Dr Robertson who gave me some further particulars of the cases.

Dr Robertson's attention was first seriously attracted to the prevalence of the condition in October 1927, although previously to that cases had come under his notice. He has had some 200 cases in all, most of whom were adults (male and female) with some children. All his patients were Jews and consumers of rye bread: no case was observed in a person who did not consume rye bread. Unfortunately detailed clinical records of the cases were not available, so that

precise discussion of them was somewhat difficult. It is noteworthy that in cases which showed a rise of blood pressure, discontinuance of the consumption of rye bread was followed by a fall of blood pressure, for instance, a patient with a blood pressure of 169 mm. showed a pressure of 140 mm. 14 days after ceasing to consume rye bread.

I was able to see two of the patients and obtained the following information from them.

Patient A, aged 48, was an habitual eater of rye bread, consuming about half a pound a day. About Christmas 1925 he first complained of coldness of the hands and feet. He stated that shortly afterwards his left thumb began to "gather" and within two months the same thing happened to his left great toe and right fourth toe. His left index and second finger also turned black. He was admitted to Salford Royal Infirmary where his toes healed but a portion of the terminal phalanx of the second finger had to be amputated. In the early summer of 1927 his right middle finger went black. In addition to the above trouble he complained of severe burning pains in the hands and toes, muscular weakness, headaches, constipation and general malaise. He was a somewhat heavy smoker (20 or more cigarettes per day which he has now reduced to 10 or 12). He did not eat rye bread whilst in hospital but resumed the practice when he was discharged. On Dr Robertson's advice he ceased eating rye bread at the beginning of this year. When I saw this patient his complexion was sallow, his muscles were flabby and there was a general lack of tone. Both hands were bluish, cold to the touch, and the right hand was much swollen. The left hand showed evidence of severe circulatory disturbance; the nails were brittle and yellow, and there was considerable proliferation of the horny substance. The terminal pad of the middle finger together with the nail were absent. On the right hand the terminal phalanx of the middle finger was black and gangrenous. The gangrenous portion showed a fairly well-marked line of demarcation and was only slightly malodorous.

The patient stated that he had much improved in general health since he ceased to eat rye bread, and he thought that the condition of his right hand had also improved and the pain therein was now slight.

Patient B, aged 43, was a tailor. His indisposition started two years ago with coldness of the feet, weakness of the knees and pain. He has also suffered from headaches. From time to time he experienced an intolerable itching of the skin as if an insect was crawling up and down his back. He has removed his clothing as often as nine times a day in the belief that he was harbouring a flea or other insect parasite. He was first seen by Dr Robertson on January 31st, 1928, who instructed him to cease eating rye bread, he did so and rapidly improved, being quite well again some two months later.

Dr Robertson also gave me some particulars relating to another patient who had suffered during 1927 from coldness in the limbs, blanching of the fingers and severe formication. His blood pressure at the end of December 1927 was 179 mm. At this time he ceased to eat rye bread, and at the beginning of

February 1928 his blood pressure had fallen to 163 mm. without any further treatment.

As already stated Dr Robertson saw about 200 cases, all of which, with the exception of Patient *A* who developed gangrene, showed similar signs and symptoms to Patient *B*. All have recovered after ceasing to eat rye bread. In one of the patients convalescence was more prolonged than in the others, and on inquiry Dr Robertson discovered that this patient had continued to eat rye bread contrary to his orders.

The above is a summary of the whole of the clinical evidence available. It is obviously incomplete and unfortunately it is now impossible to fill the many gaps. Nevertheless such evidence as there is indicates clearly the existence of an outbreak of definite illness amongst a particular class of the community; a class distinct from other classes and characterised by the unusual custom, in this country, of eating rye bread. The outbreak of illness which has affected this class conforms in many respects to the train of events which follow the consumption of ergot in appreciably toxic amounts.

It remained therefore to ascertain whether the rye used for making the bread consumed by these patients contained ergot, and if so whether the amount of ergot present was sufficient to account for the conditions observed in the sufferers.

SOURCE OF THE RYE USED FOR BREAD MAKING.

A considerable quantity of rye is grown in England and Wales: no less than 50,062 acres were sown in 1925 but of this only about 30,000 acres were allowed to ripen, the remainder being ploughed in as green manure.

Practically the whole of the rye used for bread making in Manchester is grown in South Yorkshire. One firm of rye millers in Manchester appears to have, substantially, the monopoly of supplying rye meal to the Jewish bakers in that city. The milling process is extremely simple; the rye is merely ground into meal in a stone-mill.

As a rule the miller does not screen the rye grain nor submit it to any process before it is ground into meal. The Manchester miller above mentioned asserts that he invariably screens the rye, but there is some doubt as to whether this was the general practice previous to the outbreak of illness. A miller in Liverpool informed me that he never screens or fans his rye before milling because the good quality of the grain which he uses makes such preliminary treatment unnecessary.

It would appear that in general rye is not cleaned or screened before being ground into meal.

The rye meal is made into bread by mixing one part of meal and four parts of wheaten flour with salt and yeast and adding sufficient water to produce a stiff dough. The dough is allowed to stand for 12 or more hours and is then baked into 2 lb., 4 lb., and 8 lb. loaves, and is sold at about 1*d*. per pound more than ordinary wheaten bread.

There is another variety of bread which is made in the same way from rye flour instead of meal, but the amount produced of this variety is small.

The firm of Manchester millers make only rye meal and not rye flour; since the outbreak of illness they ceased milling rye meal and met the demands of their trade by purchasing Canadian milled rye flour which is guaranteed to be free from ergot.

Evidence of the presence of ergot in the rye milled in Manchester.

The Medical Officer of Health for Manchester obtained for me samples of rye grain, rye meal, and rye flour from the Manchester firm of millers already referred to and these samples were taken by me to the Royal Gardens, Kew, where I conferred with Mr Cotton the Keeper of the Herbarium. Mr Cotton agreed that there was a fair quantity of ergot sclerotia in the sample of rye grain and that ergot also appeared to be present in the sample of rye meal. The Public Analyst for the City of Manchester also examined samples of rye grain, rye meal, rye flour and wheaten flour with which the rye meal is mixed before making into bread. He informed me that from 340 grm. of rye grain he was able by hand picking to isolate 3·3 grm. of ergot, which represents approximately, 0·9 per cent. of ergot in the sample of rye grain. It was not of course possible to isolate ergot from rye meal by this simple method of hand picking, but by making an alcoholic extract he was able to estimate the amount of ergot present by the depth of colour of the extract. In this way he came to the conclusion that the rye meal contained about 1·5 per cent. of ergot.

Toxicity of samples of rye.

At an early stage of the investigation undertaken by Dr Robertson and Dr Ashby, the latter asked Dr Macdonald, Assistant to the Professor of Physiology, University of Manchester, to test the toxicity of some samples of rye meal and rye bread. Dr Macdonald informed me that he was unable to detect the presence of ergot alkaloids in the samples. He was able however to detect by biological methods the presence of histamine in both samples.

The public analyst prepared an extract of ergot sclerotia by soaking them in a mixture consisting of 75 per cent. of absolute alcohol and 25 per cent. of 5 per cent. aqueous solution of tartaric acid for 12 hours. The extract was filtered, evaporated to dryness, neutralised with ammonia and redissolved in water. This aqueous solution was tested biologically by Dr Macdonald with negative results so far as toxicity was concerned.

It seems probable that these negative results may have been due to one or both of two causes. In the first place the toxic alkaloids are soluble in acid alcohol but are practically insoluble as free bases in water at neutral reaction. It may be that for this reason the extract prepared by the public analyst was devoid of activity. In the second place it has been proved that ergot rapidly loses its toxicity when kept dry (Möller).

Grünfeld has shown that 4 grm. of newly gathered ergot is sufficient to cause marked illness in hens, whereas ergot five months old has hardly any toxic action. In July and August the minimal toxic dose of ergot is 1 grm.; in September and October, 2 grm.; in November and December, 4 grm.; in January and February, 8 grm.; in March and April, 12 grm., whilst in May and June the ergot has become completely inactive.

It is possible, therefore, that the ergot examined by Dr Macdonald which was at least six months old may have lost most of its toxicity.

It was decided to put the matter to a further test and this was done through the kindness of Dr H. H. Dale, C.B.E., F.R.S., by Mr J. H. Gaddum, B.A., M.R.C.S., at the National Institute for Medical Research. A sample of ergot obtained from the rye used by the Manchester miller and more than six months old was submitted to Dr Dale; extracts were prepared from this with acid alcohol and brought into suitable form for physiological trial. By testing its power of annulling the stimulant effect of adrenaline on the plain muscle of the rabbit's uterus, the extract was estimated to contain ergotoxine in a proportion representing 0·01 per cent. in the original ergot. Another extract was then tested by observing its effect in reversing the action of adrenaline on the blood pressure of the "spinal cat." From this experiment it was estimated that a quantity of extract corresponding to 5 grm. of the original ergot contained $\pm$ 0·5 mgrm. of ergotoxine, which is equivalent to a proportion of about 0·01 per cent. in the original ergot. Both experiments therefore gave concordant results and indicated that the ergot contained about 0·01 per cent. of ergotoxine.

Dr Dale informed me that he has, at different times, tested a large number of samples of ergot and has found that a content of 0·1 per cent. of specifically active alkaloid (ergotoxine, ergotamine) was not uncommon, and that proportions higher than this were rare. This investigation of ergot from the Manchester rye would therefore indicate that the ergot, after many months keeping under conditions unfavourable to the preservation of its toxic qualities, contained only about one-tenth of the ergotoxine which would be found in fresh ergot of high value from the pharmaceutical point of view and of corresponding high toxicity for man when taken in food. These results are, therefore, not inconsistent with the possibility that the outbreak of illness in Manchester may have been due to ergot poisoning[1].

THE TOXIC DOSE OF ERGOT.

Robertson and Ashby estimated that the dose of ergot in a half-pound loaf of rye bread may be as high as 22 grains. This estimate is open to criticism, and it is probable that much less ergot than this was present in the bread.

The Public Analyst for Manchester concludes that the rye grain contained 0·9 per cent., which may be assumed to be a fairly reliable estimate. In the

[1] The methods employed by Mr Gaddum in this investigation are given in the appendix at the end of this report.

making of rye bread it is usual to add wheaten flour in the proportion of four parts of wheaten flour to one part of rye meal, which may be taken as being equivalent to the original rye, so that on the basis of an original 0·9 per cent. of ergot in the rye this proportion becomes reduced to 0·18 per cent. in the mixed flour. The water required to make the loaf reduces this percentage to about 0·13 per cent. of ergot in the finished loaf, which is equivalent to about 4·5 grains of ergot in a half-pound loaf. Ashby and Robertson estimated that a half-pound loaf contained 22·85 grains of ergot, but they omitted to take into account the fact that the flour mixture used in making rye bread contains only 20 per cent. of rye meal.

It remains, therefore, to consider whether the amount of ergot estimated above, when consumed daily in rye bread, is sufficient to produce ergot poisoning and the signs and symptoms which characterised the outbreak of illness described above.

In the following table is given the estimated amount of ergot found to produce symptoms of ergotism in ten outbreaks of this illness which have been recorded.

Start of toxic action following consumption of rye bread	Dosage	Remarks	Reference
Two months	0·2 grm. of ergot daily for one month	Gangrene	Debove, *Soc. Méd. des Hôp.* 27 Feb. 1880
Few days	1 grm. of ergot daily	Intestinal symptoms	Uberti, in Kobert, p. 110, *v. infra*
	0·1 % in meal	Not hazardous	Kobert, *Lehrbuch der Intox.* II, 1906, 613
	1·0 % in meal	Kursh and Tomsk epidemic of 1903	*Ibid.*
	1·0 % in rye grain	Poltava epidemic, 1881	Griasnoff, *Lond. Med. Record*, XI, 1883, 78
Four days	3·5 % in rye grain	Gangrene	Frangue, *Med. Jour. für Nassau*, 1856
	7·0 % in rye	Novgorod epidemic, 1879	Swiatloivsky, *Lond. Med. Record*, VIII, 1880, 412
	1·0 % in rye	Cause of epidemics	Lehmann, *Arch. für Hyg.* XIX, 1893, 71
Fifteen days	1·5 % in bread	Gangrene	Bougean, *Lancet*, 1845, i, 701
Days—months	2·0 % in rye	Frankenberg epidemic, 1879	Meuche, *Deut. Arch. für klin. Med.* XXXIII, 1883, 246

It will be observed that the quantities are in some cases not in excess of those found in Manchester, but the data are not sufficiently detailed to enable the actual amount of ergotised grain consumed to be ascertained in all cases or to say whether the rye was diluted with other flour before being made into bread.

It must also be borne in mind that just after harvesting ergot is at its maximum toxicity and this toxicity rapidly diminishes with age, so that quite a small dose of fresh ergot might produce symptoms whilst the same dose, say six months later, would almost certainly be inactive. It will be noted that the

outbreaks of illness in Manchester synchronised with the consumption of freshly harvested grain when its toxicity would be greatest and the dose required to produce illness would be correspondingly small.

TOXICOLOGY.

Ergot posioning manifests itself in two distinct types of illness which are not usually associated even in severe outbreaks. The first type is known as "gangrenous" and is characterised by muscular weakness, particularly in the limbs, spasmodic muscular contractions, tingling and formication. Later there is intense pain in the extremities, and it is this symptom which has given to the disease the name of "St Anthony's fire."[1] The extremities become numb and lose sensation; eventually local circulation ceases and gangrene, usually dry with a well-marked demarcation line, supervenes. The second type is termed "spasmodic" or "convulsive" and appears to be more acute than the gangrenous type. It is characterised by headache, a sense of heaviness in the head, giddiness, clonic and tonic cramps, muscular weakness, pains in the abdomen, cutaneous sensations, constipation and general lethargy. The two types are not clearly defined and it is not known whether they have a similar origin and represent stages or degrees of intoxication or are distinct entities due to different intoxicants.

The disease in some of its characters closely resembled Raynaud's disease. Ehlers, in his publication *L'Ergotisme*, states that more than one of Raynaud's own cases were certainly due to ergot. Two or three of the cases cited by Raynaud were in the habit of eating rye bread, and a third shortly before the appearance of the disease had consumed 60 centigrams of ergot.

There is another disease, endarteritis obliterans, characterised by progressive gangrene, which occurs particularly amongst Jews, but the reason for this incidence is not known. Even amongst Jews the disease is rare but its occurrence should be borne in mind in considering the differential diagnosis of ergotism.

THE BIOLOGY OF ERGOT.

Ergot or *Claviceps purpurea* is a fungus belonging to the subclass of Ascomycetes.

It attacks all cereals and some grasses, but is of particular importance in connection with rye because it decreases the quality and yield of the grain and renders it injurious when consumed.

The infection varies with the season and locality and is favoured by moisture. Grasses, and more especially rye, in some seasons and in some fields are so heavily infected that nearly every head is involved.

The loss of rye in Germany due to ergot infection was estimated at 1·6 per cent. of the average yield of the crop of 1894 which was a wet season; the average annual loss is about 0·3 per cent. In Connecticut in 1917 the proportion of ergot in the rye crop ranged from 1 to 5 per cent. (Atanasoff).

[1] For discussion of the historical outbreaks see Creighton and Haeser.

The following is a brief outline of the life-history of the fungus.

The fungus attacks the flowers of the rye plant; its mycelium develops in the ovary of the flower before fertilisation; on the surface of the plant it forms a continuous layer of hyphae from which immense numbers of gonidia are formed by abstriction. These gonidia are embedded in a mucilaginous substance popularly known as "honey dew." This substance is eaten by insects which thus convey the gonidia to other flowers where they develop and reproduce the mycelial form of the fungus. This stage is known as the Sphacelia-form. When the rye is ripening the grain is replaced by a dense mass of mycelium which now assumes a fusiform shape of from 1 to 3 cm. in length and 2 to 3 mm. thick; this mass is hard and dark purple on the surface and is known as the *sclerotium*. This is the form in which ergot occurs in the harvested grain. The sclerotium falls to the ground and remains dormant during the winter; it germinates in the following spring giving rise to a number of filaments termed stromata, bearing at their ends knobs in which are formed ascocarps containing ascospores. These are conveyed by wind to rye flowers where they develop into the sphacelia stage of the fungus.

Prevention of infection of rye.

The agricultural methods available to cope with ergot infection of rye include the use of clean seed, deep ploughing, removal of all grasses around fences, corners, etc., which are likely to convey infection, and the proper rotation of crops. Seed may be cleaned by immersion in a 20–30 per cent. brine solution on which the ergot sclerotia float whilst the rye grains sink. After separation the rye grain is washed and dried or promptly sown (Aderhold, Johnson and Vaughan). This method is probably only economically practicable for farmers who are dealing with comparatively small crops and where sunshine is adequate to ensure satisfactory drying. Unfortunately it is during wet seasons that the need for treatment is greatest.

Elimination of ergot sclerotia from rye grain.

For milling purposes it is practicable to clean the grain sufficiently thoroughly to reduce the amount of ergot to a very small fraction of that originally present in the grain. This can be effected by the introduction into the mill of suitable screening and purifying machinery, and in all cases where rye is being milled for human consumption precautions should be taken by the installation of machinery of this kind to ensure that the rye is freed, as far as possible, from ergot before it is ground into meal or flour.

Summary and conclusions.

It is impossible to say with certainty that the outbreak of illness in Manchester was due to ergot, but the evidence available strongly supports the view that ergot was the cause. The train of symptoms and pathological changes, though not necessarily peculiar to ergot poisoning, are strongly suggestive of

this origin and this conclusion is reinforced by the fact that all the sufferers consumed rye bread made from rye which contained a significant proportion of ergot. The ergot isolated from this rye, after being kept for many months under conditions which were unfavourable for the preservation of its toxic properties, was found at the expiration of this period to contain some toxin and the amount found was consistent with the ergot having been highly active when fresh and therefore quite capable of causing the outbreak of illness which developed at a period shortly after the harvest when the toxic properties of ergot are greatest.

As a result of my inquiry the following facts of interest have emerged:

1. A considerable quantity of rye is grown in England and Wales and more than half of it is allowed to ripen. The districts in which most of it is grown are Yorkshire, Lancashire, Cheshire, Monmouth and Essex. Rye in this country is seldom, if ever, free from ergot and the degree of infection varies from year to year in each district according to the season, weather, seed and other conditions.

2. Rye bread is eaten to a large extent (in Liverpool and Manchester at any rate) by Jews, and rye for these towns is obtained almost exclusively from Lancashire and Yorkshire.

3. The rye grain is usually not treated in any way before milling, that is to say, no attempt is made to remove any ergot which may be present; it is ground into meal in the condition in which it comes from the threshing machine.

4. On the assumption that some of the rye consumed in Manchester contained 1 per cent. of ergot, a half-pound loaf of bread of which this rye is a constituent would contain 4 to 5 grains of ergot. Although this is a relatively small dose, it is possible that if consumed over lengthy periods, especially if the ergot were in an actively toxic state, pathological conditions might ensue.

5. The samples of rye actually examined by the Public Analyst were not found to be toxic. This may possibly be accounted for on the ground that the method employed for extracting the toxin was not satisfactory, or to the fact that the ergot examined was at least six months old, by which time it would normally have lost most if not all of its toxicity.

6. Damp weather favours the growth of ergot and the climatic conditions of the summer of 1927 were just those most suited to the development of ergot. It is probable therefore that the rye crop was heavily infected and the ergot rich in toxins.

The clinical characters of the outbreak, so far as they have been recorded, strongly support the view that ergot was responsible; all the necessary factors and conditions for the production of illness were present and it is not surprising that it occurred.

In view of the potential danger the obvious preventive measures to which I have already referred should be put into operation. Rye crops should be grown with such precautions as to reduce the risk of ergot infection to a

minimum. Millers of rye for human consumption should install the necessary machinery to remove, so far as possible, any small proportion of ergot which the rye may contain.

APPENDIX

REPORT ON BIOLOGICAL EXAMINATION OF ERGOT SUBMITTED TO DR DALE BY DR MORGAN.

By J. H. GADDUM, B.A., M.R.C.S.

Extracts have been made by two methods:

1. That described for Extractum Ergotae Liquidum in the *United States Pharmacopœia* X.

2. 10 grm. of powdered ergot were extracted for 3 min. with 100 c.c. of a boiling solution of 60 per cent. alcohol to which 1 c.c. of 10 per cent. acetic acid had been added. The extract was poured off and the extraction repeated with another 100 c.c. of the same solution. The combined extracts were

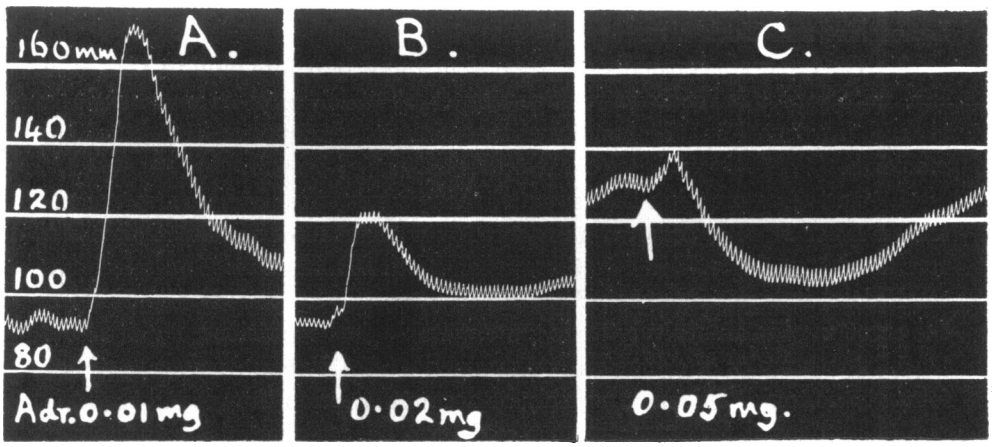

Fig. 1. Arterial pressure of "spinal cat." Effects of three increasing intravenous doses of adrenaline: *A*, before ergot; *B*, after 5 c.c. and *C*, after a total of 10 c.c. of Extract 2. In *B* the pressor action is much diminished and in *C* it is replaced by a depressor action, except for a small initial phase.

filtered and the filtrate was evaporated down to 20 c.c. and made definitely alkaline to litmus with caustic soda. (At a definitely alkaline reaction the active alkaloids become soluble in water as sodium salts.)

The first extract was tested by the method of Broom and Clark on a uterus isolated from a rabbit. The presence of the extract in the bath was found to diminish the sensitivity of the uterus to adrenaline. This effect is produced by ergotoxine and ergotamine, the specific alkaloids of ergot. A quantitative comparison with a solution of the pure alkaloid (ergotoxine ethane sulphonate obtained from Burroughs Wellcome and Co.), using dif-

ferent pieces of the same uterus, showed that the activity of the original ergot corresponded to approximately 0·01 per cent. of ergotoxine.

Though the above test has the advantage of giving quantitative results it has been found by Langecker not to be very specific, in that the same effect is also given by hydrastis preparations, and also by quinine, yohimbine, atropine, and papaverine in rather higher concentrations than are necessary with ergotamine. It was therefore desirable to confirm the above result by an independent method. For this purpose the second extract, prepared as above described and cleared by the centrifuge, was injected intravenously into a spinal cat weighing 2 kilos. It produced a profound fall of blood pressure and the injection could only be made slowly. It was found that 5 c.c. produced a definite diminution of the adrenaline response. Another 5 c.c. was then injected and a reversal of the adrenaline response was obtained. There still remained a trace of the pressor effect of adrenaline, occurring before the depressor effect, but this was completely abolished by the further injection of 0·5 mg. of ergotoxine ethane sulphonate. This dose would not have produced so complete an effect alone. It would have been expected to produce incomplete reversal such as was obtained with the extract. It is thus probable that the 10 c.c. of extract contained about 0·5 mg. of ergotoxine. This is the quantity which would be present if there was 0·01 per cent. of ergotoxine in the original grains of infected rye.

It is thought that these results prove that the rye grains contained the specific alkaloids of ergot, which are responsible for the production of ergotism, but only in about one-tenth, or less, of the proportion which is usually present in fresh ergot. The ergot in question was not fresh, and had probably at one time contained more ergotoxine than we were able to find in it.

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