Towards the end of his life Harvey wrote to a young medical man that as an explorer his own days were, alas, numbered. "But," said he, "it will always be a pleasant sight to see distinguished men like yourself engaged in this honourable arena." There spoke the true spirit of adventure, glad to hand on the torch to the younger generation. In like spirit it is good for us on this morrow of St. Luke's to pause amid the rush of life for an hour to join hands with those who have gone before and with those who will come after us. Thus is the real continuity of this College assured. And so I exhort you in Harvey's own words "for the honour of the profession to continue in mutual love and affection."

CLINICAL EXPERIENCES WITH THE NEW ALKALOID, ERGOMETRINE*

BY

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At the Centenary Meeting of the British Medical Association in 1932 I had the privilege of showing to this Section the results of work that had just been done which clearly showed that the traditional clinical action of ergot was due not to the alkaloids ergotocine and ergotamine, which had hitherto been regarded as all-important, but to a substance still unidentified.¹ At that time I was actively engaged in a combined work with the late Dr. H. W. Dudley in an attempt to identify this substance. The search was long and difficult, but was eventually brought to a successful conclusion by the isolation in pure chemical form by Dr. Dudley of a new alkaloid to which the name ergometrine was given. A description of this new alkaloid, together with its essential chemical, pharmacological, clinical properties, and method of isolation was given in March, 1935,² and subsequently amplified.^{3 4 5}

It is now sixteen months since the manufacturing chemists of this country made ergometrine freely available to the medical profession, and it is fitting at this time to endeavour to assess the usefulness of the drug in clinical practice. Before dealing with purely clinical matters it is necessary to make certain remarks concerning the position of the new alkaloid.

Nomenclature

At one time some confusion threatened to arise by announcements made from three other widely separated laboratories of the successful isolation of new ergot alkaloids having high activity of the type under discussion.⁷ These alkaloids were named ergotocin (Kharasch and Legault), ergostetrine (Thompson), and ergobasine (Stoll and Burckhardt). In the case of two of these substances the suggestion was made that they differed in certain chemical characteristics from the ergometrine discovered and described in this country. Any doubt which these claims may have aroused has now been dispelled. As the result of efforts made by Sir Henry Dale, a friendly exchange of samples has been effected between the different laboratories and, following comparative tests carried out by the various workers concerned, a combined letter has now been issued in which the four alkaloids are definitely stated to be identical.⁸

It is fitting to mention that the manufacture and sale of ergometrine is, and always has been, entirely free from

patent rights, nor is the name in any way protected. From the time of its discovery the methods of preparation have been openly published for the benefit of scientific workers the world over. On the other hand, the three other names suggested for what is now admitted by all concerned to be one and the same alkaloid appear in all cases, at one time or another, to have been subject to some kind of proprietary protection; and the methods by which isolation was accomplished have not yet been published.

The name ergometrine, besides being free from commercial interests, is also the name proposed by the workers who in 1932 first demonstrated the presence of the new substance in ergot, and who in 1935 identified the substance as a new alkaloid and gave the first chemical and pharmacological description by which the substance could be identified by other workers. It may be supposed that these reasons have been effective in establishing the use of "ergometrine" as the scientific name of the new alkaloid in countries other than this. "Ergometrine" is also the name by which the substance is known in clinical medicine in this country and in Europe generally.

It should be mentioned, however, that the Council of Pharmacy of the American Medical Association has decided to rename the alkaloid for clinical use in the U.S.A.⁹ This decision, it has stated, was made because the names in use were objectionable because (1) they were registered trade names, or (2) they were therapeutically suggestive. The first objection does not apply to ergometrine, and one must therefore suppose that the name was criticized because of its therapeutic suggestiveness. In answer to this it has been pointed out that the familiar word "ergot" has for the physician a much greater suggestion of special uterine action than has the Greek root to which objection is taken, and that by choosing "ergonovine" as the new name the American Council has shown that it has no difficulty in swallowing the "ergo" camel while straining at the "metrine" gnat. The decision appears to be a somewhat pedantic application of a principle which in certain instances may possibly be useful, but which even in the best circumstances inevitably results in creating confusion in medical literature.

In passing, it may be pointed out that the Council's action is in keeping with its decision a few years ago to alter the name of the pure crystalline vitamin C, which its discoverer Professor Szent-Gyorgyi and his collaborators had named ascorbic acid. In an inconsistent fashion, however, the Council takes no exception to the use in the United States of certain other names of far greater therapeutic suggestiveness than that of the substance under discussion. The alkaloids morphine and narcophine are examples of this. Finally, during more recent months no fewer than three other new ergot alkaloids^{10 11 12} (unlikely to have any clinical significance) have been discovered, a circumstance which makes the name "ergonovine" a particularly unfortunate choice.

Characteristics of Ergometrine

Ergometrine has the formula $C_{19}H_{23}O_2N_3$; the molecule is therefore much smaller than that of the ergot alkaloids previously known. It is remarkable for the rapidity with which it is absorbed from the alimentary canal, a feature clearly differentiating it from the other ergot alkaloids. It is also reasonably stable, is resistant to boiling, and keeps well in crude ergot extracts. Prepared in the form of the hydrochloride or certain other salts, it keeps well in the purified form in dry state or in ampoules of solution. It is highly active in promoting contractions of the puerperal uterus, and even in large doses is free from undesirable side effects—again a feature which distin-

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guishes it from the other ergot alkaloids previously known. Finally, the possibility of producing peripheral gangrene by its repeated use is apparently non-existent.

Mode of Action

It is frequently stated that, in contradistinction to posterior pituitary extracts, ergot preparations act on the uterus by causing prolonged firm contraction of the uterine musculature. Detailed study of mechanically recorded tracings of uterine activity show that in the doses used in clinical work this does not accurately describe the mode of action. The essential effect is the production of a rapid series of contractions which, after sufficient dosage, follow each other so closely that the uterus as a whole has no time to relax, and a state of spasm therefore results. It must be noted, however, that great muscular activity continues throughout this stage. As the effect passes off, the contractions again become spaced out, and again the uterus may be able to relax between individual contractions. This second stage tends to persist for many hours.

All the physiologically active ergot alkaloids behave in this manner, ergometrine being no exception. Ergometrine is, however, peculiar in the rapid onset of its action. After oral administration the uterine response appears in about seven and a half minutes, after intramuscular injection in three and a half minutes, and after intravenous injection in three-quarters of a minute.

It has been supposed by some that the action of ergometrine is a fleeting one—similar in this respect to the uterine action of histamine. This is quite inaccurate. The ergometrine effect lasts for as long as three to four hours. Although this may not be quite so long as the action of the ergotamine-ergotamine group of alkaloids (which to be fully effective must be given by injection), it is long enough for all ordinary purposes. If in special cases a longer action is desired, the oral dose of ergometrine may be safely repeated at four-hourly intervals.

Use in Post-partum Haemorrhage

From what has been said it will be gathered that the chief use of ergometrine is in the prevention and treatment of post-partum haemorrhage.* Here the ergometrine effect is seen at its best. If after the delivery of the placenta the uterus is unduly relaxed, the administration of ergometrine, 1 mg. by mouth or 0.5 mg. by injection, will quickly cause a firm contraction of the organ. If severe haemorrhage has already set in, it is strongly recommended that the drug should be given by the intravenous route. For this purpose one-third of the standard size ampoule may be injected or, for those who wish accurate dosage, a special ampoule containing 0.125 mg. is manufactured. An effect may be looked for in less than one minute.*

It may pertinently be asked whether ergometrine has any advantage over pituitary extract in the conditions mentioned. I believe that it has. Pituitary extract tends to be erratic in its action, and in rare cases appears to be without effect. Moreover, it will occasionally cause alarming symptoms, especially if the patient is already suffering from that little-understood condition of "obstetric shock." In shocked patients a repetition of the dose is especially harmful, and in one case in my own experience, and in other cases which have been detailed to me by my colleagues, the repeated administration of pituitary extract has apparently been an important factor in determining a fatal issue.

This unfavourable action of pituitary extract is probably due to a constrictor action on the coronary vessels

* Direct injection through the abdominal wall of 0.5 mg. of ergometrine into the uterine muscle is another effective method of producing a rapid contraction, and is specially commended by Professor Beckwith Whitehouse.

of the heart resulting in a depression of function of an already embarrassed organ. On the other hand, ergometrine in clinical doses has no influence on the cardiovascular system, and has in fact been given in full dosage to patients suffering from severe shock without any harmful effect appearing.

Use in Labour

Like the other ergot alkaloids, the mode of action of ergometrine makes it unsafe for use in labour.* Even when doses so small as 0.05 mg. are used, a dangerous alteration in uterine action may be produced. There appears to be little margin between a dose which merely augments labour pains and a dose which produces contractions following in such rapid succession that there are no intervals of adequate relaxation. Fœtal death may result. I cannot, therefore, subscribe to its use as a safe means of expediting labour.

Curiously enough, ergometrine if given before the onset of labour has but little effect on the uterus. The factor inhibiting contractions during pregnancy—whatever it may be—is normally so strong that the small doses of ergometrine which have been tried have usually failed to produce a recognizable action. Larger doses would in all probability have more effect, but for the reasons already mentioned I regard this proposal as prohibitively dangerous for both mother and foetus.

Caesarean Section

Ergometrine may be used as a preliminary to incision of the uterus during Caesarean section, but it will be found to have what is apparently a very variable action. The explanation of this is obvious when it is remembered that the effect of the drug is very slight until labour sets in. If, therefore, the section is performed during labour, prompt and firm contraction of the uterus may be looked for, especially if the substance is administered by intravenous injection. If, however, the patient is not in labour at the time of the operation very little effect will be apparent.

In spite of this, it is usually found that when the foetus has been extracted the uterus retracts well and quickly becomes firm. The contraction induced is not so powerful as that seen after the administration of pituitary extract, but for that very reason the uterine muscle is easier to sew up and the suture material is less likely to "cut out."

Incomplete Abortion

It has been stated by American workers⁵ that the new alkaloid has been used with success in cases of incomplete abortion. My own experience is a little disappointing. Ergometrine certainly causes the uterine contractions to be speeded up, as can be easily observed in patients who feel a rhythmical uterine colic, but it is seldom that this stimulation is successful in causing the uterus to evacuate its contents when the unaided contractions have already proved to be of no avail. In this respect ergometrine is neither better nor worse than pituitary extract. It is, however, a reasonable drug to give when bleeding is free, and it is sometimes useful in tiding a patient over until other means of treatment are available.

Menorrhagia

Experimental work has shown that while the ergot alkaloids in clinical use are much less active on the non-pregnant uterus than on the parturient organ, they still have a definite effect, especially when given during menstruation. Ergometrine is decidedly more active in this respect than ergotamine. It is therefore reasonable to use this drug in cases of abnormal or excessive bleeding

from the non-pregnant organ in which the haemorrhage is not due to some condition demanding surgical treatment.

It may be mentioned that the effect on the non-pregnant uterus is much less than that of pituitary extract, or of the purified vasopressor principle, pitressin. These latter preparations, however, must be given by injection, and their employment is not free from the risk of inducing intense uterine colic and vasomotor disturbances if they are given during menstruation.

Involution of the Puerperal Uterus

The question of involution of the puerperal uterus has been left to the last because of the great variety of opinion which has been expressed on the subject. Personally, I believe that it is a mistake to attempt to interfere with the normal behaviour of the organ during the puerperium.* As has been pointed out, ergot acts by causing great muscular activity in the form of a rapid succession of contractions of the uterus, and its action is much more than to cause the muscle to become firm or, as it has been expressed, "blood-tight." This abnormal activity when maintained for eight or ten days is probably as much a hindrance as a help to the involution of the organ. While it may be true that occasionally a uterus is abnormally sluggish during the puerperium, and that blood and debris may in consequence accumulate within the cavity, and while this condition may perhaps be avoided by the routine and repeated administration of ergot preparations, I prefer to wait for a sign of abnormal uterine behaviour to appear before interfering with the normal action of the organ.

During the last year patients under the care of the Obstetrical Unit of the British Post-Graduate Medical School have been divided into two groups. One group has received ergometrine immediately after delivery and thrice daily during the puerperium. The other group, consisting of alternate patients, is used as a control and no variety of oxytocic drug is administered. Careful daily measurement is made of the height of the uterine fundus. Several hundreds of patients have now been observed, and, although a detailed analysis of the results has not yet been made, it is my impression that involution is exactly alike in the two groups. At one time ergotamine was substituted for ergometrine; no change in uterine involution was observed as the result of this. From these experiments it may be tentatively concluded that, while there is no evidence that the routine administration of ergot preparations during the first week or ten days of the puerperium is harmful, there is also no evidence that involution is accelerated.

Before leaving this subject I should like to make a special protest against routine and repeated administration of ergot in cases of actual uterine sepsis. If, as is usually agreed, the correct treatment of a septic hand or limb is to keep the part at rest, there can be little or no justification for reversing the principle in the case of the infected uterus.

Exophthalmic Goitre and Migraine

During the past few years a new use of the ergotoxine-ergotamine group of alkaloids has come into prominence. One of the characteristic pharmacological actions of these alkaloids is the inhibition of the effects which are normally produced when the sympathetic nervous system is stimulated. This property has been utilized in the treatment of certain diseases in which the sympathetic control is overactive, as, for example, in exophthalmic goitre. Now, ergometrine has been found to be almost devoid of any such effect on the sympathetic nervous system, and it is therefore extremely unlikely that this new alkaloid will be of any value in the conditions mentioned.

Finally, in certain cases of true migraine the ergotoxine-ergotamine group of alkaloids, when injected in doses of 0.25 to 0.5 mg., has been found to be extremely effective in aborting an attack, or in preventing its occurrence in those patients who have prodromal symptoms.¹³ Since the mechanism of this action is quite unknown, only actual trial can answer the question whether ergometrine will be equally useful, and information concerning such tests is urgently needed. The advantages of a drug which can be carried in tablet form and which is rapidly effective when taken by the mouth are so obvious that before long ample clinical trial will certainly be made.

Superiority of the Purified Alkaloid

Finally, it may be asked whether there is any advantage to be gained by using the purified alkaloid in preference to the crude ergot extracts of the *Pharmacopoeia*. There are advantages. The crude extracts will in some patients cause nausea and vomiting, and their administration by mouth is sometimes impossible, as, for example, when a patient is still stuporous after an anaesthetic. On these occasions, and on occasions when very rapid action is essential, the advantages of the purified alkaloid, which can be given by injection, are obvious.

There is, however, another matter to be considered. As was shown in 1932,¹ and recently confirmed,¹⁴ different batches of ergot vary considerably in their content of what is now known to be ergometrine. Hitherto no method of standardization has been available, and these crude extracts have necessarily been of an uncertain degree of activity, and hence inferior to the purified ergometrine when accuracy of dosage is desired. This fact may account, in part at least, for the varying opinions which have been held regarding the efficacy of the pharmacopoeial extracts. It is satisfactory to record that a recent work by Page and Hampshire¹⁴ has resulted in a practical method being devised by means of which the ergometrine and ergotoxine content of crude ergot may be separately assayed. With the next revision of the *Pharmacopoeia* it is safe to assume that a fixed ergometrine content of official ergot preparations will be insisted on.

Conclusions

From what has been said it will be realized that ergometrine can with advantage be used whenever ergot therapy is indicated in obstetrical and gynaecological work. It will also be gathered that it is my own opinion that ergometrine has supplanted the alkaloids previously in use. The new alkaloid does all that they do, does it better, and does it with less inconvenience and risk to the patient. On the other hand, in certain medical conditions in which ergot preparations have been given with the object of restraining an overactive sympathetic nervous system, ergometrine is unlikely to be of value.

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