division, this being justified by the issues at stake. The whole operation was done through one cannula. A direct vision telescope was used, and alongside this were passed the diathermy electrode and the electro-cautery. Both were used. As general anaesthesia was being employed I did not infiltrate the insertion of the adhesion with novocain, with the object of saving time. This, I believe, was a mistake, as every time the diathermy cutting wire was used the spasm phenomenon in the muscles of the chest wall occurred, which greatly increased the difficulty of the operation. When the resistance of the tissues became great, or where they were thin, the electro-cautery was used. Thus, just when the adhesion became most difficult to deal with by diathermy, it became most easy with the electro-cautery. All adhesions were divided, and the child returned to bed in good condition.

Respirations had been so deep that much air was expelled from the pleural cavity, and the lung almost re-expanded, but subsequent refills produced an excellent collapse. The child so dreaded the refills that it was decided to substitute an oleothorax for the pneumothorax. This was done gradually. A year later the child was in good health, plump, bonny, and free from symptoms, and had gained over a stone in weight. At the time of writing she is still in good health, and I believe she will continue to remain so. Diagrams of the *x*-ray pictures show the appearances at different stages.

THE ACTION OF ERGOT PREPARATIONS ON THE PUERPERAL UTERUS

A CLINICAL INVESTIGATION WITH SPECIAL REFERENCE TO AN ACTIVE CONSTITUENT OF ERGOT AS YET UNIDENTIFIED*

BY

CHASSAR MOIR, M.D., F.R.C.S.ED.

REGISTRAR TO THE OBSTETRIC UNIT, UNIVERSITY COLLEGE HOSPITAL, LONDON

With a Note by

SIR H. H. DALE, M.D., F.R.S.

DIRECTOR, NATIONAL INSTITUTE FOR MEDICAL RESEARCH, HAMPSTEAD

In a previous paper[1] a method was described by which the contractions of the puerperal uterus could be recorded in graphic form. The apparatus is a modification of that used by Bourne and Burn[2] to study the effect of oxytocic drugs administered during labour; it consists of a sterilized rubber bag, passed into the uterus with full antiseptic precautions, and connected by water-filled tubing to a mercury manometer. A light float on the manometer carries an ink-point, which records variations of intrauterine pressure on a slowly revolving drum. This apparatus registers the spontaneous contractions of the puerperal uterus, and shows very clearly the variations of activity brought about by suckling or by the administration of drugs.

The previous work† dealt with the action of the ergot alkaloids, ergotoxine and ergotamine, and the conclusions reached were these:

1. That both ergotoxine and ergotamine were very active in stimulating contractions in the puerperal uterus.

2. That while the precise action varied in different cases, every effect produced by the one drug could be matched by a similar effect from the other.

3. That the drugs were comparatively slow in taking effect: by intravenous injection four to ten minutes; by intramuscular injection fifteen to forty-five minutes; and by mouth thirty-five minutes to one hour or longer. When the drugs were given by the mouth the action was erratic, and in most cases not nearly so well marked as when given by injection.

4. That the rise in the base line of the tracings (which may be taken as a measure of the tonicity of the uterus) was of moderate degree, and was seen only during the time that the drug was exerting its maximum effect: it was produced by doses of 0.5 mg. or more given by injection.

AIM OF PRESENT INVESTIGATION

Having found that the method used to study the clinical action of the ergot alkaloids was capable of yielding very clear results, I decided to extend the scope of the inquiry, and to investigate the effect of other constituents of ergot, and of the various pharmaceutical preparations of the crude drug.

In 1913 Carr and Dale,[3] assuming, as then seemed justifiable, that the activity of ergot was due to ergotoxine, pointed out that worse methods of preparing the extractum ergotae and the extractum ergotae liquidum could scarcely be devised than those recommended by the *British Pharmacopoeia* of 1898 (which was then current). In the case of the first preparation the ergotoxine was precipitated during manufacture; in the case of the second the ergotoxine was not soluble in the watery solution used for extraction. Since that date it has frequently been said that the extracts in question are inert and useless preparations, although the statement has sometimes been qualified by a somewhat vague suggestion that the putrefactive bases (particularly histamine), which are also present in the extract, might possibly stimulate the uterus to contract. An unsatisfactory state of affairs was thus created, for it was obviously absurd to start with an expensive drug, to eliminate the active alkaloid, and then to allow non-specific putrefactive amines to form when these same substances might be much more easily and accurately produced in other ways. Such was the position when the present Pharmacopoeial Committee was formed, and it was therefore natural that one of its first acts was to constitute a special subcommittee to advise on a new and better method of preparing the ergot extracts.

Ergot has been of the nature of a treasure chest to pharmacologists, and the immense amount of work which has been done on this drug is evidenced by the number and variety of the chemical bodies which have been isolated. Some of these substances, such as histamine, are known to owe their presence in great measure to bacterial or enzyme decomposition during manufacture, and this leads to much uncertainty in the composition of the finished product, since but little control can be held over these processes. Of the various bodies isolated only two (other than the alkaloids) are believed to have an appreciable effect on the uterus. These are histamine and tyramine.

HISTAMINE AND TYRAMINE

Histamine (ergamine) is stated by Burn[2] to be present in the British pharmacopoeial liquid extract of ergot to the extent of 0.01 per cent. Two drachms of the extract (which is the dose commonly used for single administration) thus contains less than one milligram. Bourne and Burn have studied the effect of histamine given subcutaneously during labour. They found that doses of less than 2 mg. of the base were ineffective. A dose of 2 mg. produced vigorous contractions for fifty minutes, followed by a period of inertia. No details were given of the effect when administered by mouth. In the puerperal patients I have given histamine acid phosphate by the mouth in doses equivalent to 2 mg., 6 mg., and 8 mg. of the base. In no case were any contractions seen which could be attributed to the drug. The effect when given by intramuscular injection was different.; a patient receiving a dose equivalent to 1 mg. of the base showed in less than one minute a very marked flush of the skin, which persisted for about

* From the Obstetric Unit, University College Hospital.

† The work on ergotoxine and ergotamine was carried out at the request of the Therapeutic Trials Committee of the Medical Research Council.

an hour and caused much discomfort. The pulse rate was considerably increased. The effect on the uterus was almost immediate, but was slight; after the lapse of one minute the contractions were augmented but were very irregular, and the rise of base line was negligible.

Barger[4] states: "The amount of tyramine in liquid extracts of ergot is much too small to be of practical importance." Bourne and Burn found that tyramine had only a very fleeting effect when injected in a dose of 10 mg. intravenously. This method of administration was presumably chosen because tyramine is known to be very rapidly destroyed by the liver. Two puerperal patients were given tyramine by the mouth in doses of 60 mg. and 80 mg. respectively. In the first case no change was noted in the uterine action. In the second case the uterus remained inert for ten minutes, then showed some irregular contractions over a period of half an hour. The contractions resembled those of the spontaneous variety, and were quite unlike those produced by ergot preparations. After a further half-hour the uterus again became inert. There is thus good reason to believe that tyramine, like histamine, is without importance in the action of ergot preparations intended for oral administration.

It is possible that, although these drugs when given separately produce (or do not produce) certain effects, they might, when given together, modify each other's action. To eliminate this possibility a proprietary preparation containing histamine, tyramine, and ergotoxine ethanesulphonate (0.033 per cent.) was given to a patient in a dose of 2 drachms by the mouth. This is roughly equivalent to 2.5 mg. of the alkaloid, and is twice the maximum recommended dose of the preparation. No effect was seen for forty minutes, after which fairly strong contractions began to appear characteristic of the ergotoxine type.

These experiments show that of the active constituents hitherto identified in ergot only the alkaloids ergotoxine and ergotamine are of clinical importance.

LIQUID AND SOLID EXTRACTS OF ERGOT

To contrast the effect of the active with the inactive ergot preparations, a watery extract of ergot was specially prepared in strict accordance with the regulations of the 1914 *British Pharmacopoeia*. Judged by all previous work this preparation ought to have been inert, for analysis showed that it contained only a trace of alkaloid; the extract was used in three cases in doses of 4 drachms,

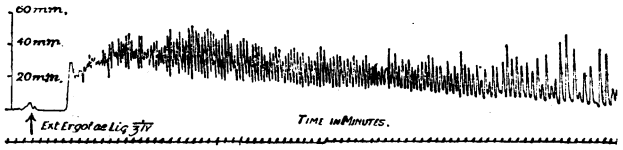

FIG. 1.—Extractum ergotae liquidum (*B.P.* 1914) 4 drachms by mouth.

3 drachms, and 2 drachms respectively. It was with the greatest surprise I found that, far from being inert, this preparation surpassed by great measure the activity of any drug which I had previously used in the same manner. An equally surprising fact was that the effect appeared in a remarkably short time. In one case only four minutes elapsed between the swallowing of the extract and the onset of powerful uterine contractions (Fig. 1). In character the contractions were notably different from those due to ergotoxine or ergotamine. They were frequent (two or three to the minute), regular, of fairly great excursion, and there was a rise in the base line to an extent much greater than observed with any other drug.

Several other samples of *B.P.* Ext. ergotae liq. were then used in doses of 2 drachms. The following are details of these preparations:

1. Sample freshly made from a second supply of ergot.

2. Sample purchased in the open market; known to have been in stock in chemist's shop for more than four months.

3. Sample purchased in open market; known to have been in partly used stock bottle with cork stopper for more than fifteen months.

4. Sample purchased in open market; known to have been in stock for more than six months.

5. Sample kindly supplied by Messrs. Allen and Hanburys; prepared six months before.

6. Sample supplied by Messrs. Allen and Hanburys, prepared seven months before.

All these samples showed an energetic action of the type just described.

In view of the pending change in the pharmacopoeial regulations, it was of interest and importance to test the liquid extract which will shortly become official.[5] Such an extract was specially prepared, and was tested on two patients in doses of 3 drachms and 2 drachms respectively. The results showed that this extract has an activity of the type described to an extent as great as, and probably greater than, that of the 1914 liquid extract.

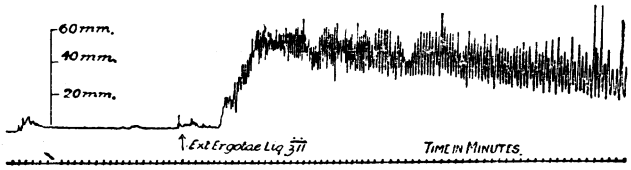

FIG. 2.—Extractum ergotae liquidum (new *Pharmacopoeia*) 2 drachms by mouth.

Bourne and Burn have made a clinical test of the liquid extracts of the *United States Pharmacopoeia* and of the *British Pharmacopoeia*, using as a control a solution of yeast extract (marmite). Three series of normal puerperal patients were observed by a ward sister and each patient was given a drachm dose three times a day from one of three bottles containing the extracts in question. The bottles were labelled "1," "2," and "3," and the identity of the contents was purposely

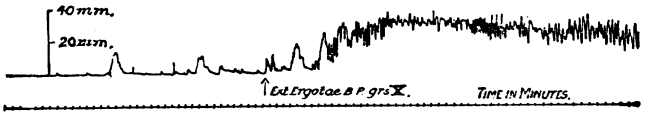

FIG. 3.—Extractum ergotae (*B.P.* 1914) 10 grains by mouth.

withheld from the observer. No difference could be detected in the character of the lochia or the rate of involution of the uterus in the three different groups of patients. One of the possible inferences which can be drawn from this experiment is that marmite is as effective as ergot extracts in its action on the uterus. In the present investigation a puerperal patient was therefore given a teaspoonful of marmite solution. The uterus remained quite inert after the administration.

Solid preparations of ergot were next tested. The extractum ergotae of the 1914 *British Pharmacopoeia* was given to a patient in a dose of 10 grains dissolved in water. Strong contractions similar to those previously described appeared in seven minutes, and there was a marked rise in the base line (Fig. 3). The preparation

was 2 years and 11 months old. A defatted ergot powder (erbolin), given in a dose of 10 grains, produced an almost identical tracing, the effect appearing fourteen minutes after administration.

UNIFORMITY OF ACTION AND KEEPING QUALITIES OF ERGOT EXTRACTS

Two questions of practical importance arise out of this work. Do all extracts of ergot show the same characteristic activity, and does storage cause any deterioration?

The fact that nine preparations from different sources all showed decided activity gives a partial answer to the first question. There was, however, some reason to believe that the different liquid extracts varied in their activity, and this suspicion has been strengthened by a later experience with a new supply of ergot. This sample was used on four occasions: in form of 20 grains of the crude powder; as a decoction from 20 grains of the powder; as a defatted powder in dose of 10 grains; and as a liquid extract in dose of 2 drachms. There was probably some activity in this ergot, but the activity was of very small order compared with that of the samples previously used. The second question on the keeping properties cannot be definitely answered without much further experiment. As far as the present work goes it can be said that the keeping properties of the prepared extract appear to be good: the most active of the liquid extracts used was one which was at least six months old; another sample, more than 15 months old, showed a good activity, while a solid extract 2 years and 11 months old was also found to be very active.

As already pointed out, the uterine contractions caused by liquid and solid preparations of ergot were, with regard to time on onset, nature, and frequency, in most striking contrast to those produced by ergotoxine and ergotamine, and it can only be supposed that they were caused by an entirely different constituent of ergot. Now, since histamine and tyramine were found to be inactive when given by the mouth, either singly or in combination, it must be assumed that the oxytocic power of the liquid and solid extracts is due to a substance whose importance has hitherto been overlooked in the investigation of ergot.

It is of interest to read the early accounts of the use of ergot.

A letter appeared in the *Medical Repository* of New York of 1808, in which Dr. John Stearns[6] exhorts a friend to try a sample of *pulvis parturiens*. ". . . Boil half a drachm of the powder in half a pint of water and give one-third every twenty minutes till the pain commences . . . in most cases you will be surprised with the suddenness of its operation; it is therefore necessary to be completely ready before you give the medicine. . . ." In 1813 the following was written by Dr. Oliver Prescott[7]: "The frequency and violence of the uterine efforts induced by ergot are not more extraordinary than its almost instantaneous operation. In twenty cases I carefully noticed the precise time it required to produce its customary effects. In two of them the increased strength of the pains and the continued action commenced in seven minutes from the time the decoction was taken; in one case it was eight minutes, in seven it was ten, in three, eleven, and in three others it was fifteen. In the four remaining cases there was no apparent operation until twenty minutes had expired." Elsewhere[8] I have found reference to a case in which "about five minutes" elapsed between the administering of 20 grains of powdered ergot and the onset of uterine activity. In more recent times (1911) Sharp,[9] reporting twenty cases in which he had used liquid extract, or infusion of ergot, stated that the effect came on after an average of ten minutes; in one case only four minutes were required for the drug to exert its characteristic action.

These extracts from early writings make it clear that the effect to which ergot owed its reputation was an immediate and powerful one, and due to a substance such as might produce the tracings shown in Figs. 1 and 2. Moreover, it is difficult to believe that ergot would ever have found a use in obstetrics had its administration been followed by a prolonged latent period, for contraction occurring after that interval would probably not have been attributed to the drug.

TABULATED RESULTS

In order to offer a comparison with the figures just quoted it may be of value to record in tabular form the actions of the various preparations given by the mouth in the present investigation.

Details of Time Required for Oral Preparations of Ergot to Take Effect

Drug	Dose	Time of Onset of Doubtful Response	Time of Onset of Definite Response	Remarks
		min.	min.	
Ergotoxine	1 mg.	120	—	No definite results in 4½ hours
Ditto	2 mg.	40	50	Contractions lasted for 1 hour only
Ditto	2 mg.	90	—	Contractions poor: for 1 hour only
Ditto	2.5 mg.	32	36	Early contractions probably spontaneous
Ditto with histamine and tyramine	2.5 mg.	34	40	Good contractions (ernutin 3ii)
Ergotamine	1.5 mg.	30	40	Contractions poor, for 1 hour only, but reappeared an hour later
Ditto	2 mg.	40	50	Contractions for 35 minutes only, but reappeared later
Ditto	3 mg.	35	110	Very inactive uterus
Ext. ergotae liq. (1914)	3iv	—	4	Immediate powerful contractions
Ditto	3iii	—	7	Immediate powerful contractions
Ditto	3ii	—	8	Immediate strong contractions
Ditto Sample 2	3ii	—	6	Immediate powerful contractions
Ditto Sample 3	3ii	—	11	Strong contractions
Ditto Sample 4	3ii	22	28	Fairly strong contractions
Ditto Sample 5	3ii	—	14	Strong contractions
Ditto Sample 6	3ii	—	9	Immediate powerful contractions
Ditto Sample 7	3ii	—	13	Very strong contractions
New B.P. Ext. ergot. liq.	3iii	—	11	Immediate strong contractions
Ditto	3ii	—	6	Immediate powerful contractions
Ext. ergotae B.P. 1914	gr. x in water	—	7	Immediate strong contractions
Defatted ergot (Erbolin)	gr. x	—	14	Immediate strong contractions

A study of the tracings from which the above figures were obtained clearly shows that the action of the ergot alkaloids when given by the mouth is slow and uncertain, yet for many years the specific effect of ergot has been attributed to them.

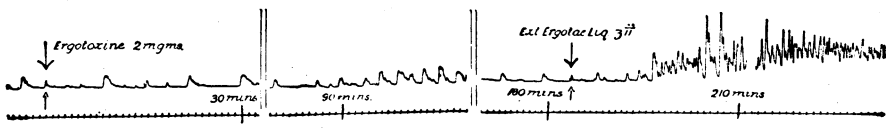

FIG. 4.—Comparison of the effect of ergotoxine 2 mg. by mouth and ext. ergot. liq. 2 drachms by mouth. The tracing was continuous, and only sections of it are shown.

Bourne and Burn state: "The specific alkaloid of ergot used in the form of ergotamine tartrate has been found to exert in the most striking way the action which has always been thought to characterize the drug." The usually held view is reflected in the following extract from the *Handbook* issued to the medical profession by a well-known manufacturing

firm: "The characteristic pharmacological therapeutic action of ergot is due to the alkaloid ergotoxine. The specific physiological effect and therapeutic efficiency of any preparation of ergot depends on the presence of this active principle. Many preparations of ergot are highly unsatisfactory and some are without any therapeutic action whatever because they contain no ergotoxine."

The experimental observations detailed in this paper stand in direct opposition to both these views, and it can be stated with reasonable certainty that the characteristic action of ergot known to the old obstetricians is due to a substance which has a prompt and energetic action, and which is not ergotoxine, ergotamine, tyramine, or histamine. From this it follows that the ergot alkaloids, hitherto supposed to be all-important, play in reality but a subsidiary part in the clinical action of the drug.

CONCLUSIONS

1. The liquid extract, and the solid extract of ergot, of the 1914 *British Pharmacopoeia*, both show great activity in stimulating contractions in the puerperal uterus.

2. Defatted ergot powder has a similar action.

3. The keeping properties of the extracts appear to be good.

4. Different samples of ergot vary in their activity.

5. The effect of the drug comes on with remarkable suddenness, and may appear within four minutes of oral administration of the liquid extract.

6. There is an increased tone of the uterus to an extent much greater than that seen with other oxytocic drugs.

7. In these and other respects the ergot extracts act in a very different manner from the purified alkaloids ergotoxine and ergotamine.

8. Histamine and tyramine, given in reasonable dosage by the mouth, have no effect on the puerperal uterus.

9. Histamine given by intramuscular injection has a slight effect on the uterus, but may produce undesirable symptoms.

10. There is reason to believe that the characteristic and traditional effect of ergot is due to a substance as yet unidentified.

It is a pleasure to express my thanks to Sir Henry Dale for encouragement and useful advice; to Mr. Davis, the Hospital pharmacist, for preparing and analysing the special extracts, and to Messrs. Allen and Hanburys for supplying the ergot preparations.

NOTE BY SIR H. H. DALE, M.D., F.R.S.

Dr. Chassar Moir has kindly kept me in touch with the progress of the observations which he now presents, and which appear to open another chapter, and probably one of great importance, in the already complicated story of ergot and its active principles. It seems to me likely that Dr. Moir will be able to make good his claim that, in the active substance now shown to be present in the ordinary liquid extracts of ergot and differing from any of those yet identified in its rapid action when given by the mouth, he has come, at last, on the track of the principle which led to the introduction of ergot into therapeutics.

Those acquainted with the present position, and its development during a quarter of a century, may be inclined to regard Dr. Moir's observations as a rebuke to the presumption of laboratory pharmacologists. They do, indeed, emphasize the danger of basing therapeutic conclusions on laboratory data without direct clinical evidence. It is only fair to state, however, that the present position has arisen, not in spite of such evidence as Dr. Moir now supplies, but for lack of it. The need has been recognized and urged by some of us throughout the period in question; but, without such direct experimental guidance from the clinic, we could only search for the principles in ergot producing certain well-defined effects in the laboratory, and hope for the proper clinical trial of the substances so identified. In this way the alkaloids ergotoxine and, later, ergotamine were found, and the bases tyramine and histamine. The only clinical evidence hitherto available appeared to strengthen the presumption in favour of the alkaloids as the essential therapeutic agents, as being the only known active substances peculiar to ergot. There was always the doubt, however, whether preparations such as the watery liquid extract might not contain some other active principle, overlooked or obscured in the laboratory tests, but acting with oral administration of the extract. I have, indeed, on more than one occasion endeavoured to get a proper experimental comparison made in the clinic between a watery and an alcoholic ergot extract when both were given by the mouth. More than one eminent gynaecologist was willing to carry out a test; but only by handing the extracts to a resident officer or ward sister, with an instruction to administer them to alternate patients as a routine and to record impressions of their respective values. It can safely be stated that, so far from affording data for a quantitative comparison, such a method would not even give trustworthy information as to whether either extract was active at all. Mr. Bourne and Dr. Burn, having made an experimental comparison of the activities of the known principles on the parturient uterus, with mechanical records of contractions, were content, in the case of the watery liquid extract of ergot, to show that the ward sister could not distinguish its action from that of a "marmite" solution, when both were given to alternate patients in the puerperium. The inference was that the liquid extract had no action; but Dr. Moir's experimental records show it to contain what may well prove to be the most important substance in ergot, from the point of view of practical therapeutics.

It is important to note that, according to Dr. Moir, the extract made with acid alcohol is at least as active, when given by the mouth, as the old watery extract; so that the gain in alkaloids is not obtained at the expense of the unknown principle. As to the nature of the latter, Dr. H. W. Dudley of this Institute has already made some progress, with Dr. Moir's co-operation, towards identifying the type of the substance in ergot responsible for this prompt action with oral administration. If a laboratory pharmacological test, specifically recognizing and measuring it, can be found, progress will be accelerated. Meanwhile, it is legitimate to hope that yet another substance from this extraordinary drug will prove to have as much general interest as its predecessors.

REFERENCES

1 Moir, C.: *British Medical Journal*, June 4th, 1932, p. 1022.
2 Bourne, A., and Burn: *Journ. Obstet. and Gynaecol.*, 1927, xxxiv, 249.
3 Carr, F. H., and Dale, H. H.: *Pharm. Journ.*, 1913, iv, 37, 130.
4 Barger, G.: *Ergot and Ergotism*, p. 170.
5 Pharmacopoeia Commission, Reports of Subcommittees. No. 8, Report of Subcommittee on Ergot, October, 1931.
6 Stearns, John: Quoted by Barger, *Ergot and Ergotism*, p. 13.
7 Prescott, Oliver: A Dissertation on the Natural History and the Medicinal Effects of the *Secale cornutum*, or Ergot.
8 Adam, Neale: *The Spur or Ergot of Rye*, p. 81.
9 Sharp, J. G.: *Proc. Roy. Soc. Med.* (Therap. and Pharm. Section), 1911, 114.