THE ACTION OF DRUGS ON MAMMALIAN UTERUS

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THE NERVOUS MECHANISM OF THE UTERUS

The literature on the nervous mechanism of the uterus is fairly complete. In 1858 Lee demonstrated the ganglia in the peripheral plexus surrounding the cervix uteri; and in 1867 Frankenhaeuser described the anatomy of the hypogastric nerve and its associated plexuses; he also demonstrated microscopically terminal, non-medullated and nucleated nerve fibrils situated between the muscle fibres of the uterus and ending in the nuclei of the muscle cells. The descriptive anatomy was verified in 1895 by Langley and Anderson,¹ who stimulated the lumbar roots which supply the uterus. Working chiefly on cats and rabbits, they showed that the uterus is supplied solely by the true sympathetic system. The sacral roots and pelvic nerve do not enter into the composition of the uterine plexus.

Electrical stimulation of the hypogastric nerve, in the rabbit, always produces well-marked contraction of the uterus associated with vaso constriction.

In some cats such stimulation produces contraction of the uterus, while in others relaxation results.

Dale² has shown that the use of ergotoxine adds a further facility to the study of this subject, by paralysing the augmentory fibres while leaving the inhibitory fibres untouched. Stimulation of the hypogastric nerve after the administration of ergotoxine produces inhibition of the uterus in all animals, thus demonstrating the presence of utero-inhibitory fibres in addition to utero-augmentory fibres in this nerve. The relative proportion of these two sets of nerve fibres will be referred to when dealing with the action of adrenalin,

1. *Journ. Physiol.*, Vol. XIX, 1895.

2. Dale, *Journ. Physiol.*, Vol. XXXIV, 1906.

and the presence of peripheral nerve cells will be considered with the action of nicotine.

The present investigations have been made entirely on the isolated uterus; the attention has been confined solely to those drugs which act either on the uterine muscle or on some portion of the peripheral nervous mechanism. Under these conditions no interference is possible from alterations in blood pressure or from central excitation.

METHOD

An isolated mammalian uterus kept in Ringer's solution at a temperature between 30° C. and 38° C., and supplied with oxygen, will live and continue its rhythmical movements for several hours; if it be hung up and attached to a lever these movements can be recorded.

There are, however, certain difficulties to contend with in all investigations on isolated mammalian organs. The chief of these is the necessity for artificial heating. This is especially important in the case of the uterus, because its movements are extremely sensitive to very slight alterations of temperature. It was found, however, that the simple method of applying a bunsen to the end of a metal bar passed through the water bath surrounding the beaker of Ringer's solution was the most satisfactory. Experience soon showed the amount of gas necessary to keep the bunsen at such a height that the Ringer's solution should record a constant temperature of 37.5° C.

The method adopted for recording the movements was as follows:—The upper ends of both cornua were fixed to a lever by means of a thread tied to the ovaries, while the upper end of the vagina, which was detached with the uterus, was fixed to the bottom of the beaker, in which the viscus was perfused with 300 c.c. of Ringer's solution. Sometimes the cornua were separated, the division being made through the longitudinal axis of the vagina. This did not interfere with the activity of the uterus, while it allowed of control experiments being performed on the same animal. A suitable tonus is imparted to the uterus by a carefully-adjudged weight,

Most of the experiments were performed on the uteri of cats and rabbits. Other animals, the bitch and guinea pig, were occasionally used for control purposes. It may be stated generally, that the effect of drugs was similar in all animals used. The animals were killed usually by pithing.

The drugs were added directly to the Ringer's solution.

The oxygen was supplied at a continuous rate of about seventy small bubbles a minute.

NORMAL MOVEMENTS

The normal movements of the uterus show considerable variations in different animals, and the degree of activity in responding to physical and chemical stimuli is equally inconstant. In the pregnant uterus, as a rule, the movements are much more pronounced and vigorous than in the non-pregnant uterus. This is principally due to the large hypertrophy of the organ in this condition. On the other hand, the poorly-developed uterus of young animals never gives good results.

The regularity of the movements is disturbed by alterations in the temperature, and sometimes such small changes as 0.2°C . or 0.3°C . produce a definite alteration in the tone of the muscle.

Alterations in the rate of oxygen supply also has an appreciable effect on the uniformity of the rhythm.

In the absence of oxygen the uterus remains inert, and when the oxygen supply is deficient the spontaneous movements are feeble.

One uterus may respond well to certain drugs, while another equally well developed uterus of a similar animal, and under similar conditions, may respond hardly at all. This has led me to suppose that the period of the menstrual cycle at which the experiment is performed may influence the results.

Pregnancy has a special effect on the action of drugs on the uterus. Adrenalin, for instance, by stimulating the sympathetic, relaxes the non-pregnant uterus of a cat, but contracts a pregnant one. This may be due to a positive increase in the number of augmentory fibres during pregnancy, or to a change in the muscle

cells which renders them more responsive to impulses from the augmentory fibres. The uterus of a cat produces the most uniform movements, and, therefore, gives the most satisfactory results. The guinea pig's uterus, besides being fragile, is very erratic, and is the most sensitive to variations of temperature.

The commonest type in all animals is a continuous see-saw movement without intervals. Sometimes a fuller relaxation or a stronger contraction would alternate at regular intervals with smaller movements, at a mean tonus. Or the smaller movements may be absent, and a stage of quiescence, lasting about two or three minutes, is broken by a strong contraction comprising the whole or greater part of the contractile power of the muscle. In these cases the tonus, of course, cannot be altered except by diminution in the amplitude of the contractions. Another type, seen chiefly in the guinea pig's uterus, is a strong contraction followed by a gradual relaxation broken at intervals by small secondary contractions.

These spontaneous movements sometimes commenced as soon as the uterus was attached to the lever. They were usually visible in the animal before removal. Sometimes, however, the shock of removal caused a cessation of the movements, which lasted for a variable length of time, and a careful adjustment of the tonus by alteration of the weights was necessary to initiate them.

A rise of temperature, or an increase or decrease of the oxygen supply, in some cases was sufficient to start them.

In a few uteri, artificial alterations of tonus, produced by moving the lever up and down with the hand, was necessary to initiate spontaneous movements. When once started they usually continued for many hours under good conditions.

EFFECTS OF ACIDS AND ALKALIES

Alkalies in small amount are essential for the spontaneous movements of the uterus, and for keeping the organ in the best physiological condition. When the alkali is increased the effect is to augment the tonus, while the spontaneous movements gradually diminish, until death of the muscle ultimately occurs at a high tonus. Diminution

in alkalinity of the perfusion fluid lowers the tone of the uterus. When the acid reaction is obtained, the movements are gradually arrested. If the solution be suddenly rendered strongly acid, then a forcible contraction occurs, and the muscle dies in contraction. If, however, the acidity be at once neutralised, the tone and movements may recover. (Fig. 1.) These results may be compared with the well-known effect of acids and alkalies on striped muscle and on the heart.

DRUGS ACTING ON THE NERVOUS MECHANISM

In the first series the following drugs are considered :—Pilocarpine, physostigmine, and colchicine. These drugs are all stated to act on 'nerve endings.' They cause augmentation of peristalsis in the small intestine, having a greater affinity for the vagus than for the splanchnics. They ignore the sympathetic supply to the iris and submaxillary gland, and have only a very slight action on the cardiac sympathetic.

After atropine—which paralyses the vagus, or, at all events, those portions of it which are excited by the drugs under consideration, while leaving the sympathetic nerve endings unaffected or only very slightly affected—these drugs are still unable to produce inhibition of peristalsis in the small intestine, showing, apparently, that they do not act on the splanchnic fibres. These drugs do not apparently all act on the same parts of the nerve endings. Physostigmine is capable of constricting the iris after atropine, but not after nicotine. The converse is the case with pilocarpine.¹

In considering the action of these drugs on the uterus, it is necessary to remember that both augmentory and inhibitory fibres are supplied by the sympathetic, and that the relative proportion of these two sets of fibres varies in different uteri, the preponderating set being readily ascertained by means of adrenalin, as will be described later. By analogy with the intestine, one would expect that the action of this group of drugs would be slight; it would be exerted on both sets of fibres equally, and the result would depend, therefore, upon the predominating set.

1. Dixon and Malden, *Journ. Physiol.*, Vol. XXXVII, 1908.

Fig. 1.—Uterus of cat, showing action of acid and alkali. HCl given at the first mark, NaHCO_3 given at the second mark. Upstroke=contraction. Time=minutes.

Fig. 2.—Non-pregnant uterus of cat, showing action of pilocarpine (10 mgms.). Upstroke=contraction. Time=minutes.

Fig. 3.—Uterus of cat, containing four ova. Colchicine (1.5 mgms.) given at the first arrow, and repeated at the second, raised the tone of the uterus. Atropine (1 mgm. at the third arrow, and 2 mgms. at the fourth) still further increased the tonus. Time=minutes.

Fig. 4.—Non-pregnant uterus of cat. Adrenalin (1-1000 m i) given at the first arrow. The drum was stopped for ten minutes, until the spontaneous movements had recovered, and then nicotine (10 mgms.) was given at the second arrow, and produced relaxation followed by contraction. Adrenalin (1-1000 m i) given at the third arrow produced contraction of the uterus. Time=minutes.

Pilocarpine.—To a certain extent this expectation is realised with regard to pilocarpine. The most frequent result with this drug is augmentation of tone with some increase in the amplitude of the spontaneous contractions. (Fig. 2.) This effect is not well maintained.

Relaxation of uterine muscle is very difficult to obtain with pilocarpine. I have, however, observed it after paralysing the augmentory fibres with ergotoxine. In one experiment on a pregnant uterus of a cat, the two cornua were separated, and one was kept in a solution of ergotoxine for half an hour. Pilocarpine produced slight relaxation in the ergotised cornu, and slight augmentation in the other cornu.

The action of this drug on the uterus is completely antagonised by atropine.

Pilocarpine, therefore, has a special affinity for the augmentor fibres of the sympathetic, since in the non-pregnant cat, *i.e.*, when the development of inhibitory fibres is maximum, this drug still augments the movements. The action is clearly on nerve endings, because it is eliminated by atropine, and, moreover, ergotoxine, which paralyses augmentory nerve endings, converts the stimulant action of pilocarpine into a very mild inhibitory one.

Physostigmine.—Physostigmine always augments the movements and the tone of the uterus. Its effect is better maintained than is that produced by pilocarpine, and is produced with smaller doses. This was the case with all animals used, and under all conditions. This augmentation occurred after atropine, and was not apparently influenced by atropine. Physostigmine also produces its effect after nicotine.

This drug is considered to produce a direct stimulant effect on plain muscle in addition to its action on nerve endings (Harnack). It would be expected that this additional property would have greater influence on the uterus than one which depended on sympathetic nerve endings. This would account for its action being better maintained than that of pilocarpine as well as for the fact that its effect is produced after atropine and nicotine.

Colchicine.—Colchicine is purely an augmentor of uterine muscle, and this effect occurs chiefly in rabbits where the augmentory fibres predominate both in pregnancy and non-pregnancy. This augmentation is considerably greater than that produced by pilocarpine. In the cat's uterus the action varies with the condition. In the case of the pregnant uterus in which adrenalin augments the movements, colchicine also raises the tone, whilst in the non-pregnant condition this drug has very little action. An inhibitory effect was never obtained by colchicine even after a previous dose of ergotoxine.

Large doses of colchicine destroy the movements of the muscle. The action of colchicine on the uterus is not antagonised, but rather increased by atropine. (Fig. 3.) This is interesting in view of the fact that atropine antagonises the effect of colchicine on the heart, respiration, and intestines.¹ The action of colchicine on the uterus is, however, prevented by ergotoxine, and, therefore, is produced on the augmentory nerve endings.

Adrenalin.—It has been already abundantly shown that adrenalin excites all sympathetic nerve endings, and that its effect on the uterus in all cases corresponds exactly with that obtained by electrical stimulation of the hypogastric nerve.²

It has been further shown that the augmentor fibres of the sympathetic nerve can be paralysed by ergotoxine so that a pregnant uterus, which under ordinary conditions actively contracts with adrenalin, after ergotoxine becomes relaxed.³

As I shall show later, my experiments demonstrate conclusively that nicotine also influences the action of this drug so that if adrenalin be allowed to act upon the non-pregnant uterus of a cat, instead of inducing relaxation of muscle as normally, after nicotine it gives rise to marked contraction. The action of adrenalin is of great importance as a means of determining the action of the sympathetic nerves. It has been of much value in ascertaining the relative proportion of the augmentory and inhibitory nerve fibres to the uterus.

1. Dixon and Malden, *Journ. Physiol.*, Vol. XXXVII, 1908.

2. Elliott, *Journ. Physiol.*, Vol. XXXII, 1905.

3. Dale, *Journ. Physiol.*, Vol. XXXIV, 1906.

The augmentor fibres invariably predominate in the rabbit's uterus under all conditions, so that adrenalin produces a rise of tonus. By first paralysing these augmentor fibres with ergotoxine, adrenalin can be used to demonstrate the presence of inhibitory fibres,¹ since under these conditions the uterus relaxes both to electrical stimulation of the sympathetic nerve, and to the administration of adrenalin. In the cat, the results vary with the condition of the uterus. Adrenalin raises the tone of a pregnant uterus, except after ergotoxine. Cushny believes that inhibition by adrenalin occurs in cats only with virgin uteri, but I have obtained it in the uteri of two cats during lactation. Subinvolution of the uterus was, in these cases, complete. In every non-pregnant cat in which adrenalin has been given at the onset of an experiment, I have obtained relaxation of the uterus.

The reverse effect, however, is sometimes obtained on the non-pregnant cat by the use of adrenalin after the administration of other drugs. In three experiments on these animals adrenalin augmented the tonus of the uterus after the administration of nicotine, when the initial effect of adrenalin had been inhibition. In two of these, nicotine was the only drug given previously. In two other experiments, although the initial effect of adrenalin had not been determined, I obtained a rise of tonus in a non-pregnant cat's uterus with this drug after previously administering pilocarpine, atropine, and nicotine. Pilocarpine and atropine alone do not produce this reversion. It appears, therefore, that nicotine has a distinct power to reverse, in some way, this action of adrenalin on the uterus. (Fig. 4.) As adrenalin acts on nerve endings, this power of nicotine must be exerted either on these nerve endings or on the muscle itself. It is not a paralysis of the inhibitory nerve endings, for if ergotoxine be added after the reversion has been effected, the adrenalin action is once more reversed, and produces inhibition.

The relation of nerve endings to muscle is, as yet, insufficiently understood. Nicotine alters this relation so that the muscle is rendered more responsive to impulses derived from the augmentor

1. In one experiment adrenalin produced no result after ergotoxine. This occurred in the pregnant uterus of a rabbit at full term.

nerves, thus turning the balance in their favour. This reversion is not always effected by nicotine; possibly when it does not occur the inhibitory nerves are very greatly predominant.

Stewart,¹ when discussing the effect of stimulation of the hypogastric and pelvic nerves on the bladder, incidentally makes the following statement:—‘Nicotine seemed to affect the proportion between the rise and fall in the internal pressure of the bladder produced by stimulation of the hypogastric.’

In one experiment adrenalin produced augmentation in the non-pregnant uterus of a cat to which cocaine had been previously administered. The initial effect in this experiment, however, had not been ascertained.

Whether adrenalin produces contraction or relaxation of the uterus, its effect soon passes off. A repetition of the dose then produces the same effect. This is in contrast to the effect produced by nicotine, where the return to the normal tonus is due to depression or paralysis of the nerve following on the stimulation.

Inhibition of the uterine movements by adrenalin usually results in relaxation of the muscle in addition to cessation of movements. In some cases relaxation is absent. I presume that in these cases the spontaneous movements were occurring originally at full relaxation, so that adrenalin was unable to relax the muscle any more. Thus the action of adrenalin is to a certain extent a measure of the tonus at which the spontaneous movements are produced.

Cocaine.—Cocaine augments the tonus of the uterus of both cat and rabbit in all conditions. (Fig. 5.) It probably acts on the sympathetic nerve endings, the effect being analogous to the contraction of the dilator iridis, the inhibition of intestinal peristalsis, and the acceleration of the heart also produced by this drug, evidence as to the seat of action in those cases being fairly complete. Cocaine never relaxes uterine muscle. Ergotoxine does not influence its action, and this might be regarded as evidence that it acts on the muscle, but nerve endings are now believed to be of such a composite nature that it is possible for ergotoxine to antagonise adrenalin while

1. *American Journal of Physiology*, Vol. II, p. 190, 1899.

not interfering with that portion of the nerve ending on which cocaine acts. Cocaine, then, whilst increasing uterine tonus by exciting sympathetic nerve endings, acts differently from adrenalin, because its effect is not removed by ergotoxine. It shows none of the characteristics of a true muscle poison.

Nicotine.—Langley and Anderson,¹ in their experiments on cats and rabbits, showed that some of the sympathetic fibres to the uterus passed by the inferior mesenteric ganglia, and proceeded to more peripheral ganglia on the course of the hypogastric nerve. They also showed that nicotine paralysed these peripheral ganglia as well as the more central ganglia.

Nerve cells are also present in the ganglionated plexus on the walls of the uterus and vagina. They are under the peritoneal coat of the viscus, and were of necessity removed with the uterus in all my experiments.

On an isolated uterus of a cat previously ergotised so that only the inhibitor fibres were responsive, nicotine produced immediate relaxation followed by a gradual recovery of the tonus and of the spontaneous movements. (Fig. 6.) A repetition of the dose produced no further effect, while adrenalin administered after the nicotine still produced its usual action. Nicotine had presumably first stimulated and then paralysed some other more central part of the peripheral inhibitory plexus than that upon which adrenalin acts. A similar result can be obtained with nicotine on an isolated coil of small intestine in which also peripheral nerve cells are present. It seems, therefore, that when nicotine produces a result on isolated viscera that receive their nerve supply from the sympathetic, its action is mainly on peripheral nerve cells. This action is identical with that obtained on more central ganglia by intravenous injection of nicotine in intact animals, viz., stimulation followed by paralysis. This fully explains the result obtained with nicotine on the utero-inhibitory nerves as demonstrated on the ergotised uterus. There is no means of paralysing the inhibitors while leaving the augmentors untouched in order to demonstrate the action of nicotine on the augmentors.

1. *Journ. Physiol.*, Vol. XIX, 1895.

Fig. 5.—Non-pregnant uterus of cat. Cocaine hydrochloride mgms. 1, 2 and 4 given respectively at the first three arrows. Adrenalin given at the fourth arrow produced contraction of the uterus. Time = minutes.

Fig. 6.—Non-pregnant uterus of cat previously ergotised to paralyse the augmentor fibres. Nicotine (10 mgms.) given at the first arrow, and repeated at the second. This shows stimulation followed by paralysis of the inhibitor nerves. The lever moves down during relaxation of the uterus. Time = minutes.

Fig. 7.—Non-pregnant uterus of cat. Nicotine (10 mgms.) produced relaxation of the uterus followed by contraction. Time = minutes. The lever passed below the level of the drum during relaxation of the uterus.

Fig. 8.—Uterus of cat. Action of ergotoxin (4 mgms.). Time = minutes.

Fig. 10.—Uterus of rabbit, containing six ova. Action of tinct. strophanthus (0.6 c.c.). Time = minutes. Upstroke = contraction.

Fig. 9.—Uterus of guinea pig. Action of BaCl_2 (8 mgms.). Previous to administration of this drug no spontaneous movements were present.

Fig. 11.—Uterus of rabbit. Action of quinine hydrochloride (2 mgms.). Time = minutes.

The action of nicotine on the uterus, in which both sets of nerves are responsive, is more difficult to explain. To a certain extent it depends, like that of adrenalin, on the predominant set. Fig. 7 represents the result obtained with a non-pregnant uterus of a cat, in which adrenalin produced decided relaxation. It will be noticed that nicotine at first produced relaxation as in the ergotised uterus, and this was followed, not by a gradual recovery, as in the former experiment, but by a sharp contraction. The spontaneous movements then recommenced at a higher tonus.

In another experiment (Fig. 4) on a non-pregnant cat, the action of adrenalin was first determined. The relaxation of the uterus which it produced was not great, probably because the muscle was nearly fully relaxed at the time the adrenalin was given. When the spontaneous movements returned 10 mgms. of nicotine were given, and produced relaxation equal in extent to that produced by adrenalin, but lasting only a short time. A strong contraction of the uterus then followed, succeeded by spontaneous movements at a relatively high tonus. The initial relaxation of the uterus is not present in all non-pregnant cats.

In the pregnant uterus of cats, and in the rabbit's uterus, in both of which the augmentory fibres predominate, and in the non-pregnant uterus of some cats, nicotine produces an initial contraction followed by exaggerated spontaneous movements at a high tonus. Relaxation is not produced by nicotine in these uteri.

Apocodeine prevents the stimulant action of nicotine on the uterus, in doses not sufficient to destroy the action of adrenalin.

I have already referred to the power of nicotine to reverse the action of adrenalin from inhibition to augmentation of the uterine movements. I have shown also that this property of nicotine cannot be explained on the ground that it paralyses inhibitory nerve cells, but that it is due to some more peripheral change in the relation of augmentory nerve endings to the muscle by which the latter is rendered more responsive to augmentory impulses. I have shown, also, that in those uteri in which the inhibitory nerves predominate, the nerve-cell excitation produced by nicotine, which at first results

in relaxation of the muscle, later produces contraction, and that finally the spontaneous movements continue at a higher tonus than formerly. I believe that this additional action of nicotine, in virtue of which it increases the irritability of augmentory nerve endings, accounts for all the three effects just enumerated, since none of them occur after ergotoxine, which paralyses these nerve endings.

It has been stated that nicotine stimulates plain muscle directly. Wertheimer and Colas attempted to show that nicotine stimulated the heart muscle directly, because it quickened the beat in an atropinised animal from which the cardiac sympathetic ganglia had been removed; Dixon¹ has shown that this effect is not produced if apocodeine be previously injected.

These experiments appear to show that nicotine acts on peripheral nerve cells: it stimulates both augmentors and inhibitors, and the stimulation is followed by depression of the nerve cells. When the inhibitory fibres predominate relaxation of the uterus is produced, but is followed by contraction and continuation of the movements at a higher tonus. It is clear that a comparatively small cause can alter the relative influence of the augmentor and inhibitory nerve fibres in the uterus. Pregnancy increases the influence of the augmentors, and nicotine exerts a like effect. Since nicotine does not paralyse the inhibitory nerve endings, it can only be supposed that it produces this effect by increasing the irritability of the augmentor nerve endings or of the muscle; the evidence is in favour of the former. This additional action of nicotine is on nerve endings because it influences the action of adrenalin.

Apocodeine prevents the initial stimulant action of nicotine on the uterine nerve cells. The spontaneous movements of the uterus can be revived by adrenalin after partial suppression by apocodeine.

Atropine antagonises the action of pilocarpine on the uterus, as on all other viscera, but it does not prevent the action of nicotine and adrenalin. Langley and Anderson have shown that atropine does not interfere with the results of electrical stimulation of the sympathetic to the uterus.

1. *Journ. Physiol.*, Vol. XXX, p. 105; 1903.

Given alone, atropine sometimes raises the tonus of the uterus. This effect is seen also when atropinè is given after colchicine. (Fig. 3.)

It is thus evident that if atropine acts on nerve endings in the uterus, this action must be very slight, and is chiefly exerted on that portion of them upon which pilocarpine acts.

DRUGS ACTING ON PLAIN MUSCLE DIRECTLY

Those drugs which act on plain muscle fibre directly naturally form an important group when dealing with such a muscular organ as the uterus. Many of the so-called abortifacients are included among these drugs. They act alike on all plain muscle fibre throughout the body, and are regarded as muscle poisons.

Those which in moderate doses stimulate the muscle are:—Strophanthus, squills, digitalis, apocynum, barium, lead, ergot, and quinine. Others destroy the movements. These are alcohol, chloroform, chloral, magnesium sulphate, hydrocyanic acid, and nitrites. The characteristic effect of stimulant muscle poisons is, besides strengthening the spontaneous contractions, to cause a considerable rise of tonus. The effect is better maintained than similar ones produced by drugs acting on the nervous mechanisms. Four milligrammes of ergotoxine (Fig. 8) maintained an increased peristalsis and tonus for three-quarters of an hour before the effect began to subside. Twenty-four milligrammes of barium chloride (Fig. 9) will continue its effect for several hours, and ultimately cause the death of the muscle. Strophanthus produces an equally powerful effect. (Fig. 10.) Quinine, although causing a great initial increase of tonus, does not maintain it so well. (Fig. 11.) Squills soon begins to destroy the spontaneous movements while maintaining the increased tonus. Digitalis is much less powerful. The tincture¹ of digitalis in this respect appears to have only one-tenth of the toxicity of the tinctures of strophanthus or squills. Apocynum produces a rise of tonus only. The spontaneous movements are destroyed by small doses of this drug.

Lead produced no results in my earlier experiments. In these

1. When the tinctures have been used, the alcohol has always been previously removed by evaporation.

the peritoneal covering of the uterus was undivided, and the muscle not directly exposed to the perfusion fluid, and was, no doubt, protected by an impervious coat of lead albuminate. Later, I divided the uterine wall so as to permit access of the fluid to the muscle fibres and into the interior of the uterus. I then obtained a powerful rise of tonus with lead, with death of the muscle in systole.

On increasing the doses of these drugs above that which produces the most beneficial results, the spontaneous movements begin to disappear, and finally the muscle dies in systole. Small doses of apocynum are sufficient to produce diminution of these movements; 0.2 c.c. of the tincture of apocynum produced a similar result to 0.4 c.c. of tincture of squills and 4 c.c. of tincture of digitalis. Apocynum, it should be remembered, is perhaps the most irritant poisonous member of the digitalis group of drugs—at least so far as its action on general tissues is concerned.

The results obtained with the digitalis group are comparable with their recognised action on the heart.

The muscle depressants need only a brief allusion. They are important chiefly as they include certain anaesthetics and narcotics used in midwifery.

Chloroform.—It was found that in animals anaesthetised by chloroform until the corneal reflex was abolished and then killed by bleeding, the uterus was just as active on removal as that from a pithed animal.

If the animal was killed by chloroform, and especially if this was done rapidly by a large initial dose, the spontaneous movements of the uterus were entirely suppressed, and the muscle fibres were fully relaxed; 0.05 per cent. of chloroform in the perfusion fluid arrested the uterine movements and lowered the tone of the muscle.

Chloral also relaxed the uterine muscle in much the same way.

Alcohol.—Drugs administered in alcoholic solution never produced satisfactory results.

One cubic centimetre of absolute alcohol added to the perfusion fluid, making a 0.3 or 0.4 per cent. solution, arrested the movements of the uterus, and produced relaxation of the muscle,

Hydrocyanic acid and magnesium sulphate at once destroy the uterine movements. Amyl nitrite produces a temporary depression.

The muscle poisons are more powerful in their action on the uterus than those drugs which act on the nervous mechanism. The direct muscle stimulants produce, as the principal feature of their action, a large and well-maintained rise of tone. The digitalis group are all uterine stimulants; strophanthus in this respect comparing favourably with ergot. Barium also has a powerful action on the uterus.

CONCLUSION

It will be observed from these experiments that the reaction of the uterus to drugs is compatible with its nature as a plain muscular organ supplied by the sympathetic nerve.

It must be remembered that both utero-inhibitory and utero-augmentory fibres are supplied by the sympathetic system, and both may be stimulated by the same drug. The transformation of the uterus during pregnancy may alter the relative influence of the two sets of fibres; nicotine appears to produce a similar change in the nervous mechanism.

I have great pleasure in acknowledging my indebtedness to Dr. W. E. Dixon for many valuable suggestions.