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THE ACTION OF VARIOUS DRUGS

and

ANIMAL EXTRACTS ON UTERINE CONTRACTIONS.

THESIS submitted for the degree of M.D.

by

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Object of the Research.

The **clinical** evidence as to the action of the so called "ecbolics and oxytoxics" is so conflicting that any method which will definitely prove a drug to have a definite action on the uterus, is of value.

The graphic method of recording uterine contractions offers a **practical** demonstration of the value of any drug as to whether it has any actual effect on the uterus and it is surprising how little has been done in that direction.

For instance even yet, in obstetric practice, there is considerable doubt as to whether Quinine has any beneficial effect in labour. Hence I determined to record graphically the effect, if any, of the more commonly used "uterine" drugs on the uterus.

Also I desired to try the effects of extracts of the various organs on the uterus as again our knowledge in that respect was equally indefinite and especially I desired to try the effects of extracts of Placenta, Ovary and Uterus.

SHORT HISTORICAL ACCOUNT OF UTERINE CONTRACTIONS.

To Harvey, who first discovered the circulation of the blood, we also owe the discovery of the uterine movements.

Till his discovery the uterus was not known to possess the power of movement, the foetus being supposed to deliver itself by its own muscular exertions.

This point Harvey settled by actually observing the action of the uterus, having cut open the abdominal walls of a parturient dog, while labour was in progress.

This observation was confirmed by many others but till 1857 no great advance took place as observers had concentrated their attention in tracing out the nervous connections of the uterus, in that year however Calliburtes demonstrated the power of the uterus to contract apart from the influence of the nervous system, by excising the pregnant uterus and finding that the uterine movements continued so powerful as to expel the foetus.¹

In 1864 Körner noted that the movements of the uterus continued even after all the nerves leading to it were divided.²

These/

N:B. For references see Bibliography at end of

Thesis.

These results were followed to their logical conclusions by the interesting experiments of Sir J. Y. Simpson¹ which I will quote more in detail. Sir J. Y. Simpson removed the spinal cord from D₁ downwards in sows a few days before labour was due. Some died, in others labour came on and progressed regularly. In each case all the foetuses were born except the last one. The whole series passed from the uterus into the vagina, one behind the other, and each in its proper membranes. The uterine contractions proceeding from the Fundus to the Cervix were sufficient to expel the foetus from the uterus, each foetus when it reached the vagina was pushed out by the one behind, but the last foetus stuck as there was nothing to transmit the uterine expulsive force, for the abdominal and vaginal muscles being under the influence of spinal nerves had been rendered powerless by destruction of the spinal cord.

These experiments were confirmed by Reiman in the cat and Golt and Ewald in the bitch.

These experiments show that uterine action can take place, independent of brain and spinal cord and contractions of the uterus take place rhythmically and regularly and are of such strength as to expel its contents when its connections with the central nervous system/

system are severed. In 1880 Rein did much valuable work on the innervation of the uterus and came to the following conclusions:-

- (1) The severance of the uterus from all its sympathetic nerve connections does not interfere with the possibility of conception, pregnancy and labour.
- (2) All the phenomena connected with conception, pregnancy and labour are possible in a uterus cut off from all connection with the cerebro-spinal nervous system.
- (3) The cervical ganglia of the uterus have no importance as automatic uterine centres.

Yet it is well known clinically how impulses from the brain and spinal cord can guide and influence uterine movements - thus ~~irritation~~ of the mammae, hot and cold rectal irrigations and stretching of the Cervix readily set up uterine action.

In 1879 Von Rohrig first demonstrated the existence of a centre for the control or co-ordination of the uterine actions. He found that Asphyxia which induced uterine contractions and abortion, would do so if the spinal cord was severed in the dorsal region but not if the lumbar cord was destroyed.

Serres working in rabbits and guinea pigs proved that excitation of the lumbar spinal cord set up uterine contractions and abortion

More/

More recently Langley and Anderson have shown that stimulation of the nerves from the 3rd, 4th, 5th, 6th lumbar sympathetic ganglia caused pallor and contractions of the uterus, but stimulation above the third or below the sixth had no such effect.

These experiments prove the existence of a centre in the Lumbar Spinal Cord which may regulate or control the actions of the uterus and through which reflex stimuli and cerebral impressions operate. Michael Foster considers that the efferent impulses which issue from the lumbar centre are not so much of the nature of directly excitatory impulses as of impulses of an augmentor kind increasing and developing the intrinsic contractions of the uterus itself. So much for the nervous mechanism and now to return to the uterus itself.

Kebrer in 1863 and Reimann later in 1869 proved that the uterus contracted automatically and rhythmically.

The uterus removed from the body and kept warm was seen to contract and relax and portions of the uterine wall behaved in a similar way, also exhibiting coiling or spiral movements. The existence of uterine movements was now established and the next advance took place in 1878 when a series of observations were made to find the direct action of hot and cold/

cold water on the uterus. This was by Runge who, experimenting on the uterus in situ, found that it could be stimulated directly by hot water, increasing contractions resulting followed by paralysis, whilst cold water produced tetanic contractions.

This brings us to 1882 when Frommel first attempted to record the uterine movements graphically. He connected the uterine cavity with a water manometer, by means of a cannula introduced into the vagina and brought in contact with the neck of the womb. From the manometer a tube lead to a Marey's tambour, which by means of a lever, recorded on a revolving cylinder the uterine movements. He came to the conclusion that the uterus of the rabbit - in all conditions (virgin, pregnant and puerperal) presented spontaneous rhythmical contractions.

Dembo in 1883 denied the existence of spontaneous uterine contractions - he examined the uterus of a great many non-pregnant animals and failed to get spontaneous movements. He considers Frommel's results due to manipulation and the mechanical stimulation of his apparatus.

Jacob in 1884 adopted Frommel's method but fixed Frommel's apparatus to an isolated horn of the uterus, to exclude vaginal contractions, and he was first to record graphically the effect of drugs - namely Chloral/

Chloral, Curara and Morphine - all of which he found in large doses to diminish the action of the uterus, but small doses had no effect.

Strychnine he found increased the contractions.

He also demonstrated the effect of electrical stimuli applied to various parts of the cord and uterus and concluded that an excitor centre for the uterine movements was present in the lumbar cord and an inhibitory centre in the medulla oblongata.

This latter has not been substantiated.

In 1886 followed the well known results of Milne Murray on the action of hot and cold water on the uterus.

This brings us to 1891 when Helme working in the Royal College of Physicians' Laboratory did a large amount of work in the physiology of the uterus and on the uterine circulation. He also tried the effect of several drugs - including several preparations of ergot.

Since then Kardinoski and Franz have published numerous experiments with the uterus in situ but exposed to the air and hence, as Cushing points out, introducing a large source of error, and results cannot be taken as accurate.

In other experiments Helme, Kardinoski and Frönz eliminated this source of error by recording movements of the excised uterus in a bath of warm saline or by perfusing/

perfusing vessels with Locke's Solution.

Cushny again points out in his article on the movements of the uterus in the Journal of Physiology (1906 - 07) "that these experiments show uterine contractions are not dependent on impulses from the central nervous system, but movements of the excised uterus can scarcely be regarded as typical and normal without investigation of the intact animal. The only experiments in which movements of the uterus in situ are recorded - a normal temperature being maintained and the abdominal contents not exposed to air - are a few performed by Kardinouski, and later by Dale, (Journal of Physiology 1906,) in his experiments on the active principles of ergot and a few of those of Franz".

Cushny, therefore, claims to have been among the first to obtain graphic records of the uterine movements, the uterus being in situ, and kept from exposure to the air; the abdomen having been opened under normal saline kept at a constant temperature of 37° - 39°C .

He recorded the movements as follows:- two small hooks were passed through the peritoneal coats of one horn of the uterus about one inch apart, and then, by means of thread and pulleys, the uterus pulled on a lever, writing on a recording drum.

Cushny's results are open to one objection - he states/

states he used the intact animal, yet in nearly all his experiments he states - the Hypogastric Nerve was cut as it issued from the Inferior Mesenteric Ganglia and in cats, in addition, a Fibrous band stretching from ovary to the kidney was usually cut as otherwise, he states, the movements were inhibited.

Obviously, therefore, on his own statement Cushny's results are not obtained from the intact animal.

Again Blair Bell in 1909 in his recent work on the "Physiology of the Female Genital Tract" has performed a number of experiments in which he records uterine contractions but in these experiments the animal had the brain destroyed and was kept alive by artificial respiration.

Blair Bell also tried the effects of injection of extracts made from the various ductless glands on the uterus.

The action of Adrenalin on the uterus has long been worked out but it is only very recently that the enormous power of Pituitary Extract to cause Uterine contractions, has been recognised. Ovarian and Placental Extracts have also been tried but without such definite results. The experiments of Dixon and/

and Taylor with the Placenta from which they claimed to have got an extract with a specific action on the uterus - being now discredited, their results being now said to be due to decomposition products, produced in the making of their extract, from the placental tissue.


No definite opinion could be expressed about the action of ovarian extract (if any) on the uterus unless one used extracts made from the ovaries of the virgin - non-pregnant and pregnant animals. This consideration will probably explain the discrepant statements of various observers as to whether or not ovarian extract has any action on the uterus.

Kirkness working chiefly with Corpora Lutea claiming that it increased uterine contractions while Blair Bell states it rather inhibits or delays contractions in the pregnant uterus. My own experiments were chiefly with Extract of Uterus and Placenta and to a less extent Ovarian and Foetal Extracts were used but lack of time prevented my following out the latter as fully as required.

Experiments with extracts from the other ductless glands were also made for purposes of comparison and are included in the results.

Observers/

Observers have always been looking for a substance with a specific action on the uterus - as already said Dixon and Taylor thought they had found this from the Placenta - but there is no doubt that the Pituitary Extract and the Extract prepared from the uterus itself so powerfully influence uterine contraction as to merit the claim of possessing a specific action on the uterus.



M E T H O D U S E D .

I now come to the method and apparatus which I employed and found most successful after much experiment and trial with previous methods.

The animals used were rabbits and cats. The object aimed at was to deal with the intact animal as far as possible, hence the uterus was exposed to as little manipulation as possible and its nerve connections left intact. The abdominal contents were never exposed to air as the abdomen was opened in a bath of physiological salt solution kept at a constant temperature.

In the operating practically no blood was lost and very little shock ensued to the animal, and many experiments lasted successfully five or six hours after the operation.

The apparatus consisted of a large tank on wheels filled with saline solution (.8% of Na Cl) kept at a temperature of 38° by a bunsen burner underneath. With attention it was found that for hours the temperature would vary less than half a degree - an ordinary centigrade thermometer, fixed in a large cork, and floating in the water, being constantly referred to.

At first Urethane, either alone or along with Ether, was used as an anaesthetic, but later I found ether/

ether alone, given with a tube in the trachea, most satisfactory. The animal, after the operations necessary for introducing a tube into the trachea, to give the anaesthetic, and a cannula into the right jugular vein to administer the drug later, was tied down to a board which was then immersed at an angle in the water, only the animal's head and neck protruding. This board was firmly fixed by a wooden wedge.

Next the abdominal wall was incised in the middle line from Epigastrium to Symphysis, there being no bleeding unless there was much milk in the breast tissue. Each side of the abdominal wall was then transfixed with a hook to which by a long string was attached a weight of about 10 kilogrammes, these weights were brought under the animal and hung down opposite sides of the tank.

This kept the animal rigidly fixed to the board. All this operating was done under water, the intestines being kept back by a gauze swab firmly fixed at each side of the board.

Thus the uterus was exposed, Fallopian tubes and ovaries and only the rectal end of the intestine, and bladder.

By this method, there was no bleeding, the intestines were quite out of the way and their peristalsis did not influence the uterine movements, lastly/

lastly there was no manipulation of the uterus till a small hook was passed through the peritoneal coat of the right uterine horn about one inch from the junction of the cornua.

From this a thread ran vertically up over a pulley, then by means of another pulley, pulled directly on a light aluminium lever which traced out its movements on a revolving drum. A time marker and signal were also part of the apparatus.

R E S U L T S .

Von Rohrig in 1879 described the movements of the uterus as a "fairly regular peristalsis." This is a very good definition but this "peristalsis" will stand analysing into two parts:-

(1) A wave of constriction or contraction begins at the upper end of the uterine horn and travels downwards towards the vagina - sometimes a simultaneous wave started in the opposite horn but more oftenly one wave is in advance of the other, so that spontaneous movements seemed to be general over all the uterus.

When the contraction wave reaches the vagina, relaxation begins slower and more irregular than contraction.

These movements seemed to be due to the longitudinal/

longitudinal fibres and occurred at fairly regular intervals - varying with each animal. Their strength was fairly equal or at times a strong contraction occurred fairly regularly with smaller contractions in between.

(2) There was a coiling movement, this appeared to be due to the contractions of the Broad Ligament which threw the uterus into a coiled or spiral shape, each horn approaching the other, erected into a coiled form. During contraction the uterus becomes paler, rather bluish in colour, to become red again when relaxation occurs.

Helme concludes "that the rhythmical character of the contractions is due to a primary inherent function of the muscular tissue itself and that relaxation is probably due, therefore, to the muscular fibres themselves, either from elastic reaction or active contraction in another plane".

In addition to these movements a variation in tone was observed, on the top of which the rhythmical movements were superimposed, the tonus of the uterus was raised by the slight necessary preliminary manipulation, a fall always occurring shortly after the experiment started but then remaining fairly constant in most cases - in a few cases considerable variation/

variation in tone was a feature of the experiment.

Considerable doubt exists as to whether the virgin uterus exhibits the movements of contraction and relaxation. Helme and Kurdinowski held them present whilst Franz says there are no such movements, but this was working with the excised uterus. Cushny states the virgin uterus is motionless and in virgin cats and rabbits I found no contractions could be recorded in the great majority of cases from the very beginning of the experiment in a few the necessary preliminary manipulation excited a few weak contractions which soon died away and in one case the tracing was continued four - five hours without any movements occurring. .

In Plate I. which gives a series of tracings of the virgin uterus of the cat and rabbit, the contractions excited in some cases by manipulation are well shown in Figs. 1 and 4, whilst in Figs. 2 and 3 no contractions were excited from the very beginning and as said already this was the general rule - no contractions in the virgin uterus.

The uterus in early pregnancy contracted most regularly and rhythmically, in one experiment the tracings of which are shown on Plate II a continuous tracing/

tracing was taken for four hours with only very minor alterations in the character of the movements.

In later pregnancy as shown in Plate III. the contractions are more powerful but are more irregular and never exhibit the same rhythmical character and in fact in late pregnancy when the foetal movements are superadded it is almost impossible to get a continuous tracing.

In Plate IV. is shown the contraction of the early Post Partum Uterus which are slower but of quite regular rhythm. Further tracings of the Post Partum Uterus will be seen in Plates XXV and XXVI.

As Cushny points out the uterus once pregnant never resumes its former degree of inertness but presents varying degrees of uterine movement. When the animal is in heat, contractions occur characterised by their great irregularity both as regards time and strength of contraction which is often considerable, (such a tracing is shown in Plate V.) but when the once pregnant uterus is, in what may be termed the **quiescent** stage, one can never say what the character of the contractions will be, varying with each individual case - two different types are shown in Plate IV.

In all cases, therefore, a preliminary tracing lasting/

lasting from 15 - 30 - 40 minutes was taken as the normal for that animal before any drug was injected

As might therefore be expected the virgin uterus is the least influenced by drugs, then the non-pregnant uterus in the quiescent stage, then the uterus in heat; The most powerfully and easily influenced by drugs is the uterus of early pregnancy, next the early Post Partum Uterus, then the nearly full time uterus.

These points will be clearly shown later, hence I usually tested a drug by its action on the uterus, virgin, non-pregnant and pregnant.

Lastly the uterus of the rabbit exhibits spontaneous movement more readily and is more easily influenced by drugs than the uterus of the cat. The inhibitory effect of the Hypogastric Nerve on the uterine movements is well shown in Plate VI. where in a non-pregnant cat with nerve uncut there are practically no uterine movements but marked uterine contractions ensued after the hypogastric nerve had been cut as it issued from the Inferior Mesenteric Ganglia.

In Plates VII. and VIII. are shown the effects of hypogastric stimulation. The first plate shows the/
the/

the uterine contractions of a pregnant cat of which later (see Plate VIII) the hypogastric nerve was cut and stimulated by the Faradic Current. The enormous contractions resulting show that motor fibres must also exist in the hypogastric nerve.

These experiments are interesting as corroborating to a certain extent what Cushny first pointed out that in the cat, the uterus is apparently more under the control of the inhibitory fibres in the Hypogastric Nerve than in the rabbit.

The effect of the hypogastric nerve in the virgin is purely inhibitory - the inhibitory fibres predominating over the motor fibres and inhibiting movement.

In pregnancy this is reversed, the motor fibres now predominating over the inhibitory and the enormous motor effect resulting from stimulation of the hypogastric nerve is well shown in Plate VIII.

Once pregnancy and labour have occurred, these inhibitory fibres may, but usually do not, predominate. Apparently they did predominate in the case, tracings of which are shown in Plate VI, for contractions did not occur till the nerve was divided and the inhibition cut off.

Hence/

Hence the variation in the nature of contractions in the uterus (once pregnant) and now in the quiescent stage. The uterus once pregnant never returns to its virgin condition - the nature and extent of the contractions being dependent on the extent to which the inhibitory fibres of the hypogastric recover or lose their former predominance.

In Plate IX is shown the result of a direct excitation of the uterine muscle, the wall of the uterus being pinched with a pair of forceps and increased uterine contractions resulting.

In the same animal at a later period, the abdominal aorta was clamped for 90 sec. with artery forceps, increased tone and increased contraction resulting.

This was repeated later on with similar effect. This is most interesting ⁱⁿ view of the controversy regarding the effects of compression of the aorta in cases of Post Partum Haemorrhage - it certainly favours that treatment.

My original series of tracings in support of this have been spoiled but the present tracing shows the above effect fairly clearly.

ACTION OF QUININE ON THE UTERUS.

The action of Quinine on the Uterus is the subject of a large number of memoirs and up till Cushny published tracings (Journal of Physiology, Vol. 35, 1906 - 07) showing its effect on the uterus, there was considerable doubt as to whether it was beneficial or not in labour. It is well recognised that abortion certainly occurs occasionally after its use in malaria, while in other cases labour pains may be ~~re~~ⁱⁿduced by Quinine. Many physicians use it during labour if the pains cease or if they seem too weak to expel the child. That this is ^arational method of treatment is shown by tracings in Plates XI to XIV. the unfailing reaction of increased uterine contractions following each injection of Quinine.

Another point is the increased excitability after Quinine as shown in Plate XIII. where the second dose of Quinine (quantity similar to the first) produces almost double the reaction.

That drugs affect the pregnant uterus much more readily than the non-pregnant and the virgin is well shown in Plate XIV and equally well is shown that the action/

action of Quinine is not confined to the pregnant but also affects the non-pregnant and to a less extent the virgin uterus.

From a study of these tracings it will be seen that the action of Quinine is of a more temporary nature than that of Ergot - hence Quinine should be used to increase the strength of the pains when they are weak and especially to help to expel the child - when a few strong pains may make all the difference both for patient and doctor.

The best dose would seem to be 5 - 10 grains repeated in a short time if necessary.

The exact nature of the action of Quinine is not known - it probably is a direct action on the uterine muscle.

ACTION OF VARIOUS ERGOT PREPARATIONS ON THE UTERUS.

- (1) (a) Extract Ergot. Liq. (B.P.)
- (2) (b) Inject. Ergot. Liq. (B.P.)
- (3) (c) Ergotinine Citrate. Burroughs, Welcome.
- (4) (d) Tanret's Ergotinine (Proprietary)
- (5) (e) Aseptic Ergot - Parke Davies (Proprietary)
- (6) (f) Ernutine - Burroughs, Welcome Proprietary.

These experiments with various preparations of Ergot were made, not to find out the physiological active principles and the physiological actions of these active principles; but to find what were the most active preparation of Ergot in common use and on what preparation one could most actively depend in general practice.

The physiological actions of Ergot have been most fully dealt with by H. H. Dale (Journal of Physiology Vol. 34 - 1900) and a full account of the past and present knowledge with the results of his numerous and complete experiments are given there.

Helme in his experiments with Ergot found many of his preparations quite inert and there is no doubt much of the so-called Ergot so freely given in obstetric/

as
 obstetric practice is of much value as a draught of water in so far as causing the uterus to contract is concerned.

The clinical evidence is of course necessarily indefinite but I find on enquiry at the Maternity Hospital a considerable doubt as to the exact value of much of their Ergot administration.

The first preparation used was the Liquid Extract of Ergot (B.P.) obtained from three different chemists - that from two small chemists was quite inert, large doses could be given with practically no effect. The other sample obtained from Duncan Flockhart was quite active, though of two different samples obtained from that firm one was appreciably more active than the other.

EXTRACT ERGOT. LIQ. (B.P.)

The long continued effect of Ergot on the uterine contraction is well shown in Plate 16 where Liquid Extract of Ergot was administered subcutaneously.

The action also well marked in the non-pregnant uterus is well shown in Plate 17, the same preparation being used. It is a well recognised fact that rabbits can/

can stand large doses of this drug and Plate 18 shows the effect of large doses given intravenously.

The conclusion therefore is that Ext. Ergot Liq. of the B.P. prepared by a reliable firm is of considerable value. The doubt that it may be inert is a serious drawback.

Once tested in this way I used Liq. Extract of Ergot as standard to compare other drugs. Ext. Gossypium Liq. is by some (authority see later) stated to be as powerful if not more powerful than Ergot - in Plates 19 and 20 a comparison is made of these drugs - and the tracings show much in favour of the Ergot. In Plate 21 the action of Ergot on the uterus of the pregnant cat is shown and the increased susceptibility of the cat's uterus to Ergot is well shown, much smaller doses of Ergot being required to produce quite a well marked effect compared to the rabbit.

Injectio. Ergot. Hypo. B.P.

The next preparation of Ergot used, was the official injection. This was found always active but again doses much above the usual therapeutic doses, had to be given to produce any effect. For example :-
In/

In Plate 21 , a non-pregnant cat required a dose corresponding to a normal therapeutic dose of 30 m.) to produce any effect at all.

ERGOTININE CITRATE. - gr.¹/100 Hypodermically.

This preparation had a well marked effect not so much in increasing uterine contractions as in the marked effect it had of raising the tone of the uterus. This effect is well seen in Plate 22. Again larger doses ^{than} corresponded to the usual therapeutic doses required to be given.

TANRET's ERGOTININE. m.5 - 10 Hypodermically.

A French preparation once largely used - said to contain the active principle of ergot - in doses, even much above the usual therapeutic dose, in both cats and rabbits this was practically inert even enormous doses produced a very slight effect. eg. 10 m. per kilo.

ASEPTIC ERGOT. -(Parke Davies - Proprietary)

Dose 5m. - 10 m. Hypodermically.

This preparation was active in rather larger doses than indicated. A rise of tone was a more marked feature of its result than an increase in contraction.

This is well shown in Plate 24 where it does not shine/

shine in comparison with the Liq. Extract of Ergot.

ERNUTIN. 5 - 10 m. hypodermically - Burroughs,
Welcome - Proprietary.

This preparation may be all that is claimed for it. I merely state that in my hands the results were an entire failure. This is shown in Plates 25 and 26 where excellent tracings of the Post Partum uterus are shown and the entire failure of the uterus to contract with large doses of Ernutin and the effect of a comparatively small dose of the Liq. Extract of Ergot is well shown.

Another sample was obtained and these results confirmed and typical tracings of its lack of any beneficial effect are shown on Plates 27 and 28.

SUMMARY.

Liq. Extract of Ergot - (B.P.)

An excellent preparation if given in full doses.

N.B.

Must be obtained fresh from a reliable firm who will give a guarantee that it has been tested and found active.

Injectio. Ergot. Hypodermica satisfactory -

Full doses again required.

Ext/

Ext. Gossypium Liq. - Not to be compared with Ergot. It does cause uterine contractions - Large doses required.

Ergotinine Citrate.

An excellent preparation - especially to raise tone of uterus. Full dosage required.

Tanret's Ergotinine.

An expensive comparatively valueless preparation.

Aseptic Ergot.

Action somewhat similar to Ergotinine Citrate - much larger dosage required.

Ernutine.

In all my experiments no action on uterus, using small or large dosage.

Ergot used as standard gave a marked effect. Two different samples were used and one can only conclude ^{that} I was unfortunate in my samples judging by the reliable tests through which the preparation is said to have passed before it left the maker - certainly not substantiated by my experiments.

CONCLUSION.

Ergot most valuable (^{drug} preparation) if given in full doses.

Most reliable Preparations. Liq. Extract of Ergot - Injecto. Ergot. Hypo. and Ergotinine Citrate.

ACTION OF VIBURNUM PRUNIFOLIUMON THE UTERUS.

This drug is largely given in threatened abortion and certainly it seems to exert a sedative action on the uterus as shown in Plate 29 and 31.

In Plate 29 is shown the effect of repeated doses on the pregnant uterus - the contractions certainly are diminished in volume but the most noticeable thing is the failure of the uterus to contract on injecting (Fig. 73) large doses of Ext. Ergot. Liq.

This is again illustrated in Plate 31, where the action of a large dose of Hydrastis before and after the injection of Viburnum Prunifolium is shown - the diminished effect of the second dose of Hydrastis is well marked.

Thus there would appear to be some justification for its use in threatened abortion but full doses would require to be given

ACTION OF HYDRASTIS ON THE UTERUS.

Hydrastis is said to cause rhythmic contraction of the uterus similar to those during labour. In Plates XXX. and XXXI are shown a series of tracings of the effect of Hydrastis on the uterus.

There were no rhythmical contractions induced, merely a more or less temporary increase in the contraction. The preparation used was Ext. Hydrastis Liq. B.P. (5 - 15 m.) but large doses required to be used to get much effect.

Hydrastine (the alkaloid) acted somewhat similarly, producing a more or less temporary contraction or series of contractions- it caused a certain degree of pallor of the uterus - due to the vasoconstriction but certainly did not cause the rhythmical contractions claimed for it.

ACTION OF DIGITALIS AND STROPHANTHUSON THE UTERUS.

Digitalis is said to be a Direct Emmenagogue but in no experiment did it cause actual uterine contractions. The feature of such an experiment was the enormous vaso-constriction that occurred, the uterus becoming quite pallid and apparently this vaso-constriction was the cause of what seemed to be more a rise of tone than a tetanic contraction. This is well shown in Plate XXXII.

In Plate XXXIII the action of Strophanthus is shown. It was found to be somewhat similar but there was never the same amount of vaso-constriction. In Fig. 86 the action of Strophanthus and Digitalis is compared in the non-pregnant uterus.

Digitalis would thus appear to be the best drug in conditions in which we wish to influence the vascularity of the uterus, e.g. in Chronic Venous Congestion.

ACTION OF ADRENALIN AND STRYCHNINE
ON THE UTERUS.

The action of Adrenalin is well known and the increased uterine contractions which ensue after its use are well shown in Fig. 87, Plate 34.

In Fig. 88 is shown the effect of Strychnine on the uterus. It is said to be an indirect emmenagogue but it would appear to be able to excite actual uterine contractions, probably by its stimulant action on the lumbar centre.

ACTION OF ALOES ON THE UTERUS.

Aloes is usually stated to be another example of an indirect Emmenagogue, its action being explained by saying that it caused hyperaemia of the uterus and other pelvic organs.

Cushny found that, using an old preparation of the Tincture Aloes, he got uterine contractions but not if he used a freshly prepared tincture.

In Plate XXXV is shown the effect of injection of various doses of Tinct. Aloes (B.P.), a preparation which had been bottled for 20 years and in large doses (See Fig. 91 and 92) it undoubtedly caused and increased uterine contractions.

ACTION OF AMMONIUM IODIDE AND AMMONIUM
CHLORIDE ON UTERINE CONTRACTIONS.

These ammonium salts have a very definite action on the uterus injected intravenously as shown in Plates 36 and 37, especially in the latter where the effect of gradually increasing doses of Ammonium Chloride is shown and proves Ammonium Chloride to have one of the most definite actions on the uterus.

ACTION OF CALCIUM SALTS ON UTERINE
CONTRACTIONS.

Calcium Chloride - (5 - 15 grs.)

The importance of Calcium in pregnancy and indeed in all phases of female genital activity has been shown by Blair Bell and the following tracings showing the effect of Calcium Chloride on Uterine contraction are of interest.

They confirm Blair Bell's conclusions.

- (1) No effect on virgin uterus.
- (2) Marked effect in increasing uterine contractions on pregnant uterus.
- (3) .01 gm. is most suitable dose = (10 grs. for an adult.

These results are shown in Plates 38 and 39.

Blair Bell's observations on the value of these salts in Amenorrhoea and Menorrhagia are well deserving clinical trial.

EFFECT OF GUAIAECUM ON UTERINE CONTRACTIONS.

Tinct. Guaiac. Ammon. B.P.

Mist. Guaiac. B.P.

Herman speaks so highly of Guaiacum in the treatment of Dysmenorrhoea that I was induced to try its intravenous injection - the preparations being diluted and filtered before injection into the veins.

In Plate 40 is shown the uterine contractions induced by the first preparation.

That this effect was not due to the Ammonia the B.P. Tincture contains, is shown in similar effects even more marked on using the Mistura Guaiaci. (B.P.) which contains Guaiac. Resin, Sugar, Gum Acacia and Cinnamon Water.

These results are well shown in Plates 41 and 42 and support the claim of Guaiacum to be considered a direct emmenagogue.

ACTION OF YOHIMBINE ON UTERINE CONTRACTIONS.

Yohimbine is at present used as an Aph^{ro}disiac with many satisfactory results.

A short paper has been published by Marshall and Jolly on the effects of repeated doses of this drug on the uterus, ~~etc.~~ increased vascularity and increased growth of the genital tract resulting, comparing, naked eye, animals so treated, with control animals.

In all cases in which it was used, the uterus flushed pink with blood and contractions tended to disappear. This increased vascularity only very slowly passed off.

This is shown in Plate 43, Fig. 109 is interesting in that for over an hour after the death of the animal slow uterine contractions occurred, gradually diminishing.

This abolishing of the uterine contractions is again illustrated in Fig. 110, Plate 44 and also in Fig. 113, Plate 45.

ACTION OF HARMALINE ON THE UTERUS.

I am indebted to Dr. J. A. Gunn, Edinburgh University for this drug. He, in working out the Pharmacology of this drug, found it to resemble in its actions to a certain extent Quinine.

As Quinine has such a marked effect on the uterus, Dr. Gunn suggested trying Harmaline. This in extremely small doses produced an enormous effect - the tetanus effect of such a small dose as .002 gm. and the increased contractions later is strikingly shown in Fig. 3, Plate 44, continuous tracings with Fig. 112, Plate 45.

Harmaline is the most active drug on the uterus of any tried, and clinically its use would appear to offer great possibilities. It is an African poison used as an abortifacient by the natives

EFFECT OF ACUAMBA ON UTERINE CONTRACTIONS.

"Acuamba" is another native abortifacient from the Gold Coast - it was obtained from Sir Thomas Fraser to whom the seeds had been sent - though sent to Kew they could not be identified. An extract of the seeds was made and its power to excite uterine contraction is well shown in Plate 46.

It rather resembles Strychnine in its action, see Fig. 88, Plate 34, which shows effect of Strychnine Hydrochloride on the same rabbit.

EFFECT OF HYOSCINE AND MORPHINE
ON UTERINE CONTRACTIONS.

This anaesthetic I used in several experiments and it did not appear to have any bad effect in reducing or weakening uterine contractions. This is an important point, as at the present time it is so largely used in labour. This is shown in Fig. 117. In Fig. 118 the uterine contractions are much reduced but the dose given is much larger than the usual dose

ACTION OF ANIMAL EXTRACTS ON UTERUS.

Ovarian - Placental - Foetal and Uterine made from Pregnant Rabbit about mid - term.

The animal was killed with chloroform and the abdomen at once opened. The ovaries were removed, minced finely and placed in a labelled capsule. In one cornua the uterine wall, over the foetal sacs was laid open and each foetus still in its membranes was shelled out.

The uterine wall thus obtained was minced up, placed in another labelled capsule. From the foetal sacs the placentae and finally the foetuses were separated, minced finely and placed in labelled capsules.

All these capsules were placed under a bell jar, over sulphuric acid and the air thoroughly exhausted.

After 24 hours the various organs were quite dry and hard and were easily powdered in a mortar - then Thymol Water was added and the various powders digested for 24 - 48 hours. Finally the various fluids were each filtered and the fluids evaporated to dryness in capsules in a drying chamber kept at a constant temperature of 37°C. - the various deposits kept in the capsules were the Extracts used.

EXTRACT OF UTERUS.

Extract made as described from wall of pregnant uterus.

This was the most powerful of the extracts made in the way described and require caution as regards dosage.

Comparatively small doses caused death in several experiments. It was found to be a very active agent in causing uterine contractions - the virgin, non-pregnant and pregnant uterus - all reacting powerfully to it.

These results are fully illustrated in Plates 48 to 51.

These experiments with extract of uterus are interesting for the only previous work connected in any way with them is that by Blair Bell who used uterine secretion got by ligating the uterine cornua of non-pregnant rabbits and using the fluid collected.

His results are much similar and my results confirm his conclusion that such a secretion would resemble in its action an active extract prepared from the whole organ."

FOETAL AND OVARIAN EXTRACTS.

Extracts made as described.

Owing to an unfortunate accident most of my tracings showing effect of injection of these extracts were spoiled.

These results were a little indefinite but tended to show that these extracts did not increase uterine contractions.

With Extract of Foetus - Figs. 128 and 130, Plate 52 a slight fall of tone always occurred immediately after injecting and such an injection usually produced a slight convulsion as shown in Fig. 130 - it had apparently no effect on the pregnant uterus.

With Ovarian Extract there was no effect on the virgin and non-pregnant uterus as shown in Fig. 129 while in its effect on the pregnant uterus the conclusion of Blair Bell that it has a restraining influence on uterine contractions is probably correct, and certainly in my few tracings, will show that it does not cause uterine contractions.

N.B.

This ovarian extract was made from the whole organ including Corpora Lutea.

PLACENTAL EXTRACT.

Placental Extract was supposed by Dixon and Taylor who did a large amount of work with it, to contain a specific substance which caused uterine contractions.

This claim of the specificity of placental extract was actually put forward by them but since then doubt has been cast upon this point and the effects they describe are said to be produced by products of decomposition their extract has been found to contain.

The Extract of Placenta made in the manner already described could not possibly have undergone decomposition, and my experiments would appear to support the latter view as no contractions were induced even in the pregnant uterus on injecting varying doses of this Placental Extract.

This lack of an increased uterine contraction is shown in Plate 53 - shown as typical of a series in which none of the results claimed for Placental Extract were obtained.

PITUITARY EXTRACT.

Pituitary Extract - (Burroughs, Welcome & Co.,)

The marked effect, which this extract made from the fresh infundibulum has in increasing uterine ^{of} contractions, has been shown in several papers, late (Blair Bell and Dale) and its enormous power in inducing uterine contractions is shown in Plate 54.

N.B.

The enormous effect which it also has on the intestine was strikingly shown, the coils of intestine being thrown almost into convulsions by the waves of peristalsis, involving both longitudinal and circular muscle fibres

THYROID.

Liq. Thyroidei (B.P.)

There was no effect on the virgin uterus but quite a marked effect was found on the pregnant uterus as shown in Plates 55 and 56.

These results agree with those of Blair Bell, who found also that the Blood Pressure always fell slightly and also noted tendency to convulsions on repeated doses.

ADRENALIN.

See Plate 34.

In conclusion I cannot close without first expressing my sincere thanks to Professor Sir Thomas R. Fraser, not only for the laboratory facilities which he so kindly offered me but above all for his kindly interest and stimulating criticism during the entire course of my Research.

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