THE ACTION OF DRUGS ON THE UTERUS

By N. C. Sharpe, B.A., M.B.

Fellow in Pharmacology at the University of Toronto

THE marked advance in our knowledge of the pharmacology of the uterus has led to a long series of experiments being carried out in this department, which were in part designed to control the teaching, and in part to serve as demonstrations for its students. The material thus gathered has served as the basis of the present paper. The action of drugs on the uterus must now be considered from our knowledge of the physiological properties of the uterine muscle. It must be the endeavour to put this clearly before our readers in order that the action of drugs may logically follow.

The uterus is continually undergoing slow rhythmic movements. As usually observed, these consist of contractions of the circular and longitudinal muscular layers. These contractions may be observed in the intact animal, and also in the excised organ when perfused—i.e., when an artificial blood consisting of an oxygenated saline is run through its vessels, or when the organ is placed in a bath of the same solution. The power to execute these movements, therefore, resides in the organ itself. Usually they are not great in excursion or in strength. They are increased at the menstrual period. Undue strength of these contractions probably accounts for the type of dysmenorrhœa often observed in nervous working-girls, in which there are sharp rhythmic pains.

The contractions change in character as pregnancy occurs. In the early stages, they seem more active; they become slower and less frequent as pregnancy advances, but increase in strength till, at full term, the true labour pains occur. After the expulsion of the fœtus they are again not so marked, until the secondary pains expel the placenta. The movements continue during the period of involution, and, indeed, our observations confirm those of Cushny,[1] who states that they are more active then than before labour.

The problems connected with the nervous control of the uterus are as yet not completely decided. It receives fibres from the gangliated cord of the sympathetic. This supply arises from the

Read before the Ontario Medical Association, May 23rd, 1912.

roots between the last thoracic and the fifth lumbar—varying somewhat in different animals—and passes through the white rami communicantes to the ganglia, thence to the inferior mesenteric ganglion, and from there, via the hypogastric, to the uterus. Stimulation of these fibres causes contraction of the uterine arterioles, and relaxation followed by contraction of the uterine musculature in the non-pregnant cat, contraction in the pregnant cat and in the rabbit, whether pregnant or non-pregnant. The fibres pass to both circular and longitudinal coats. It is on these sympathetic endings that adrenalin and ergot act.

It also seems probable that the organ receives a nervous supply from the nervi erigentes, or sacral pelvic nerves, as well, as do the other organs of the pelvis, bladder, rectum, and genitals. Langley and Anderson[2] state that these sacral nerves, which arise from the second to fourth lumber roots, send neither motor nor inhibitory fibres to the uterus, and that those observers who have reported results from the stimulation of them, have stimulated sympathetic nerves as well. Pilocarpine and atropine, which act elsewhere on sacral nerves, exhibit characteristic analogous actions on the uterus. In our experiments they have exercised this characteristic action on the excised organ, so that their action cannot, as is suggested by Dale and Laidlaw,[3] be due to their action on the adrenal gland, increasing or decreasing its characteristic secretion. Pilocarpine increases the rate and strength of the contractions when these are present, or causes them to appear if not already visible. Cushny[4] states that the characteristic effect of pilocarpine varies with the physiological state of the organ, and parallels that of hypogastric stimulation. Pilocarpine nearly always causes an increase in the tone of the uterus, and this effect is promptly neutralized by atropine.

The uterine nerves are undoubtedly connected with a centre in the lumbar region of the cord, and through it with the cerebrum. As is well known, emotions often markedly affect the uterine movements. The action of morphine and anæsthetics, when used to decrease the uterine movements, probably produce their effects through these centres. Drastic purgatives, and other irritants to the intestinal canal, probably produce their effects on the uterus reflexly through the lumbar centre, owing to the congestion that they set up. Langley and Anderson noted that, in animals with a bicornuate uterus, a stimulus applied to one horn not infrequently led to a contraction in the horn of the opposite side.

From the standpoint of therapeutics there are two properties of uterine muscle which are of fundamental importance, tone and contractility. When drugs are given for their action on the uterus,

the desire is to increase or decrease either one or both of these properties. Tone may best be defined as that state of partial contraction in which a muscle normally is, and depends, in the case of unstriped muscle, probably upon its chemical state. At all events, we know that the action of certain drugs which act upon it do change its length, and also the ease with which it can be stretched. After the uterine muscle has completed a contraction, the pressure of the contents within it is the important factor in causing the muscle to regain its original length; the greater this pressure the greater and quicker the relaxation. But the extent to which such a relaxation takes place, whether the pressure can, in other words, cause it to regain or surpass its previous length, depends upon the tone of the muscle. When the tone is low it is easy for the pressure to cause it to regain the length it had before the contraction began, or, if the tone has decreased, the same pressure will tend to stretch the muscle to an even greater extent. But with increase in tone a greater pressure than before will be needed to bring it to its original length. After the expulsion of the fœtus the uterus should contract firmly, and its tone should rapidly increase, and, as the pressure within should be slight, but slight relaxation should occur. If, however, the tone be poor, the slight pressure exerted by the blood oozing from the placental site will be sufficient to bring about relaxation, and each step in relaxation will lead to increase in hæmorrhage.

The object in giving drugs before labour is complete, must be to increase the tone, so that the uterine wall remains closely applied to the child in its passage through the pelvis, and, at the same time, to increase the force and frequency of the uterine movements, so that the bag of waters may be firmly forced down on the os and bring about its dilatation. In the bicornuate uterus of animals the increase in tone becomes of even greater importance, as it tends to keep the walls of the tube closely applied to the fœtus and prevents it kinking under the pressure of the abdominal muscles. After the delivery of the membranes and placenta, increase in tone becomes the most important requisite, in order to keep the walls of the cavity as closely applied as possible to each other.

In labour the dilatation of the neck is due to its passive relaxation, owing to the force exerted by the rhythmical contractions and the increase in tone of the upper part of the uterus pressing the bag of membranes upon it. Polaillon showed that when the area of the orifice is 1 sq. cm. the pressure on the membranes was 110 grammes, when completely dilated it was 95 sq. cm. and the pressure forcing the head down was estimated at about 10 kilogrammes (roughly 22 lbs.) at each contraction. Mathew Duncan has

estimated that the pressure necessary to cause rupture of the amnion, varies between 1·8 and 17 kilogrammes—4 to 37 lbs.

Schatz,[5] Polaillon[6] and Westermark[7] have found that the constant tonic pressure exerted upon the uterine contents during delivery in any individual case, remains constant as long as no change takes place in the volume of the contents, but varies, in different cases, from 20 mm. to 70 mm. of mercury in different individuals—a variation of from 6 to 21 oz. per sq. in. The average, constant, uterine pressure is thus about 35 mm. of mercury per sq. cm., or about 10·5 oz. per sq. in. Polaillon finds that the whole pressure exerted upon the surface of the ovum—1400 sq. cm. or 200 sq. in.—is about 66 kilogrammes—145 lbs. During a uterine contraction, there is an additional average pressure of 46 mm. mercury per sq. cm.—13·8 oz. per sq. in.—or 88 kilogrammes—193 lbs.—on the whole surface of the ovum. The total pressure during a contraction, therefore, will be 154 kilogrammes, or 338 lbs., or an estimated work equivalent to raising nearly 22 lbs. to the height of one yard,—9 kilogrammemeters. Out of five hundred and eighty-seven estimations by Westermark[7] on women at the period of delivery, the lowest pressure on the uterine contents noted was 20 mm., the highest 220 mm. These pressure values were, of course, greatly increased when the abdominal muscles and diaphragm took part in the pain. In this case, during the expulsive period, values averaging 400 mm., or four times that of the uterus alone, were brought into play. One cannot hope by the use of uterine drugs to change this, the greatest expulsive force.

The tracings shown have been taken by two methods, either the contractions of the muscles alone have been recorded by means of a lever system, or the intra-uterine pressure has been recorded as well by means of a rubber bag inserted into one of the fœtal sacs. The animals, of course, were rendered completely unconscious previous to any operation being undertaken. In all cases, a rise in the curve shows an increase in contraction, a fall, relaxation. For example, in Tracing 1 there are shown three contractions previous to the injection of ergotoxine, subsequently there are very many. That they succeed one another more rapidly is evident; it is also apparent that the general level of the curve has risen; there has been an increase in tone which only gradually falls to its original level.

The drugs, whose action is supposed to be on sacral endings, such as pilocarpine, atropine, and physostigmine, play little part in therapeutics. The drugs, whose action is upon the sympathetic, hypogastric endings, are of great importance.

Adrenalin is pharmacologically, though not therapeutically,

one of the most important of this group. Although in cats it often causes a relaxation of the non-pregnant uterus, it always causes contraction in the pregnant animal; clinical experience seems to bear this out for man. Tracing 2 shows a typical adrenalin effect. It will be noted that the uterine contraction, though very marked, is of very brief duration, and is accompanied by no rise in tone. Indeed, in our experiments, a subsequent decrease in tone has been very common.

Ergot also acts on these sympathetic endings. The activity of ergot in its ordinary pharmaceutical preparations shows such marked variability,[8] that it is fortunate that during the last few years we have had isolated for us its active principles. Probably the most important is the water soluble principle para-hydroxy-phenyl-ethylamine,—sold under the trade name of tyramine. The action of this body is indicated in Tracing 3, which shows a marked increase in rate and strength of uterine contraction, and also a marked rise in tone; a highly desirable result. This body, which was first studied by Barger and Dale,[9] seems to promise to become of some importance. The earlier isolated principle, the amorphous alkaloid, ergotoxine, also gives very marked results, consisting, in general, in both increase in contractility and a rise in tone. Tracing 4 is a fairly typical example. Large doses of this substance produce, however, a depression of the nerve endings, which in smaller doses it stimulates, and this makes it inadvisable to use it in repeated doses.

Pituitary extract acts also on these same endings, and in our experiments has almost invariably given us both a marked rise in tone and also an increase in the rhythmic movements. Tracing 5 is characteristic.

With these last three drugs we have always been able to produce some pharmacological effect, but have encountered the difficulty that we have not always been able to produce any given type of result. Before the birth of the child it is important for the clinician to bring about not only increase in contractility, but also some rise in tone, though the first is the more important in most cases; that is to say, to produce an effect similar to that shown in Tracing 1, and not merely a rise in tone such as is shown in Tracing 5. Post-partum, a rise in tone is much the more important, and Tracing 5 would illustrate a successful result. Unfortunately we are not able to foretell which result will be obtained from any given dose, and in consequence we consider those clinicians who refuse to use them before birth justified, though doubtless they may be of value in this stage. Post-partum, they are, we believe, of undoubted value.

Our experiments with hydrastine have yielded less certain

results than we have been able to obtain with the ergot preparations, or with pituitary. Quinine, the sovereign remedy in malaria, has been known to cause abortion, and not a few Italian physicians have recommended its use in obstetrics. Cushny[1] found in his experiments that small injections in animals usually produced a short series of contractions, but no increase in tone. He also adduced some evidence to show that its action is upon the muscle itself.

In our experiments, also, we have only seen increase in rate and strength of the contractions, and practically no effect on tone. The increase has in no case been very striking. Tracing 6 is a very typical one. In this tracing the upper line represents intra-uterine pressure, the large waves the change in length of longitudinal muscle.

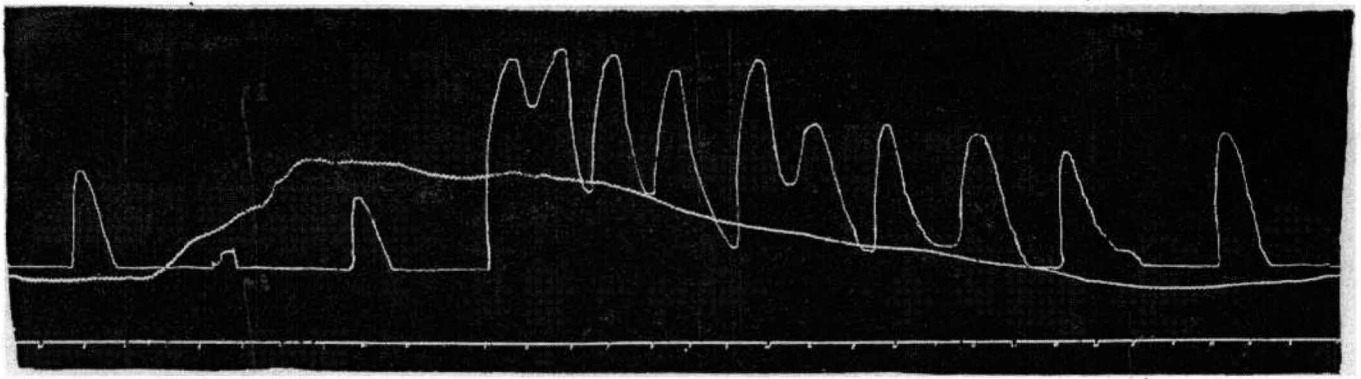
Barium also acts on the uterine musculature directly. Its effect is chiefly on tone, the rhythmic movements being little effected by small doses, but being entirely obscured with large ones, owing to the very marked rise in tone.

We have practically no knowledge of drugs which are capable of decreasing uterine tone or contractility. In some of our experiments we have been able, apparently, to do this by the use of nitrites, in others we have been completely unsuccessful. The increase in tone brought about by pilocarpine can be relieved by atropine, and it is possible that this drug might be of service in some cases of dysmenorrhœa, when the pains are dull and persistent.

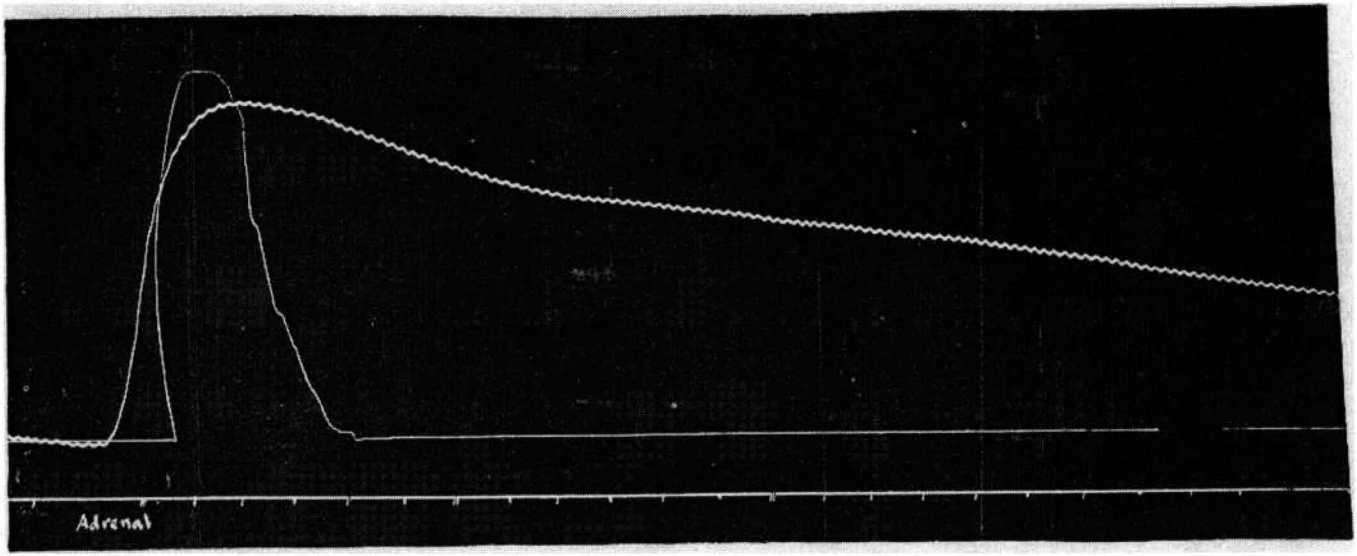
The central control, however, of the organ must not be forgotten. Alcohol seems to be completely without effect, even when given intravenously. Anæsthetics cause, undoubtedly, a relaxation and slowing, or even arrest, of uterine movements in some cases. The direct effect on the uterus seems to be slight, but their effect on the movements of abdominal muscles is often very marked. According to Kehrer,[10] morphine in small doses increases the uterine movements, while in very large doses they are somewhat depressed. It must not be forgotten that the absence of pain brought about by the exhibition of this drug, enables the patient to participate in the necessary abdominal movements with much greater success.

References:—

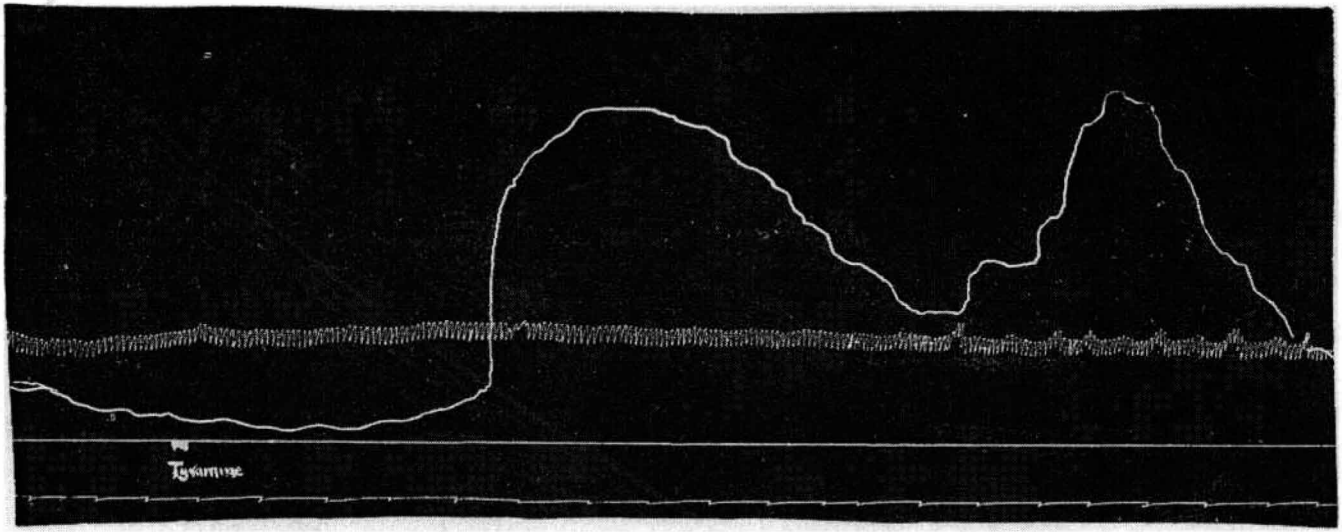
1. Cushny, *Jour. of Physiol.*, 35; 1906. p. 1.
2. Langley and Anderson; *ibid*, 19, 1895, p. 122.
3. Dale and Laidlaw; *ibid*, 44, 1912, p. 12.
4. Cushny, *ibid*, 41, 1910, p. 233.
5. Schatz, *Arch. f. Gynæc.*, 3, 1872, p. 58.
6. Polaillon, *Arch. de Physiol.* 7, 1880, p. 1.
7. Westermark, *Scand. Arch. f. Physiol.* 4, 1893, p. 331.
8. Cronyn and Henderson, *Jour. of Pharm. and Exp. Ther.*, 1, 1909, p. 203.
9. Barger and Dale, *Jour. of Physiol.*, 41, 1910, p. 19.
10. Kehrer, *Arch. f. exp. Path. u. Pharm.* 58, 1908, p. 366.



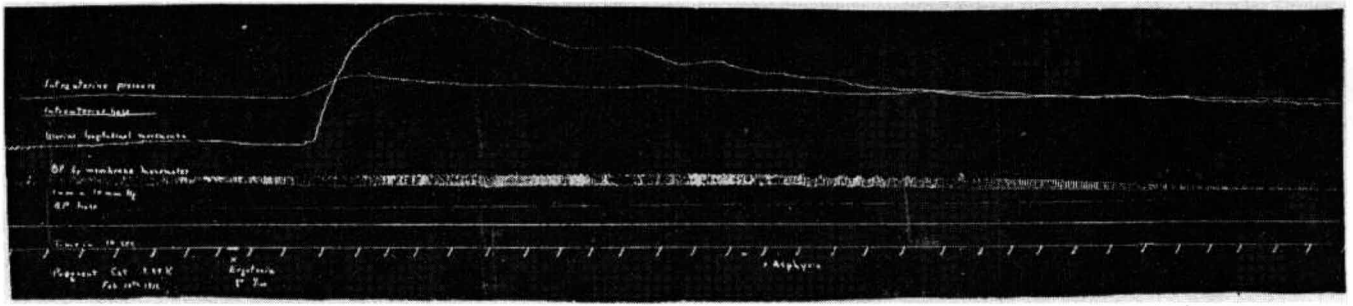
TRACING 1.—Cat, pregnant, near full term. Ergotoxine, 1·3 mg., intravenously showing uterine contractions, blood pressure, and time intervals of 10 sec. Illustrating Dr. Sharpe's article: "The Action of Drugs on the Uterus."



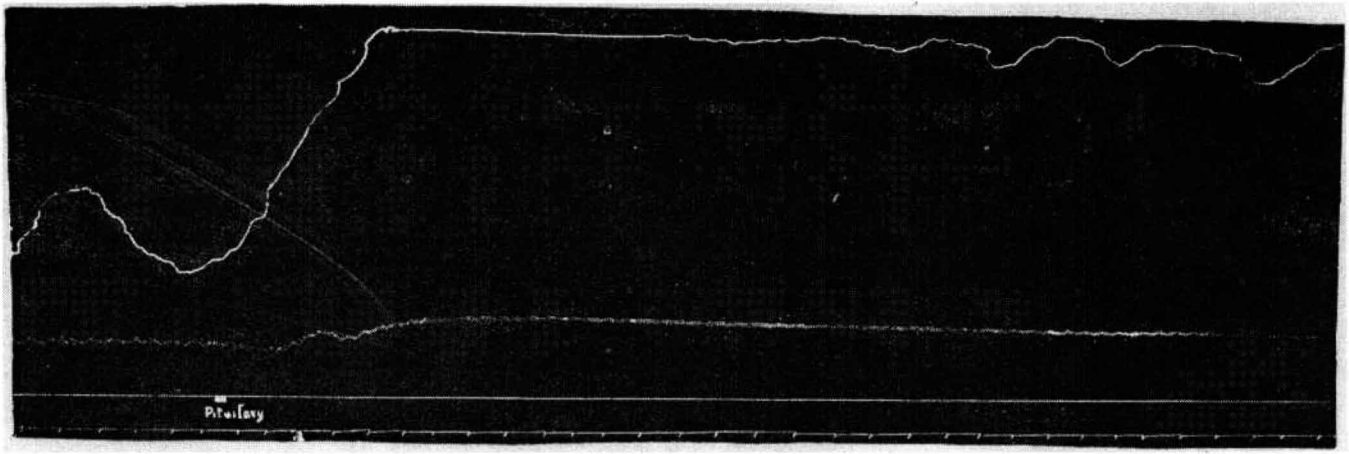
TRACING 2.—Cat, intracerebral magnesium chloride, in shock, blood pressure 35 mm.Hg. 0·5 cc. 1-1000 adrenalin. Note single uterine contraction and slow fall of pressure. Illustrating Dr. Sharpe's article: "The Action of Drugs on the Uterus."



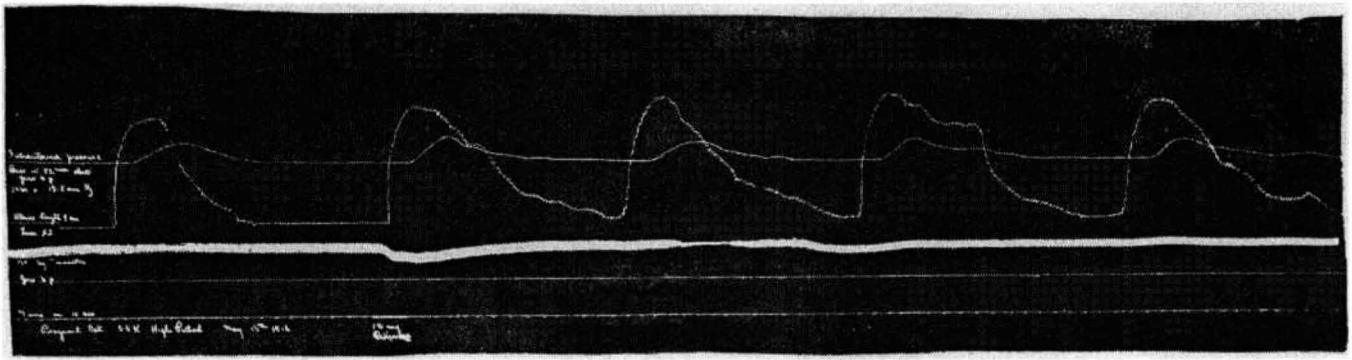
TRACING 3.—Pregnant Cat, Uterine Contractions. Tyramine, 5 mg. Illustrating Dr. Sharpe's article: "The Action of Drugs on the Uterus."



TRACING 4.—Illustrating Dr. Sharpe's article: "The Action of Drugs on the Uterus."



TRACING 5.—Pregnant Cat, Uterine and Blood Pressure Tracings. Pituitary Extract. Illustrating Dr. Sharpe's article: "The Action of Drugs on the Uterus."



TRACING 6.—Pregnant Cat. Quinine, 10 mg. Illustrating Dr. Sharpe's article: "The Action of Drugs on the Uterus."