a suprarenal cortex, and only occasionally to a malignant tumour.

Not infrequently hyperplasia or neoplasia (adenoma) of the pars anterior of the pituitary also leads to virilism in women. With hyperplasia there is usually acromegaly. It is interesting to note that a marked change to virilism does not occur in women as the direct result of these lesions after the menopause, although, as we know, in many after that epoch certain masculine characteristics, such as hair on the face, are common. Similar changes may follow oöphorectomy with the artificial menopause.

With cortical suprarenal tumours the changes observed in women are remarkable. Many grow beards, and some appear in fairs as the well-known bearded women. They may have the voices of sergeant-majors, and be rough and aggressive in manner. When seen early, removal of the offending tumour may lead to retrogression of most of the masculine characteristics, but the altered larynx never reverts to its former shape and size.

With acromegaly there is a limited change towards masculinity with amenorrhoea. The voice invariably deepens. In one case I found that the clitoris had become so greatly hypertrophied that it was causing the patient much distress. Acromegaly in men, as Harvey Cushing has shown, causes increased virilism, just as do suprarenal tumours.

Feminism in Men

A change in characteristics towards femininity is seen in men who have destructive lesions of the pars anterior of the pituitary, such as may be caused by cysts in that organ or by suprasella tumours. In these circumstances the syndrome known as dystrophia adiposogenitalis is present. Hair disappears from the face and pubes, while the contour of the body and limbs assumes a feminine type. After castration, too, a certain degree of feminism develops. No doubt in all these circumstances the masculinity-maintaining mechanism is interrupted.

SUMMARY

The relation of the sex-directing factors of heredity and sex-chromosomal constitution have been discussed, and the continued sex differentiation in vertebrates through the sex-determining action of organs of internal secretion has been described, together with the nature of the later general sex characteristics brought into being by the endocrine genital system.

Sex aberrations from biological, sociological, legal, and medical points of view have been considered.

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THE SUBSTANCE RESPONSIBLE FOR THE TRADITIONAL CLINICAL EFFECT OF ERGOT

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In 1932 one of us (C. M.)[1] drew the conclusion from clinical experimentation that the characteristic and traditional effect of ergot was caused, not by ergotoxine, ergotamine, tyramine, or histamine, but by a substance still unidentified. Previously it had been generally held by pharmacologists that aqueous extracts of ergot were valueless because they lacked the supposedly essential alkaloids. The experiments then described showed that, far from being inert, the much-criticized *B.P. 1914* liquid extract of ergot had a most remarkable oxytocic activity, and we believed that the clinician was fully vindicated in his dogged belief in the efficacy of the old-fashioned preparation. In spite of some criticism and scepticism our clinical and chemical observations kept us convinced of the truth of our conclusions, and we are now able to prove their correctness by reporting the isolation of the substance to which ergot rightly owes its long-established reputation as the "*pulvis parturiens*." We propose to name it "ergometrine."

Isolation of Ergometrine

The rapidity of action after oral administration of appropriate crude ergot extracts suggested that the active substance was a relatively simple compound, and our preliminary chemical investigations supported this view. We found that it was precipitable by phosphotungstic acid, and that when submitted to the Kossel-Kutscher method of fractionation it appeared in the "lysine" fraction. We also observed that it could be precipitated by mercuric sulphate and recovered from the precipitate by decomposition with hydrogen sulphide.

Large quantities of *B.P. 1932* extract were accordingly fractionated by a combination of these methods, but although we repeatedly obtained from the "lysine" fraction material which showed typical activity, we failed consistently to obtain any crystalline salts or derivatives of the base which was undoubtedly present. When we found that the active "lysine" fraction gave colour reactions similar to those of the known ergot alkaloids, and that the active substance could be extracted with chloroform from alkaline solution, we suspected that it was a more complex base than we had originally imagined. We therefore modified our procedure, taking advantage of the chloroform solubility of the substance in order to avoid the laborious application to crude extracts of the methods for the isolation of bases that we had until then employed. Our new method of extraction led us with unexpected rapidity to the isolation of the substance for which we were seeking, and was carried out in the following manner.

Defatted ergot powder was extracted with hot dilute sulphuric acid. After filtration the liquid was treated with barium hydroxide solution in slight excess. The precipitate was discarded, and excess of barium was removed by treatment with carbon dioxide. The filtered alkaline solution was then concentrated in a vacuum to small volume and treated with alcohol, which precipitated much sticky material. The alcoholic solution was con-

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centrated and the residual fluid was extracted with chloroform, into which the active principle passed. It was then removed from the chloroform by shaking with dilute sulphuric acid. The chloroform-soluble material was again extracted from the acid solution, after this had been rendered alkaline, to ensure its freedom from contamination with small amounts of mother-liquor carried over mechanically in the first chloroform extraction.

The second chloroform extract was then evaporated to dryness. A dark resinous residue was obtained in which crystalline material was observed. Chloroform was cautiously added until a limpid solution resulted, and crystalline material remaining undissolved was collected and washed with a little chloroform. From 10 kg. of defatted ergot 0.82 gram of these crystals was obtained, which proved, on clinical trial, to be the active principle we were pursuing.

Chemical Nature and Properties of Ergometrine

One portion of the isolated crystalline substance was recrystallized from benzene, from which it separated in long needles, and another from dichloro-ethylene, which yielded rectangular aggregates of prismatic needles. In both cases the decomposition point of the recrystallized substance rose about 20° above that of the original material, and lay at 150° to 152° after previous darkening.

Ergometrine is moderately soluble in chloroform, benzene, and dichloro-ethylene, and may be recrystallized from these solvents. It is very soluble in methyl and ethyl alcohols, acetone, and ethyl acetate, and cannot be recrystallized from these; evaporation of its solution in any of them results in a gum-like residue. It is appreciably soluble in cold water, to which it imparts a reaction alkaline to litmus, and dissolves readily in dilute acids. It is slowly oxidized on exposure to the atmosphere, acquiring a brown colour. It gives the dimethylaminobenzaldehyde and glyoxylic acid colour reactions common to the known ergot alkaloids.

SPECIFIC ROTATION

Although the solubility of ergometrine in chloroform at room temperature is too small for accurate determination of the specific rotation, it was desirable to make the observation in this solvent for comparison with other ergot alkaloids and, in particular, with sensibamine.

$[\alpha]_D$ of the material recrystallized from benzene = − 45° (0.1 per cent. solution in chloroform).

ANALYSIS

Duplicate analyses of the substance recrystallized from benzene and dried in a vacuum at 70° gave the following values: C 71.46 : H 7.38 : N 11.66 per cent. These results are presented with the reservation that slight modifications may be necessary when larger quantities are available, which will permit more drastic purification to be carried out. It would be premature to assign a formula to ergometrine until further analyses of the base and of its derivatives have been made.

The properties so far examined suffice to distinguish ergometrine from all the previously described ergot alkaloids, including the recently discovered ergoclavine and sensibamine. Direct comparison with ergoclavine has confirmed the fact that it is chemically distinct from ergometrine. No such comparison has been possible with sensibamine, and the brief description of its preparation, given in the patent specification, suggested a similarity with ergometrine in its behaviour towards solvents. The solubility of ergometrine in chloroform is, however, much less than that of sensibamine, and the specific rotations of the two substances, − 45° and + 125° respectively, preclude the possibility of their chemical identity. The clinical and pharmacological properties, reported below, are also conclusive proof that both ergoclavine and sensibamine are different from ergometrine.

Ergometrine must be classed as an alkaloid, evidently allied to, but probably simpler than, any of those which have already been isolated from ergot. A knowledge of its properties may possibly result in improvement of the method of isolation, and render it more readily available for clinical use. Full details of its preparation and chemistry will be published by one of us (H. W. D.) elsewhere in due course.

Clinical Action of Ergometrine

The striking difference after oral administration between the mode of action of ergotoxine and ergotamine on the one hand, and that of crude liquid extracts of ergot such as those of the *British Pharmacopoeia* (1914 and 1932) on the other, has already been reported.[1] The two alkaloids, given in doses as large as 2 to 3 mg., provoke uterine contractions, erratic and relatively feeble in character, after an interval of thirty-five minutes or considerably more, while the liquid extract causes strong contractions, which set in five to ten minutes after administration of the drug. The onset is sudden, and accompanied by pronounced uterine spasm, which appears to be caused by a succession of contractions so rapid that the organ as a whole has no time to relax. This stage lasts for about an hour, and is followed by a second stage, during which the uterus shows regular, vigorous, isolated contractions, continuing for an hour or more.

Clinical tests of the recently discovered alkaloids sensibamine[2] and ergoclavine have been performed, and these substances display, after oral administration, the ergotoxine–ergotamine type of action, to which group in this respect they must be added.

In strong contrast to the action of these alkaloids is that of ergometrine. Orally administered in a dose of 0.5 to 1 mg. it provokes, after an interval of six and a half to eight minutes, contractions identical in mode of onset and general character with those produced by active liquid extracts of ergot (see Fig. 1). Ergometrine may also be

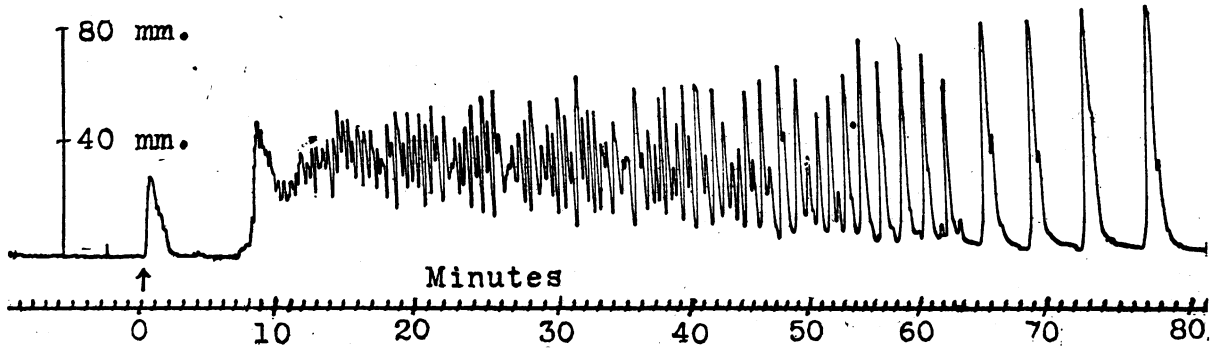

FIG. 1.—Tracing of uterine contractions made on sixth day of puerperium by intrauterine bag method, showing the effect of 0.5 mg. ergometrine given by mouth. The arrow shows moment of administration. (Note.—An isolated spontaneous contraction occurred simultaneously with the administration of the drug.)

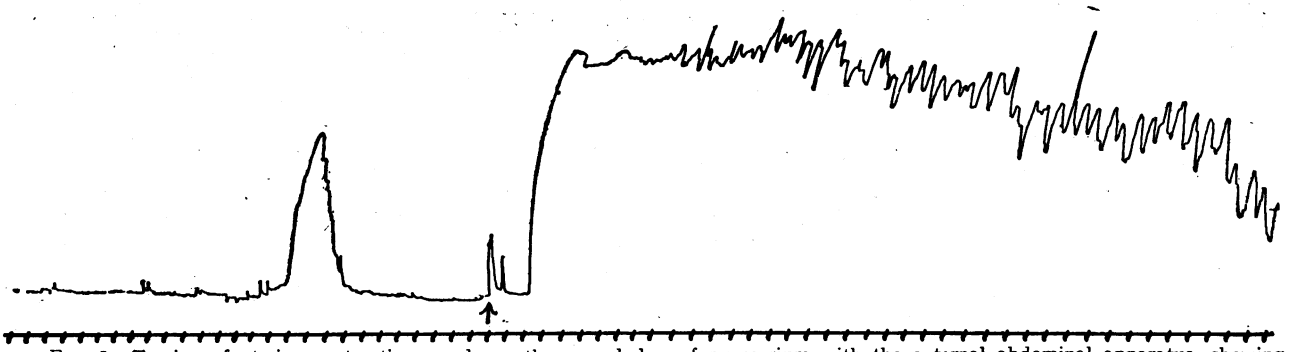

FIG. 2.—Tracing of uterine contractions made on the second day of puerperium with the external abdominal apparatus, showing the effect of 0.05 mg. ergometrine administered intravenously. Time is marked in minutes. The arrow shows moment of injection.

given by injection. An adequate dose for intramuscular administration appears to be 0.25 to 0.5 mg., which produces strong uterine action in three and a half to four and a half minutes. In two cases ergometrine has been given intravenously in doses of 0.05 and 0.1 mg. respectively. In one a strong response followed in 110 seconds and in the other in 65 seconds (see Fig. 2).

These observations also distinguish ergometrine from the ergotoxine–ergotamine group; the latter alkaloids are slow to act, even when given by injection, requiring about twenty minutes after a dose of 0.5 mg. intramuscularly, and six to seven minutes after 0.25 mg. intravenously. It will thus be seen that ergometrine has a pronounced action in a dosage smaller than that required in the case of the previously known alkaloids, and that it greatly surpasses them in its speed of action—a most valuable property in obstetrics.

Whereas ergotoxine, ergotamine, and ergoclavine, when given in a dosage large enough to produce a definite action on the uterus (for example, 0.5 mg. by injection), not infrequently produce in the patient a feeling of depression, headache, nausea, and even vomiting, the new substance in useful clinical dosage is remarkably free from such side-effects. This has often been proved by seeing the patient eat a large lunch or fall asleep after the administration of the test dose.

Method of Testing for Activity

The method by which these observations were made has already been described, and need be only briefly mentioned now. A thin rubber tube, ending in a small rubber bag, is passed into the uterine cavity on the seventh day of the puerperium. Great care is taken with regard to asepsis and antisepsis, and, amongst other precautions, the bag is first liberally lubricated with a glycerin solution containing mercuric chloride (1 in 1,000). By means of tubing filled with water the bag is connected to a manometer, which traces the variations of intrauterine pressure on a slowly revolving drum. This method was based on Bourne and Burn's well-known work on the parturient uterus, and was modified in the first place in order to test the clinical action of ergotoxine and ergotamine—work carried out on behalf of the Therapeutic Trials Committee of the Medical Research Council. More recently another means of recording uterine contractions has been evolved, which makes use of an apparatus to record the changes in uterine shape felt through the abdominal wall. This method has the great merit of simplicity, and has proved useful in exploratory experiments, but it is not so accurate or so dependable as the first one.

It may be asked why the presence and significance of this alkaloid in ergot and its extracts has escaped discovery during the many years of pharmacological investigation to which the drug has been subjected. In fact, its recognition in complex extracts by the ordinary methods of laboratory experiment on animals and isolated organs would be so difficult that success on those lines would be highly improbable. Preliminary observations already indicate that, on isolated strips of the resting uterus, ergometrine would not reveal itself by any distinctive and characteristic effect in preparations containing the other alkaloids, and especially in those containing histamine, with its intense activity under such conditions. In experiments conducted in Sir Henry Dale's laboratory during the course of our investigation, in which records were made of the contractions of the non-pregnant uterus of an unanaesthetized bitch by insertion of a balloon through a fistulous opening, it was not possible to recognize any characteristic result when extracts active on the human puerperal uterus and now known to contain ergometrine were given by the mouth. It may be that records from the uterus of a puerperal animal, even under anaesthesia, will be found to give evidence of a distinctive activity of ergometrine on oral administration now that the latter is available in pure form for comparison with the earlier-known alkaloids. The difficulties, however, of making and interpreting such observations at all stages of the isolation on a series of animals suitable for the purpose will be sufficiently obvious. Observations by such methods would, at best, be at a very great disadvantage in comparison with those made on a series of comparable and co-operating human subjects. That the latter method has provided an effective guide to the isolation of a principle which laboratory tests had not even recognized is not difficult to explain.

Since the only criterion of the presence of ergometrine was its characteristic action, after oral administration, on the human puerperal uterus, the clinical method described had, of necessity, to be used to determine the distribution of activity throughout the entire course of chemical fractionation, and up to the time of the discovery of the crystalline active substance over 140 such tests had been performed.

Pharmacology of Ergometrine

Sir Henry Dale and Dr. G. L. Brown will undertake a full pharmacological investigation of ergometrine as soon as adequate supplies are available. In the meantime, we have their permission to record that they have tested it with respect to vasomotor reversal in the pithed cat and abolition of the motor action of adrenaline on the isolated uterus of the rabbit, which are well-known effects of the hitherto isolated alkaloids of ergot. Ergometrine raises the blood pressure of the cat and stimulates contraction of the rabbit's uterus, and it slightly reduces the response to adrenaline. This effect is, however, so weak in comparison with that of ergotoxine that it may possibly be due to slight contamination of the specimen of ergometrine with one or other of the known alkaloids. It will be possible definitely to settle this question when larger quantities of ergometrine are available, to which more drastic methods of purification may be applied; for, although the recrystallized material appeared to be homogeneous it is well known that complete removal of

closely allied contaminants from such a compound is difficult.

Since, however, the hitherto known alkaloids of ergot are quantitatively indistinguishable from one another by these pharmacological tests, the above experiments differentiate ergometrine from all of them, including the recently described alkaloids ergoclavine and sensibamine, which have been examined in Sir Henry Dale's laboratory. A paper by Dr. Vartiainen, dealing with ergoclavine and sensibamine, is now in the Press. The identity of the action of ergoclavine with that of ergotoxine has already been reported by Kreitmair.[3]

General Considerations

The isolation of ergometrine, without doubt the constituent to which ergot owes its introduction into medicine, will enable accurate decisions to be reached with regard to the relative values of the other clinically active alkaloids. It is already evident that ergometrine is the essential constituent of extracts intended for oral administration, while ergotoxine, ergotamine, ergoclavine, and sensibamine are relatively unimportant, and may possibly even be undesirable in such preparations. One of us (C. M.) proposes later to deal fully with the question of the usefulness of the various ergot alkaloids in obstetrical practice.

The pronouncement of the Ergot Subcommittee of the Pharmacopoeia Commission that "ergotoxine is to be regarded as the active principle for which ergot preparations are administered, and all preparations should be standardized from this point of view," appeared to be reasonable at the time when it was made, but the discovery of ergometrine destroys its scientific basis and proves it to be misleading. It seems clear that ergometrine should now be regarded as the most important active principle in any ergot preparation intended for oral administration, and the problem of the preparation of suitable extracts will have to be re-examined in the light of the knowledge now available. Whether, for example, the *B.P. 1932* liquid extract, designed to contain the total alkaloids of the drug, is more or less desirable in clinical practice than some form of watery extract so made as to contain predominantly the ergometrine and very little of the ergotoxine-ergotamine group should be considered.

The question of standardization, too, will require examination. The colour reaction upon which the official method of assay is based is common to all the known alkaloids of ergot, including ergometrine. As at present applied it measures only the total alkaloidal content of an extract, and gives no information regarding the amount of the most important therapeutical constituent. With a knowledge of the properties of ergometrine it may be possible to devise a method for its determination in official preparations, and so put the assay of ergot extracts on a satisfactory basis in relation to their clinical efficacy.

Since this paper was written a communication by Koff[4] has come to our notice. Using the same clinical method of testing as we have employed, he has demonstrated that the substance responsible for the characteristic clinical effect of orally administered ergot preparations is associated with the alkaloidal fraction, and he states that removal of ergotoxine from the latter does not impair its activity. These exploratory experiments are in accord with our identification of ergometrine as the active alkaloid concerned.

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ENCEPHALOMYELITIS SIMULATING DIPHTHERITIC PARALYSIS

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The clinical picture of diphtheritic paralysis is an extremely characteristic one, and as a general rule few other conditions are likely to be mistaken for it. The main reason for this is that paralysis of the palate is hardly ever met with in childhood from any other cause. It is, however, decidedly rare, as has been emphasized by J. D. Rolleston,[1] for neuritis to occur in any but severe and well-established cases of diphtheria, though the work of Walshe in Egypt suggested that under certain conditions it might do so.

We considered that the cases here described were worth recording, because they suggest that diphtheritic paralysis is at the present moment being simulated by a disorder of an entirely different nature, and that a new significance should be attached to some of its most typical symptoms. The fact that these cases were all seen in one hospital during the course of eight weeks makes it likely that they are not rare, and it may well be that palatal paralysis may become of some value as a sign of the disorder which we believe these children to have suffered.

Case Records

The four cases were admitted to the Victoria Hospital for Children during December, 1934, and January, 1935. All of them were seen by one of us (N. H.), and all pathological examinations were carried out by the other (S. W.).

CASE I

Girl, aged 12. Admitted on December 12th, 1934, under the care of one of us (S. W.). History: slight sore throat ten days previously, followed on the next day by weakness of both legs. A throat swab had been taken and found negative to K.L.B. She was removed to a fever hospital, but further swabs were negative, and she was therefore discharged.

On admission, when seen by one of us (S. W.), she was bright and happy, sitting comfortably in bed and looking well. Cranial nerves and arms were normal; abdominal reflexes present. Both the lower limbs were very weak, but there was no localized paralysis or wasting. The knee- and ankle-jerks were absent. Muscle tone was poor. Plantar reflexes were not obtained. There was no gross sensory change.

On December 14th she had improved somewhat, but was unable to support her weight. Movements of the legs were weak and ataxic. On the 18th she could stand, and on January 3rd she walked unsteadily. On the 7th she walked quite well; the knee-jerks were just obtainable and the plantars flexor. Muscle tone was still poor. On discharge to a convalescent home, on January 24th, she had completely recovered, and both knee- and ankle-jerks were easily obtained.

CASE II

Boy, aged 3 years and 10 months. Admitted on January 11th under the care of Dr. Firth. History: a month previously he had suffered from a sore throat; a swab taken at another hospital had been negative. His elder brother had been diagnosed as suffering from diphtheria on December 28th, 1934. During the last few weeks the child's legs had gradually become weaker.

On admission there was considerable weakness of the legs, with absent knee-jerks and sluggish ankle-jerks. There was no movement of the palate on phonation. All other cranial nerves were normal. He was rather drowsy, and talked little; the voice was somewhat nasal. Faucial and nasal swabs were negative to K.L.B. Lumbar puncture showed the fluid was under considerable pressure. It was clear, and contained a few lymphocytes only. Chlorides: 772.

[1] *Proc. Roy. Soc. Med.*, 1934, xxvii, 1421.