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THE ACTION OF THE SO-CALLED FEMALE REMEDIES ON THE EXCISED UTERUS OF THE GUINEA-PIG *

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Introduction: The present paper is an introduction to a study of the so-called female remedies, drugs which have had more or less extensive clinical use, but which have not been subjects of thorough pharmacologic or clinical study. Judging from the large number of preparations of a proprietary or "patent" nature containing one or more of these drugs that are on the market at present, we must regard them as still extensively used. The purpose of the investigation was to determine whether any of the group possessed actions that could be referred to the uterus.

In this paper are presented their actions or lack of action on strips of the excised uterus of the guinea-pig. The method has certain limitations. A few experiments on strips of intestine indicate that the action is in no manner specific to the uterus. It seems safe to conclude, however, that if there is a positive action on the excised uterus, whether stimulation or depression, that a similar action would be exhibited on the uterus in situ if the drug reached the organ in a like concentration; such experiments on the uterus in situ are contemplated. In the text certain conclusions are drawn relative to the concentration of the drugs used in this work and the possibility of like concentrations being obtained in the body.

It may not be amiss to state at this place, that while a large number of the drugs studied exert definite actions on strips of the isolated

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uterus, it is highly improbable that the concentrations necessary to elicit the action could be introduced into the body.

Methods: The usual methods were followed. A longitudinal strip of the uterus of the guinea-pig was attached to a muscle lever and immersed in a bath (50 c.c.) of Tyrode's fluid, kept well oxygenated by a constant stream of oxygen. The bath was kept at a fairly uniform temperature, about 38 C., although occasional variations did not seem to influence the action. The movements of the lever were recorded on a revolving drum. Usually there was a latent period of about twenty or thirty minutes before the regular contractions were initiated; sometimes the latent period was shorter and often much longer. Six experiments were usually carried on at the same time, strips from the same

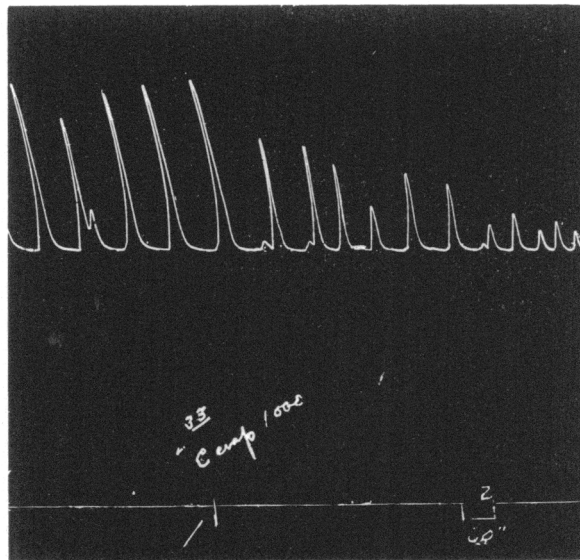


Fig. 1.—*Aletris farinosa* (unicorn root); Experiment 65b; the evaporated fluid extract to make a 1 to 1,000 solution was added at "1"; "2" is a time tracing of sixty seconds.

uterus being used. Frequently all strips from a given uterus failed to contract; again one strip failed to contract and others contracted well. In the later stages of pregnancy, when there is a larger amount of tissue, parts of the uterus were occasionally kept on ice over night and used on the next day, and rarely on the third day. As others have found, the pregnant uterus, especially in the later stages, usually contracts more vigorously than the virgin uterus and there are fewer inactive uteri in the pregnant group; for this reason the pregnant organ was usually employed. The action of a given drug sometimes presented differences between the virgin and the pregnant uterus; these differ-

ences will be discussed under the individual drugs. After obtaining a satisfactory control tracing of the normal contraction, the drug was added to the bath and the tracing continued for about fifteen minutes before transferring to fresh stock solution; occasionally the drug was allowed to act for a much longer period.

Preparations of the Drugs Used: ¹ The fluidextract, the evaporated fluidextract and the infusion were employed. The fluidextract was used in the larger number of experiments, for the results with it did not differ materially from those with the evaporated extract. The fluidextracts used contained from 40 to 60 per cent. alcohol. Control experiments, with percentages of alcohol about the same as the fluidextracts made in the bath, were practically without action on the strips of the uterus; nevertheless, a large number of control experiments were made with the evaporated fluidextracts of most of the drugs and with but few exceptions, to be discussed under the individual drugs, the results did not differ materially from those of the fluidextract. Further, all but three of the fluidextracts (*Chamaelirium luteum*, *Leonurus cardiaca* and *Dioscorea villosa*) precipitated when added to the bath, and as many of the precipitates were very heavy, it was thought that a more intimate mixture would occur if the fluidextracts were added directly to the bath. When evaporated, the fluidextract was not exposed to a temperature higher than from 50 to 60 C.

Concentration of the Drugs Used: It was aimed to use a concentration of the drug that would approximate, therapeutically, the concentration in the blood under the most favorable conditions. If we assume that the average dose of the fluidextracts (2 c.c.) be absorbed promptly and equally distributed throughout the tissues of the body, the concentration in an adult (60 kg.) would be about 1 to 30,000; if all of the drug remained in the blood, a phenomenon, of course, that is inconceivable, the concentration would be about 1 to 2,000. The majority of the experiments were made with a much higher concentration than this (1 to 1,000); in other words, the concentrations used were greater than the highest conceivable concentration that could be

1. All the preparations used were furnished by the American Medical Association chemical laboratory. The crude drugs were identified and found true to name as follows: by Prof. Henry Kraemer: *Aletris farinosa*, *Caulophyllum thalictroides*, *Cypripedium pubescens*, *Dioscorea villosa*, *Ichthyomethia piscipula*, *Leonurus cardiaca*, *Mitchella repens*, *Passiflora incarnata*, *Pulsatilla pratensis*, *Scrophularia nodosa* (*marylandica*), *Scutellaria lateriflora*, *Senecio aureus*, *Valeriana officinalis*, *Chamaelirium luteum* and *Acer spicatum*; by Prof. E. N. Gathercoal: *Viburnum opulus*, *Viburnum prunifolium* and *Cnicus benedictus*. One each of the following fluidextracts was made by L. E. Warren of the American Medical Association chemical laboratory from the authentic drugs: *Acer spicatum*, *Viburnum prunifolium*, *Viburnum opulus* and the bark of the stem of the *Viburnum prunifolium*; all other fluidextracts were made by different firms and their identities were not established, but as the actions of two preparations of each drug were similar, their identity is probably authentic.

obtained therapeutically. As there were many exceptions to the average result, this strength was increased to 1 to 500 with some of the drugs without altering the type of action; occasionally more dilute solutions were effective. The strips were placed in fresh Tyrode solution before the addition of a different drug.

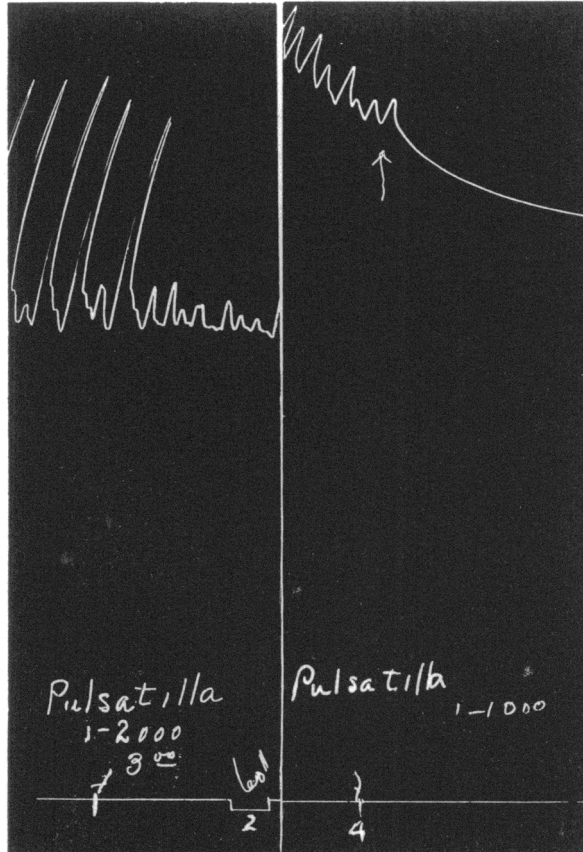


Fig. 2.—*Pulsatilla pratensis* (pulsatilla); Experiment 91c, late pregnancy: the fluidextract to make a 1 to 2,000 solution was added at "1"; contractions were not resumed and when placed in a fresh bath the strip went into a state of very great tone, and pulsatilla, 1 to 1,000 at "4" again caused cessation of the contractions. The tracing is interrupted between "2" and "4."

The Phenomena to Be Discussed: The action of the drugs was examined as affecting the rate and amplitude of excursion and the state of the muscular tone, these being considered the factors that determine the stimulant, depressant or negative action of the drugs. The rate may be considered an indication of the muscular irritability; the excursion, of the expulsive or parturient efficiency, and the tone as

an indication of the postpartum, styptic and, together with the excursion, of the abortifacient efficiency of a drug. The term "rate" always refers to the number of contractions per unit of time, and not to the duration of the individual contraction. The degree of relaxation of the strip was taken as the indication of the muscular tone. There is a close interrelation between rate, amplitude and tone. Under average conditions an increased rate usually prevents complete relaxation, so that apparently the muscular tone of the strip is increased. In such

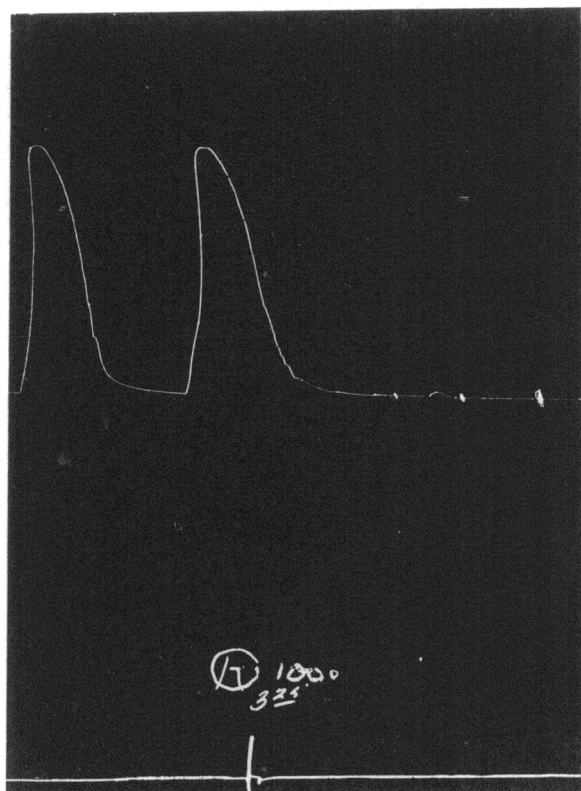


Fig. 3.—*Ichthyomethia piscipula* (Jamaica dogwood); Experiment 98d, late pregnancy; the fluidextract was added at "1" to make a 1 to 1,000 solution.

cases, however, there may be no actual increase of the tonicity of the muscular substance. Occasionally there was either an increase or decrease of tone with little or no change in rate or amplitude of the contractions. This would indicate a direct action on the muscular tone. In vigorously contracting uteri the rate is usually infrequent, so that there is plenty of time for complete relaxation. Under such conditions there may be considerable variation in the rate and amplitude without variation in the tone; this is especially true in advanced

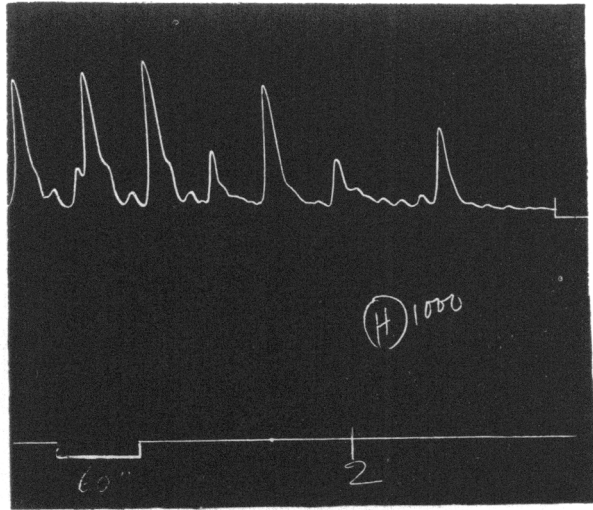


Fig. 1. *Scrophularia marylandica* (figwort): Experiment 88b, late pregnancy. The fluidextract to make a 1 to 1,000 solution was added at "2"; no contractions were made for ten minutes after the end of the tracing, when the experiment was terminated.

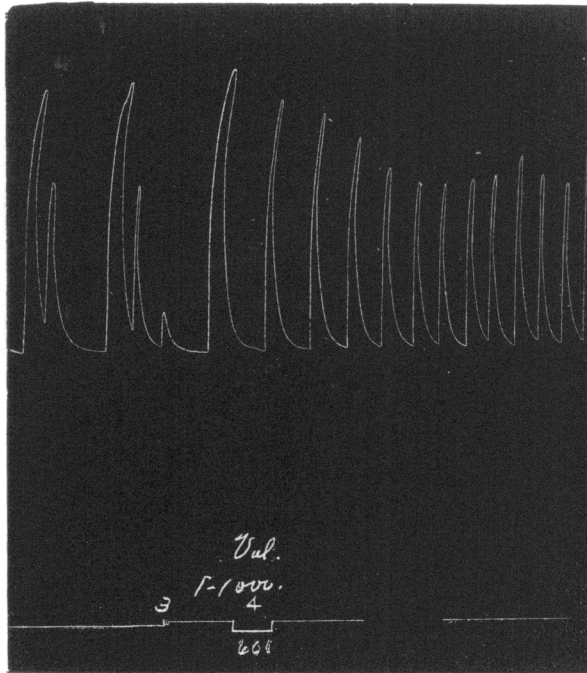


Fig. 2. *Valeriana officinalis* (valerian): Experiment 51b, about mid-term pregnancy. The fluidextract to make 1 to 1,000 solution was added at "3"; "4" is a thirty-second interval.

stages of pregnancy. There are, however, instances of very great amplitude of excursion with rapid rate, so that here, too, an increase in tone may be more apparent than real. With this one exception, the impression that we have gained from this work is that the amplitude of the excursion is of greater import in judging the action of a drug than is the effect on the tone of the muscle. Indeed, it seems to us

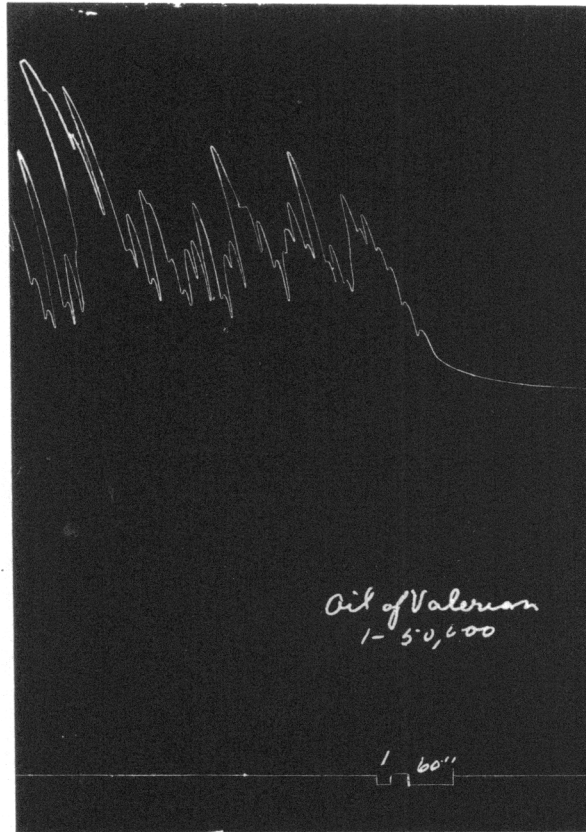


Fig. 6.—Oil of valerian; Experiment 109f, late pregnancy; oil of valerian to make a 1 to 50,000 solution introduced at "1"; the strip made a few small contractions later.

that there may be an actual muscular depression with apparent increase of the tone, for there are instances of an increased rate with a decreased amplitude of excursion in which the strip does not relax to the original state for lack of time only.

A good illustration in point is furnished by the work of Lieb² on viburnum. Lieb states that this drug increases the rate and tone, but diminishes the amplitude; the impression is that the drug really stimulates. Judging from his illustration, we conclude that there is no stimulation, for we think that fre-

2. Lieb: Am. Jour. Obst., 1914, lxxix, 28.

quent small contractions are much less efficacious than fewer more vigorous ones, in expelling a fetus at any rate.

Of course, variation in amplitude (decrease or increase) may be balanced by variation in rate (increase or decrease), so that the end-result is practically the same. The points in question are well illustrated in the valerian series. This drug, with very few exceptions, considerably lessened the amplitude of the excursions, while the tone was unaffected in somewhat more than one half the experiments, and occasionally apparently increased. However, the tone

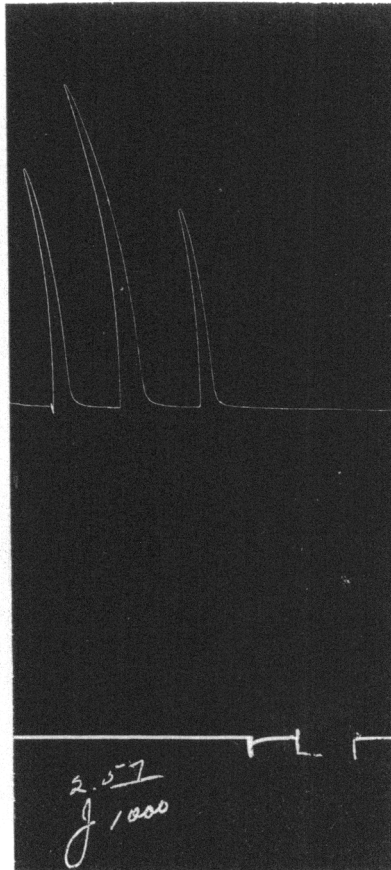


Fig. 7.—*Cypripedium pubescens* (lady's-slipper); Experiment 93d, late pregnancy; the fluidextract to make a 1 to 1,000 solution was added at "1"; no contractions were made for six minutes after the end of the tracing; this is a greater depression than the average experiment shows; "2" is a time tracing of sixty seconds.

was decreased, as a rule, in those experiments in which there was a decreased rate, thus allowing time for more complete relaxation of the muscular strip. On the other hand, the tone was unaffected or occasionally even increased when the rate was somewhat increased (this usually secondary to a considerably lessened amplitude). When the rate was unchanged the tone was lessened. There were exceptions to these generalizations.

Natural Variations in Control Experiments: The action of the muscular strips varies greatly in uniformity. Frequently the rate and amplitude of contraction were quite uniform, but again very irregular. A uterus that had been contracting regularly for several minutes would miss a few contractions, or, vice versa, a strip that had been contracting poorly would begin regular vigorous contractions. This irregularity of action necessitated a large number of experiments to prevent such natural variations being taken for the action of the introduced drug.

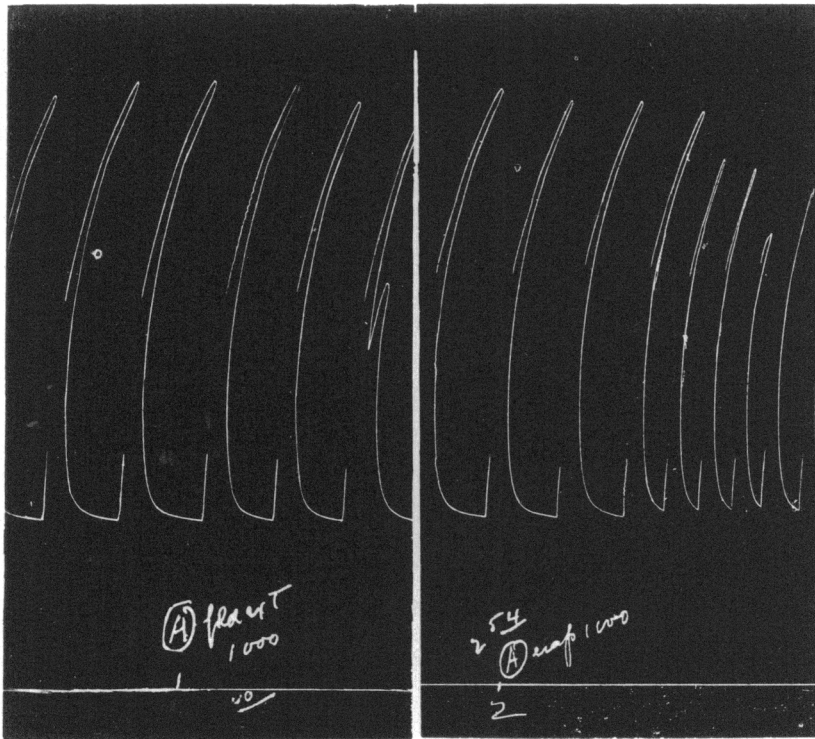


Fig. 8.—*Dioscorea villosa* (wild yam); Experiment 63b, advanced pregnancy; *Dioscorea villosa* (fluidextract) 1 to 1,000 added at "1"; at "2" the evaporated fluidextract to make 1 to 500; the tracing is interrupted for a few minutes between "1" and "2."

for not infrequently on the addition of one of the inert drugs the action changed materially, either a great increase or decrease in function, so without careful control experiments erroneous interpretations might have been made. When such results occurred with the same drug, it is significant that they were not always in the same direction, some tending toward depression and others toward stimulation of one or more functions. Frequently on transferring a strip to fresh stock

solution contractions ceased for a longer or shorter time or their character was changed completely. While the experiments with alcohol indicate that the alcoholic content of the fluidextracts played no definite part in the results, yet it may be that an occasional variable result may have been due to the alcohol. The text will show that this was but an occasional factor, if it played any part at all. Infrequently strips went into tonic contraction of indefinite duration when placed into a fresh bath. In this state they were very resistant to depressant drugs.

In view of the many natural variations, it seems best not to attempt too exact a classification, so that experimental results were considered to be negative unless they were fairly constant in nature. The experi-

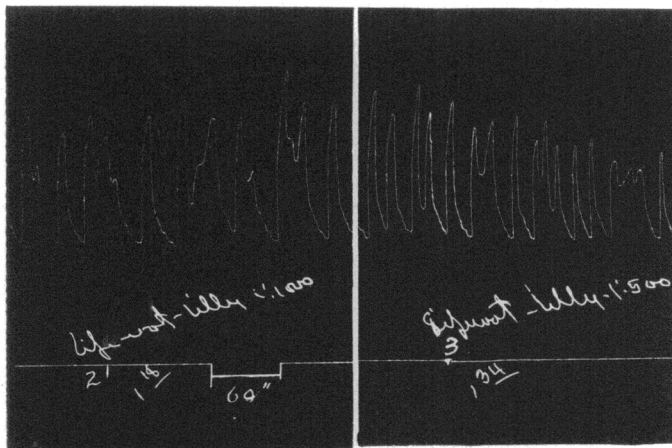


Fig. 9.—*Senecio aureus* (life root); Experiment 26a, early pregnancy; *Senecio aureus* (fluidextract) to make a 1 to 1,000 solution added at "2," and, fifteen minutes later, to make a 1 to 500 solution, at "3"; the tracing was interrupted between "2" and "3."

ments are all listed in the accompanying table, as to rate, amplitude and tone, with the different preparations of the drug and the strength of the solution used.

The Results of the Experiments: These are arranged in the text according to the degree of activity of the drug, presenting, first, those drugs that depress, the single drug that stimulates, and finally the inactive preparations:

The Depressant Group: The following drugs are markedly depressant: *Aletris farinosa*, *Pulsatilla pratensis*, *Scrophularia nodosa* and *Ichthyomethia piscipula*; somewhat less active: *Valeriana officinalis* (the oil is very active) and *Cypripedium pubescens*; possessing but slight activity: *Dioscorea villosa*, *Scutellaria lateriflora* and *Senecio aureus*.

The single stimulant drug is *Caulophyllum thalictroides*.

The inactive drugs are as follows: *Chamelirium luteum*, *Leonurus cardiaca*, *Passiflora incarnata*, *Mitchella repens*, *Viburnum prunifolium* and *V. opulus*, *Acer spicatum*, *Cnicus benedictus*, *Carduus marianus* and *Castanea dentata*.

Aletris farinosa (unicorn root): Unicorn root is an active depressant (Fig. 1). The 1 to 1,000 solution of the fluidextract decreased

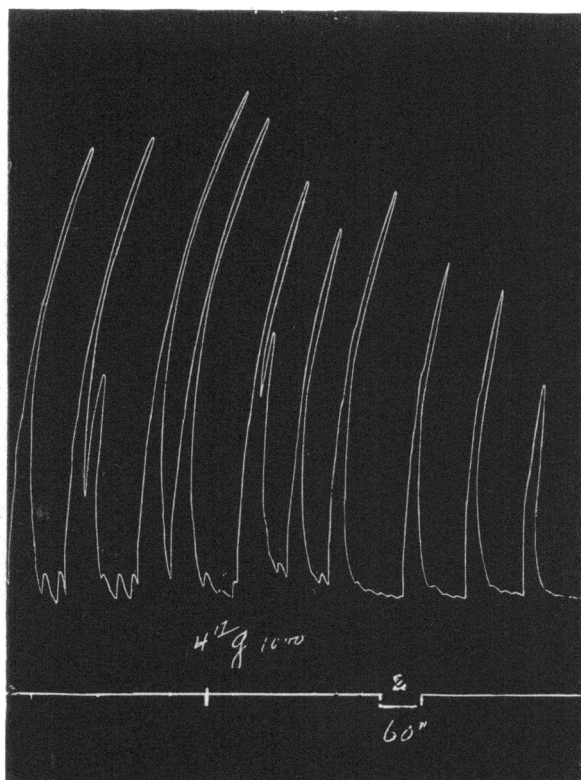


Fig. 10.—*Scutellaria lateriflora* (skullcap); Experiment 88a, late pregnancy; the fluidextract to make a 1 to 1,000 solution was added at "1"; "2" is a time tracing of sixty seconds. The action is usually less marked than in this tracing.

the amplitude of excursion in each of thirteen experiments. The results were not quite so uniform with the evaporated extract, but when the solution was increased to 1 to 500 two of the negative experiments also showed depression. The decrease in the amplitude was considerable, being quite marked in about one-half the cases; several times the contractions were interrupted on the addition of the drug and were not resumed at all. The tone was practically not affected.

The rate was usually decreased with the alcoholic preparations, but often unaffected when the evaporated extract was used. The infusion was inactive.

Pulsatilla pratensis (pulsatilla): Pulsatilla is a very active depressant, although the strips from different pigs did not react quite uniformly. The action is the same as that of the other depressant drugs, differing only in degree. Even a 1 to 2,000 solution caused a marked depression in excursion in the two experiments in which it was used (Fig. 2). When effective, the decrease in the amplitude was usually

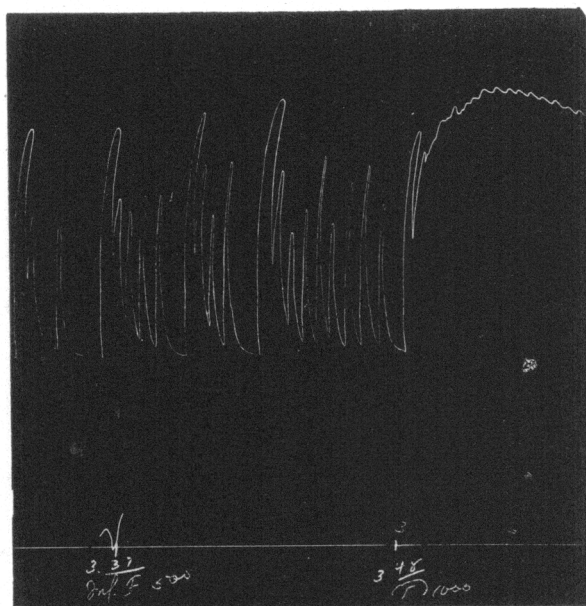


Fig. 11.—*Caulophyllum thalictroides* (blue cohosh); Experiment 84a; the infusion to make a 1 to 500 solution was added at "2" and the fluidextract to make a 1 to 1,000 solution (of the extract alone) was added at "3." The tracing shows the inactivity of the infusion and the great activity of the alcoholic preparation; the increase in tone was not due to the combined action of the infusion and the fluidextract, for the former was uniformly inactive and the latter always active.

quite prompt and considerable; once the activity ceased promptly on the addition of the 1 to 1,000 solution and was not renewed. The tone was not affected; the rate was slowed in about one-half the cases. The infusion was quite inactive in five experiments, four of them with the 1 to 500 solution and one with the 1 to 1,000.

The action was uniformly depressant on eight strips from two pigs, but with a third pig the contractions of three of six strips were not influenced by the 1 to 1,000 solution, while the others were depressed much less than the strips from the other pigs with the same strength of solution. Two of the

latter strips ceased to contract at once when the solution was increased to 1 to 500, but a third strip, aside from missing two or three contractions on the addition of the drug, contracted practically normally during about twenty minutes. The difference in the reaction in the three pigs is not explainable by the stage of pregnancy.

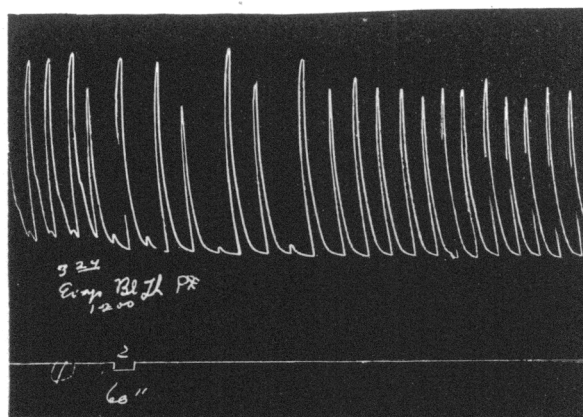


Fig. 12.—*Cnicus benedictus* (blessed thistle); Experiment 95c, about mid-term; the evaporated fluidextract to make a 1 to 200 solution was added at "1"; "2" is a time tracing of sixty seconds.

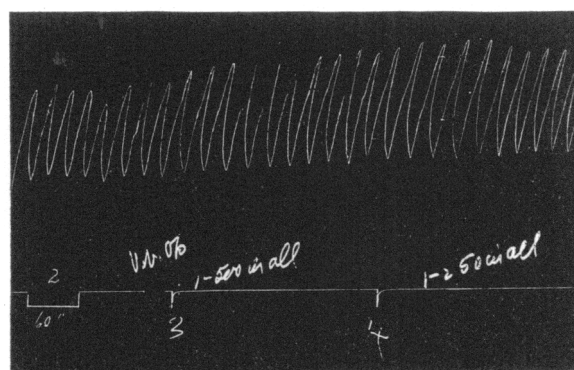


Fig. 13.—*Viburnum opulus* (cramp bark); Experiment 4, virgin cat; *Viburnum opulus* (fluidextract) to make a 1 to 500 solution added at "3," and to make a 1 to 250 solution at "4"; "2" is a time tracing of sixty seconds. (There seemed to be a progressive increase in tone and amplitude when the drug was added.)

Ichthyomethia piscipula (Jamaica dogwood): This preparation is an active depressant; on the addition of the 1 to 1,000 solution of the fluidextract after one or two less vigorous contractions, they cease entirely (Fig. 3). This was the result in five cases, four strips of which were allowed to remain in the solution for forty-five minutes

SUMMARY OF THE ACTION OF THE DRUGS ON THE RATE AND AMPLITUDE OF THE EXCURSIONS AND ON THE TONE OF THE STRIPS OF THE UTERUS *

Drug	Strength of Solution	Number of Experiments	Rate			Amplitude			Tone		
			Increase	Decrease	Negative	Increase	Decrease	Negative	Increase	Decrease	Negative
Aletris farinosa—											
Fluidextract.....	1 to 1,000	13	2	8	3	0	13	0	1	3	9
Fluidextract, evap.	1 to 1,000	12	1	2	9	1	8	3	0	0	12
Fluidextract, evap.	1 to 500	3	2	1	0	0	3	0	0	0	3
Infusion.....	1 to 1,000	2	1	0	1	0	1	1	0	0	2
Infusion.....	1 to 500	2	0	0	2	0	0	2	0	0	2
Pulsatilla—											
Fluidextract.....	1 to 2,000	2	1	1	0	0	2	0	0	0	2
Fluidextract.....	1 to 1,000	12	1	6	5	0	9	3	0	3	9
Fluidextract.....	1 to 500	2	0	1	1	0	1	1	0	1	1
Infusion.....	1 to 500	5	0	0	5	0	0	5	0	0	5
Ichthyomethia—											
Fluidextract.....	1 to 1,000	5	0	5	0	0	5	0	4	0	1
Infusion.....	1 to 500	2	1	1	0	0	1	1	0	0	2
Scrophularia—											
Fluidextract.....	1 to 1,000	8	0	4	4	0	8	0	0	2	6
Infusion.....	1 to 1,000	3	0	0	3	0	3	0	0	0	3
Infusion.....	1 to 500	3	1	1	1	0	3	0	0	0	3
Valerian—											
Fluidextract.....	1 to 2,000	5	0	2	3	0	2	3	0	2	3
Fluidextract.....	1 to 1,000	29	5	13	11	4	22	3	2	11	16
Fluidextract.....	1 to 500	14	3	9	2	0	14	0	1	12	1
Fluidextract, evap.	1 to 1,000	21	4	11	6	0	20	1	1	12	8
Fluidextract, evap.	1 to 500	6	1	1	4	0	6	0	1	1	4
Infusion.....	1 to 1,000	12	1	1	10	3	0	9	1	0	11
Infusion.....	1 to 500	8	2	1	5	1	1	6	1	0	7
Oil of valerian.....	1 to 100,000	1	0	1	0	0	1	0	0	1	0
Oil of valerian.....	1 to 50,000	4	1	3	0	0	4	0	0	3	1
Oil of valerian.....	1 to 10,000	10	0	10	0	0	10	0	0	10	0
Cypripedium—											
Fluidextract.....	1 to 1,000	8	1	5	2	0	8	0	0	0	8
Fluidextract.....	1 to 500	2	0	1	1	0	2	0	0	0	2
Infusion.....	1 to 500	3	1	0	2	0	3	0	0	0	3
Scutellaria—											
Fluidextract.....	1 to 1,000	9	0	5	4	1	6	2	0	0	9
Fluidextract.....	1 to 500	2	0	2	0	0	2	0	0	1	1
Fluidextract, evap.	1 to 1,000	4	1	1	2	0	1	3	0	0	4
Infusion.....	1 to 500	6	0	1	5	0	2	4	0	0	6

* The interpretation of the results will be found in the text.

SUMMARY OF THE ACTION OF THE DRUGS ON THE RATE AND AMPLITUDE OF THE EXCURSIONS AND ON THE TONE OF THE STRIPS OF THE UTERUS *—(Continued)

Drug	Strength of Solution	Number of Experiments	Rate			Amplitude			Tone		
			Increase	Decrease	Negative	Increase	Decrease	Negative	Increase	Decrease	Negative
Dioscorea—											
Fluidextract.....	1 to 1,000	14	6	1	7	0	8	6	3	0	11
Fluidextract, evap.	1 to 1,000	5	3	0	2	0	2	3	2	0	3
Fluidextract, evap.	1 to 500	3	1	0	2	0	2	1	0	0	3
Infusion.....	1 to 1,000	3	0	0	3	0	0	3	0	0	3
Infusion.....	1 to 500	2	1	0	1	0	1	1	1	0	1
Senecia aureus—											
Fluidextract.....	1 to 1,000	11	2	2	7	2	4	5	3	4	4
Fluidextract.....	1 to 500	8	1	4	3	1	7	0	1	6	1
Fluidextract, evap.	1 to 1,000	6	0	0	6	0	0	6	0	0	6
Fluidextract, evap.	1 to 500	3	0	1	2	0	2	1	0	0	3
Infusion.....	1 to 1,000	5	0	0	5	1	1	3	1	0	4
Infusion.....	1 to 500	8	2	0	6	1	2	5	2	0	6
Caulophyllum—											
Fluidextract.....	1 to 2,000	3	0	3	0	0	3	0	3	0	0
Fluidextract.....	1 to 1,000	11	0	5	6	0	8	3	11	0	0
Fluidextract, evap.	1 to 1,000	8	0	8	0	0	8	0	8	0	0
Infusion.....	1 to 1,000	4	0	0	4	0	0	4	0	0	4
Infusion.....	1 to 500	4	0	0	4	0	0	4	0	0	4
Viburnum prunifolium—											
Fluidextract (virgin).....	1 to 1,000	5	0	1	4	1	1	3	2	1	2
Fluidextract (pregnant)....	1 to 1,000	8	1	1	6	2	1	5	4	1	3
Fluidextract (virgin).....	1 to 500	5	2	1	2	0	2	3	3	1	1
Fluidextract (pregnant)....	1 to 500	7	1	2	4	1	2	4	2	1	4
Fluidextract, evap.	1 to 1,000	4	0	0	4	1	1	2	0	0	4
Fluidextract, evap.	1 to 500	1	0	0	1	1	0	0	0	1	0
Infusion.....	1 to 1,000	4	0	0	4	2	0	2	0	0	4
Infusion.....	1 to 500	6	0	0	6	2	0	4	1	0	5
Fluidextract (bark of tree)	1 to 500	4	0	0	4	0	0	4	0	0	4
Infusion (bark of tree)....	1 to 500	5	0	0	5	0	2	3	0	0	5
Viburnum opulus—											
Fluidextract (virgin).....	1 to 1,000	5	0	1	4	0	1	4	3	1	1
Fluidextract (pregnant)....	1 to 1,000	8	2	1	5	2	4	2	0	0	8
Fluidextract (virgin).....	1 to 500	7	1	0	6	2	1	4	4	0	3
Fluidextract (pregnant)....	1 to 500	10	3	2	5	0	6	4	0	0	10
Fluidextract, evap.	1 to 1,000	6	0	1	5	0	1	5	0	0	6
Fluidextract, evap.	1 to 500	2	0	0	2	0	0	2	0	0	2
Fluidextract, evap.	1 to 100	1	1	0	0	0	1	0	1	0	0
Infusion.....	1 to 1,000	1	0	0	1	0	0	1	0	0	1
Infusion.....	1 to 500	4	1	2	1	1	2	1	0	1	2
Infusion.....	1 to 100	1	0	0	1	0	0	1	0	0	1

SUMMARY OF THE ACTION OF THE DRUGS ON THE RATE AND AMPLITUDE OF THE EXCURSIONS AND ON THE TONE OF THE STRIPS OF THE UTERUS *—(Continued)

Drug	Strength of Solution	Number of Experiments	Rate			Amplitude			Tone		
			Increase	Decrease	Negative	Increase	Decrease	Negative	Increase	Decrease	Negative
<i>Acer spicatum</i> —											
Fluidextract.....	1 to 1,000	7	2	0	5	2	0	5	1	2	4
Fluidextract, evap.....	1 to 1,000	5	1	1	3	2	0	3	1	1	3
Fluidextract, evap.....	1 to 500	2	1	0	1	0	0	2	0	0	3
<i>Oniscus benedictus</i> —											
Fluidextract.....	1 to 1,000	8	0	1	8	1	1	7	0	1	8
Fluidextract.....	1 to 500	5	0	2	3	0	2	3	0	2	3
Fluidextract, evap.....	1 to 1,000	12	4	1	7	8	0	4	8	0	4
Fluidextract, evap.....	1 to 500	6	1	1	4	1	1	4	1	1	4
Fluidextract, evap.....	1 to 200	10	0	7	3	0	3	7	0	0	10
Infusion.....	1 to 1,000	11	2	1	8	3	2	6	3	0	8
Infusion.....	1 to 500	6	2	0	4	1	1	4	2	0	4
<i>Chamaelirium</i> —											
Fluidextract.....	1 to 1,000	12	0	3	9	0	4	8	2	2	8
Fluidextract.....	1 to 500	4	0	1	3	2	1	1	2	1	1
Fluidextract, evap.....	1 to 1,000	9	1	2	6	1	3	5	1	0	8
Infusion.....	1 to 1,000	5	0	0	5	0	1	4	1	0	4
Infusion.....	1 to 500	7	1	0	6	1	1	5	2	0	5
<i>Leonurus</i> —											
Fluidextract.....	1 to 1,000	8	2	1	5	0	3	5	0	0	8
Fluidextract, evap.....	1 to 1,000	7	1	0	6	1	1	5	0	0	7
Infusion.....	1 to 500	7	4	0	3	0	4	3	1	0	6
<i>Passiflora</i> —											
Fluidextract.....	1 to 1,000	10	1	0	9	0	1	9	0	1	9
Fluidextract, evap.....	1 to 1,000	5	0	2	3	2	1	2	2	0	3
Infusion.....	1 to 500	2	0	0	3	1	0	2	2	0	3
<i>Mitchella</i> —											
Fluidextract.....	1 to 1,000	7	2	0	5	2	3	2	2	0	5
Fluidextract, evap.....	1 to 1,000	7	0	0	7	0	0	7	0	0	7
Infusion.....	1 to 500	3	0	0	3	0	1	2	0	0	3
<i>Castanea</i> —											
Fluidextract.....	1 to 1,000	9	0	1	8	1	2	6	0	0	9
Infusion.....	1 to 500	4	0	0	4	0	1	3	0	0	4

and made but one small contraction during that time, showing that the action is persistent. The tone was practically unaffected. The infusion is not so active, for while it depressed one strip considerably, a second was not influenced at all.

Scrophulario marylandica (figwort) : Figwort actively lessened the amplitude of the excursions, secondarily decreased the rate and left the tone unaffected (Fig. 4). In each of eight experiments there was a marked decrease in excursion within from ten to fifteen minutes of the addition of the drug (1 to 1,000 of the fluidextract). Occasionally the effect was quite prompt, the contractions ceasing temporarily and then recurring some minutes later with considerably lessened amplitude. The rate was but secondarily affected, more often remaining the

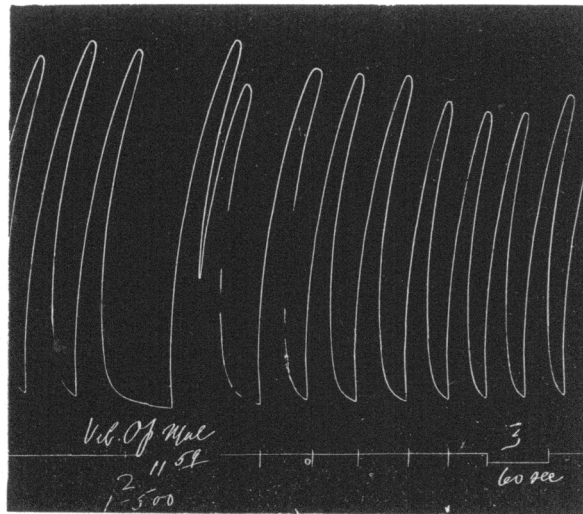


Fig. 14.—*Viburnum opulus* (cramp bark); pregnant guinea-pig; fluidextract *Viburnum opulus* to make a 1 to 500 solution added at "2."

same, but being frequently decreased somewhat. The tone was not altered. The infusion was also effective, as three cases exhibited a somewhat lessened excursion from the 1 to 1,000 solution. This action was augmented by increasing the strength to 1 to 500. When the fluidextract was added to the bath already containing the infusion, the effect was additive.

Valerian: This drug very generally depresses, especially the amplitude of the excursion, somewhat less the tone and the rate. The rate may be increased, presumably secondary to the decreased excursion. The active principle is found in the fluidextract, the evaporated fluidextract, and in the oil of valerian, but not in the infusion; it is non-

volatile at 100 C., for the distillate from the fluidextract is inactive, while the residue retains virtually the original activity. It is probably a resin. Sodium valerate is practically inactive (Figs. 5 and 6).

The Fluidextract: In some fifty experiments with the 1 to 1,000 solution of the fluidextract and the evaporated fluidextract there was uniformly a depression of the muscle strips. The most striking effect was on the amplitude of the excursions, for this was decreased almost without exception, and in practically half the experiments the decrease was rather marked. The non-

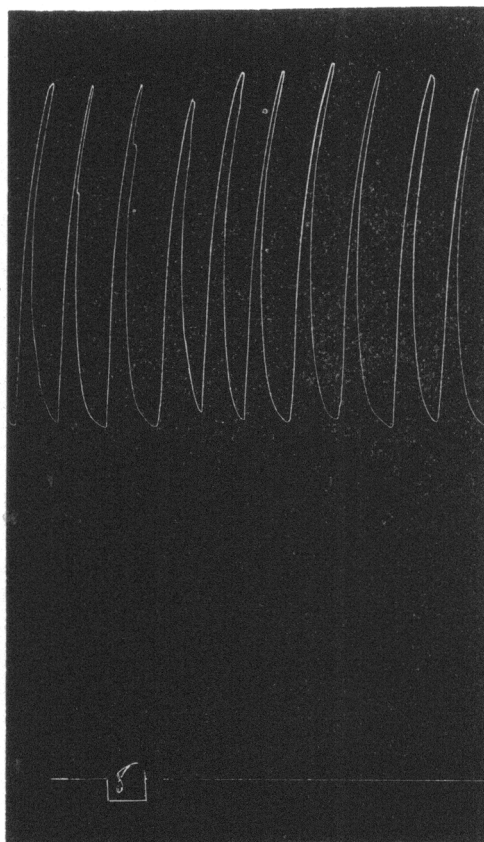


Fig. 15.—*Acer spicatum* (maple bark); Experiment 51b, about midterm; infusion *Acer spicatum* to make a 1 to 250 solution added at "8."

evaporated fluidextract was somewhat more active than the evaporated extract. The rate was also diminished, although in about half the cases only; the action was not so great as on the amplitude. In about one fourth of the cases the rate was moderately increased; however, this did not indicate increase in function, but probably was secondary to the lessened amplitude, as was discussed in the introduction. The muscular tone was also decreased in about one half the experiments, as indicated by the tracings, but, actually, probably much more frequently than this, for the frequently increased rate masked the lessened tone by preventing complete relaxation. Recovery was usually rather

slow and imperfect. With but few exceptions the strips were contracting vigorously. The depressant action was also observed in two of five experiments with the 1 to 2,000 solution of the fluidextract.

As the strength of the solution was increased to 1 to 500 the depressant action became more marked. Of fourteen experiments with the fluidextract, without exception the amplitude was decreased and with but two exceptions the tone also was diminished. The amplitude was lessened in each of six cases with the evaporated extract, although the tone and rate were usually unaffected.

The Infusion: This preparation was inactive in a large series of cases (twelve with the 1 to 1,000 and seven of eight cases with the 1 to 500 solution). The inactivity was not due to the loss of a volatile substance during the

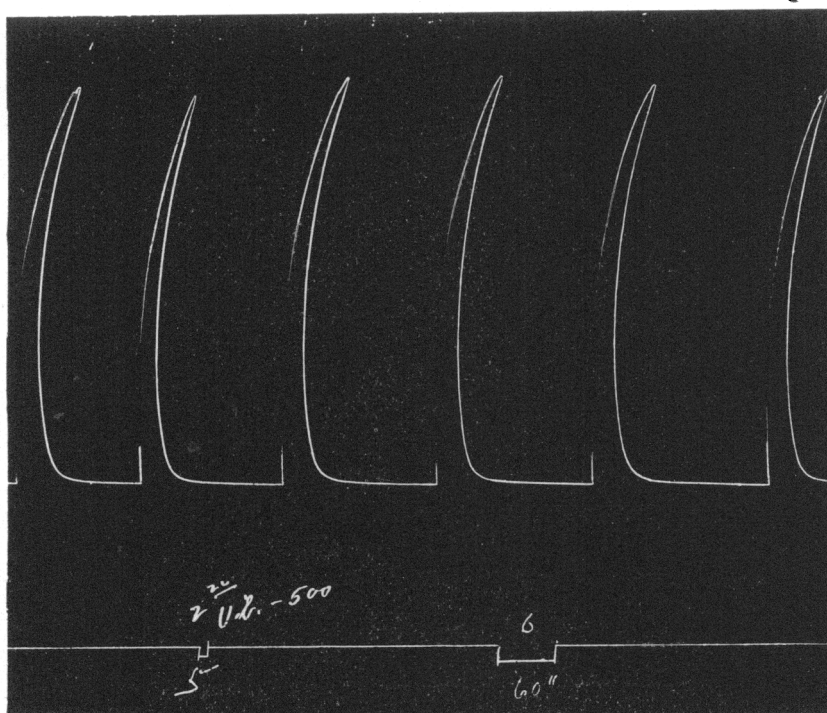


Fig. 16.—*Viburnum prunifolium* (black haw); Experiment 43b, late pregnancy; the fluidextract to make a 1 to 500 solution was added at "5"; fifteen minutes elapsed between the introduction of the drug and the end of the tracing.

making of the infusion, for infusions made in stoppered bottles at 45 C. were inactive. The distillate from the fluidextract was also practically inactive in eleven experiments, while the residue from the distillate, made up to the original volume, preserved practically the original activity of the fluidextract, proving that the active principle of valerian is nonvolatile (at 100 C.), and is not injured by boiling for a short time.

Sodium Valerate: Lieb⁷ states that sodium valerate is inactive except in high concentrations, which are toxic; the actual concentration is not stated. In our work the 1 to 1,000 solution was practically inactive, while the same strength of the fluidextract was always depressant. Three of five experiments with the 1 to 1,000 solution gave negative results and two a slight decrease in

excursion, but one of the latter contracted vigorously after one hour in the valerate. Experiments with less concentrated solutions were negative. Similar strengths were without action on strips that were in a state of high tone.

Oil of Valerian: The oil very actively depresses the strips of the uterus, so that even the 1 to 100,000 solution lowers the amplitude and recovery from the action is very slight when the strips are placed in fresh stock solution. Only one experiment was made with the 1 to 100,000 solution, but as this action was similar to the somewhat stronger solutions, this was thought to be sufficient. The dilution of 1 to 50,000 caused a very marked depression in each of four experiments under different degrees of contractions (Fig. 6). The contractions of two strips were stopped at once, one of which had been contracting moderately and the other but slightly. The vigorous contractions of one strip were inhibited during about twelve minutes. The last strip was in a state of high and increasing tone without contracting and the tone was promptly lowered by the oil. More concentrated solutions allayed contractions at once and recovery was very poor and usually absent if the strip remained in the solution of the oil for even a very few minutes; ten minutes in the 1 to 10,000 solution was usually sufficient to prevent recovery in fresh stock solution. The tone was lowered in all experiments.

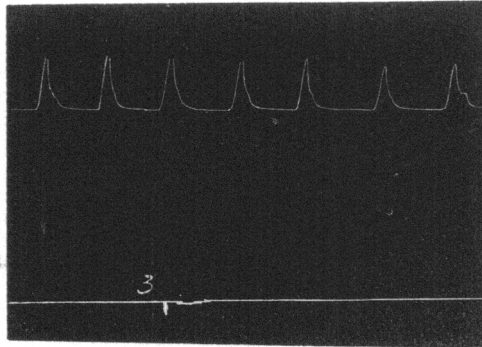


Fig. 17.—*Castanea dentata* (chestnut bark); Experiment 100a, early pregnancy; the fluidextract to make a 1 to 1,000 solution was added at "3."

Cypripedium pubescens (lady's-slipper): Lady's-slipper lessened the amplitude of the excursions moderately but fairly constantly; secondarily, it slowed the rate in part of the experiments and left the tone unaltered. This result was obtained from twelve experiments with the 1 to 1,000 solution of the fluidextract. Two cases showed considerable depression of the amplitude (Fig. 7). The results were the same with vigorously and poorly contracting strips. The infusion in the strength of 1 to 500 also lowered the excursion somewhat.

Dioscorea villosa (wild yam): in about one-half the experiments this drug caused a lowering of the amplitude, in some of them considerably, in others slightly. An increased rate usually accompanied a decreased amplitude, otherwise the rate was not affected (Fig. 8). There was an occasional increase in tone. The results were similar with the fluid and the evaporated extract. The infusion is probably inactive.

The amplitude was lessened in eleven of twenty-two experiments with the 1 to 1,000 solution. In some of them the action was so slight as to be doubtful whether it was not simply a natural variation, rather than an action of the drug. In three of the experiments with lessened amplitude the tone was considerably increased, so that probably the change in excursion was secondary to this; all other experiments were without action on the tone, so that the occasional increase in tone is without significance. Four cases with the 1 to 500 solution gave irregular results. Three experiments with the 1 to 1,000 solution of the infusion were negative; one with the 1 to 500 solution gave an increased tone, but the other was negative. Most of the strips were contracting vigorously, but the initial activity of the strip did not influence the end-result.

Senecio aureus (liferoot): Again the majority of the cases showed this drug to have no constant action on the excised uterus. There was an indication that in high concentrations the drug was depressant.

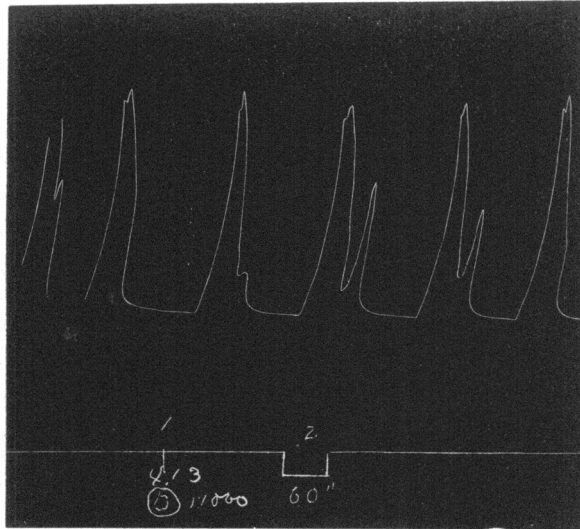


Fig. 18.—*Passiflora incarnata* (passion flower); Experiment 69f, late pregnancy; the fluidextract to make 1 to 1,000 solution was added at "1"; "2" is a time tracing of sixty seconds.

With the fluidextract (1 to 1,000) both amplitude and tone were decreased in four of eleven experiments and as the solution was increased to 1 to 500, these functions were decreased in all but one of eight cases (Fig. 9). The depression from the higher concentration was quite marked, although recovery was fairly complete when the strip was placed in fresh stock solution. In the 1 to 1,000 solution neither the infusion nor the evaporated extract exhibited any action on the strips; in the stronger solution (1 to 500) the amplitude was lessened in about one fourth of the experiments with each preparation. Even the 1 to 250 solution was without action on one strip from

the virgin cat uterus during ten minutes and caused but slight decrease in rate and amplitude in a second. A 1 to 1,000 solution of the fluid-extract of the drug made less than a 1 to 2,000 solution of alcohol.

Scutellaria lateriflora (skullcap): This drug exhibited a rather weak and inconstant depressant action (Fig. 10). The excursions were lessened somewhat in about two thirds of the experiments, the rate moderately slowed in one half of them; the tone was not affected. The slight action of the drug is illustrated by the fact that two strips contracted moderately after forty-five minutes in the 1 to 500 solution. Two of six experiments with the infusion 1 to 500 exhibited a slight depression of the amplitude.

Caulophyllum thalictroides (blue cohosh): Blue cohosh invariably caused a pronounced increase of tone or tetanus in all strips that gave any sign of activity and frequently initiated contractions in nonactive strips (Fig. 11). Rather promptly on the addition of the blue cohosh (fluidextract) the contractions either ceased entirely or became greatly lessened in amplitude, as the recording lever rose either considerably

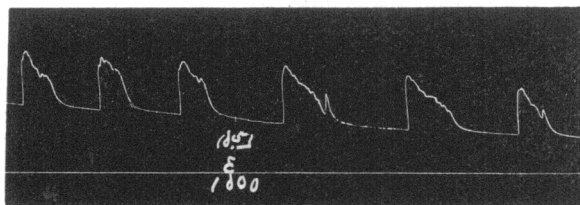


Fig. 19.—*Mitchella repens* (squaw vine); Experiment 70c, about midterm; the fluidextract in a 1 to 1,000 solution.

above, to, or just a little below the maximal point previously attained, but always considerably above the midline between the highest and the lowest levels. Occasionally, when the strip was contracting but slightly or irregularly, the contractions persisted more or less, although the tone was increased. The usual picture, however, was a prompt increase in tone with practically cessation of the contractions, whether the strip had been contracting vigorously or just moderately. The decrease in amplitude, then, seemed to be purely secondary to the marked increase in tone. This tonic state was very persistent, over an hour in a few strips, but the other experiments were usually interrupted after from twenty to forty minutes, so that the strips could be used for other drugs. However, the usual experience was that the strips seldom recovered their normal condition after remaining in the blue cohosh solution for a few minutes. The typical action was caused by the 1 to 2,000 solution in a few experiments.

Further to test the activity of the drug it was added (1 to 1,000) to twelve strips that either had shown no signs of activity after being

in the bath for from twenty to sixty minutes or had ceased to contract after a period of activity; eight of these strips gave the usual increase in tone and four of these also started to contract. The 1 to 1,000 solution also increased the tone of one of three strips that had been rendered inactive by valerian; the cohosh was added directly to the valerian solution.

The infusion was practically inactive in strengths up to 1 to 500. Four experiments were made with the 1 to 1,000 solution, which was increased to 1 to 500. In all cases control experiments, made by adding the alcoholic solution directly to the infusion, gave the characteristic increase in tone. The active principle of the blue cohosh is not extracted in the aqueous preparations.

The experiments were made with uteri in all stages of pregnancy and with the virgin uterus as well. The action was similar in all of the conditions.

Cnicus benedictus (blessed thistle): This drug has practically no action on the excised uterus; even very high concentrations (1 to 200) have little action, but tend toward depression (Fig. 12). The fluidextract and the infusion were inactive. There was evidence of slight stimulation (increased amplitude and tone) in many of the experiments with the evaporated fluidextract, but this was not sufficiently great to be of significance. All stages of pregnancy were present.

The Fluidextract: The 1 to 1,000 solution was practically inactive, for eight of nine experiments were quite negative and the exception showed but slight depression. The extracts are made with 40 per cent. alcohol, which would make less than a 1 to 2,000 solution in the bath, so that the alcohol could have exerted little if any action. Strengthening the solution to 1 to 500 resulted in moderate depression in two of five experiments. In two experiments on strips from the virgin cat the 1 to 1,000 and the 1 to 500 solutions were without action. Even the 1 to 250 solution was inactive during ten minutes in one case and but slightly lessened the tone in the other. In the latter, however, the contractions were practically unchanged during fifteen minutes, so that the decrease in tone may have been no more than a natural variation.

The Infusion: The results were negative in the majority of cases, both with the 1 to 1,000 and the 1 to 500 solutions. The exceptional results were about equally divided between slight stimulation and depression, that is, probably merely just the natural variations met in control experiments.

The Evaporated Extract: In the 1 to 1,000 solution this increased the amplitude and the tone slightly in two thirds of the experiments (eight of twelve) and increased the rate in one third of them. Part of the increase in function was probably but the normal natural variations, for in some of the experiments there is a probability that the drug was introduced before the curve had become constant. This may explain the difference between the results with the fluid and the evaporated extract. At any rate it is significant that there was no evidence of depression. In view of the uniform inactivity of the fluidextract (in about the same number of experiments) this slight variation can be of no significance. Increasing the strength of the solution to 1 to 500 decreased the number of experiments that showed stimulation to one of six, while four gave negative results and the final one gave depression. With even stronger solutions (1 to 200) there was little permanent action

on the strips, although there was depression of the amplitude in part of them. Two of ten cases were quite negative. In the others one phenomenon was quite constant. On the addition of the drug there was a temporary cessation of the contraction over a period of time corresponding to two or three contractions. Following this brief period one half of the strips returned to the normal condition and remained so during thirty minutes or more, while the others were permanently depressed, considerably in two cases and but slightly in two others. The brief period of cessation of activity could bear little significance in the intact animal unless possibly by an intravenous injection of an enormous dose. The tone was unaffected. The results were similar in vigorously and poorly contracting strips. Citation of a single experiment will illustrate the inactivity of the drug.

Experiment 99: The strip was contracting vigorously. Blessed thistle solution (1 to 200) caused a brief cessation of contraction and then for a short time the contractions were more vigorous than the normal. After ninety minutes the strip was still contracting well although the amplitude was considerably lessened. Two hours later (three and one half hours after the addition of the drug) the strip was still quite active.

Carduus marianus: Several experiments with the 1 to 500 alcoholic solution of the seed of this drug showed it to be without activity.

Viburnum opulus (cramp bark): This drug was probably without action on the excised uterus of the guinea-pig. There was, however, a tendency toward increase in tone in the virgin pig (Fig. 13) and a slight decrease in excursion in the pregnant pig (Fig. 14). In either case the action was neither sufficiently great nor uniform to merit serious consideration, except possibly as it indicated lack of depression on the virgin uterus.

The Virgin Pig: The fluidextract was used. The increase in tone was fairly constant with the 1 to 1,000 solution (four or five cases) and persisted, though with a decreasing percentage, as the solution was increased to 1 to 500. Occasionally the increase was considerable. There was an infrequent and slight increase or decrease in rate and amplitude. In one of two cases with a 1 to 250 solution there was still an increase in tone (rate and amplitude unchanged). In the second the tone was decreased slightly, possibly because there was less time for relaxation as the rate was somewhat increased. Even stronger solutions may show little evidence of depression. A 1 to 100 solution decreased the tone that had been raised by a 1 to 250 solution, but not below the normal. In a second case the tone was considerably increased by a 1 to 100 solution. Too much emphasis should not be placed on the apparent increase in tone from even strong solutions of *Viburnum opulus*, because the limited number of experiments may not exclude the natural variations in action. However, it is significant that there was no depression.

The Pregnant Pig: Two thirds of the cases exhibited a somewhat decreased amplitude with the fluidextract (1 to 1,000 and 1 to 500). The tone was not changed and the rate also was practically uninfluenced. The evaporated extract was without action except in a single case that gave a considerable increase in tone. The infusion was either quite negative or irregular in action, for a few cases showed either slight stimulation or depression. Even a 1 to 100 solution was without action. Practically all the strips from the pregnant uterus were contracting vigorously.

Acer spicatum (maple bark): This drug is said to be substituted for *Viburnum opulus*. It is probably quite void of activity, for in the majority of the experiments with the fluidextract the contractions were

not altered, although in a few experiments the excursions were slightly increased. When the strips were contracting regularly the infusion, even in strong solutions (1 to 250), did not change the curve (Fig. 15).

Viburnum prunifolium (black haw): With the possible exception of an insignificant increase in tone, *Viburnum prunifolium* was without action in this work (Fig. 16). This conclusion was drawn from a total of forty experiments. The slight increase in tone occurred with the fluidextract only, in about one half of twenty experiments. The action was similar in the virgin and the pregnant uteri. The details are found in the table. The increased tone was not secondary to an imperfect relaxation from an increased rate, for the rate was increased in but two of the experiments showing an increased tone. At best, the change in tone was always slight and probably of little significance. There was no evidence of depression in solutions up to 1 to 250 in a single experiment with the virgin cat. The infusion and the evaporated extract were without action in fifteen cases, although one of them gave a slight depression of tone. In the great majority of all experiments the rate and amplitude were unaffected and the variant cases were about equally divided between stimulation and depression.

The bark of the stem was inactive in the 1 to 500 solution of the fluidextract and of the infusion. In two experiments the 1 to 500 solution of both preparations (making a 1 to 250 in all) was inactive. In one experiment the strip was not contracting, but was increasing in tone. The tone remained above normal during fifty minutes' immersion in the viburnum, when oil of valerian (1 to 25,000) promptly lowered the tone below the normal.

Chamaelirium luteum (false unicorn): The results of a large number of experiments with this drug, in 1 to 1,000 and 1 to 500 solutions, demonstrate that it has no constant action. In the far greater number of experiments there was no demonstrable change in the movements of the strip. In the exceptional instances there was no uniformity in the action or in the function affected, indicating that they were in all probability merely natural variations. The variations may be of sufficient merit to discuss, however, for several times there was a marked increase in tone in two virgin and two pregnant uteri, the latter contracting vigorously. The action was especially noticeable in one virgin strip that had been contracting very slightly. Occasionally similar phenomena are met in control experiments, but as it occurred more frequently (four times) with this drug, it may have a little significance. Several times the strips were somewhat depressed, but increasing the solution to 1 to 500 did not further depress, so that such action was probably accidental. These experiments were met a little oftener with the evaporated alcoholic solutions, so that the alcohol was

not the cause of the depression. The infusion (1 to 1,000 and 1 to 500) was inactive.

Leonurus cardiaca (motherwort): The alcoholic solution of the drug were practically inactive, as but three of fifteen experiments gave a moderate decrease in excursion. The infusion (1 to 500) depressed the excursion, as a rule; although this was not marked and in some instances was rather doubtful, nevertheless, there was no sign of a stimulant action. It may be that a principle of slight activity is extracted in the aqueous but not in the alcoholic menstruum.

Castanea dentata (chestnut): The preparation is practically void of action, although occasionally there seemed to be evidence of slight depression. This was not of sufficient intensity to be of any significance (Fig. 17). The infusion was also without action. Nearly all the strips were very active. This preparation was used as an example of an indifferent bark to see whether the tannin or other constituents in any way influenced the activity of the muscular strips.

Passiflora incarnata (passion flower): This is an inactive drug (Fig. 18); nine of ten experiments with the fluidextract were practically negative and the exception gave an immaterial increase in tone and a decrease in amplitude. The evaporated extract gave irregular results and the infusion was negative. All the strips were contracting vigorously.

Mitchella repens (squaw vine): This also is practically inactive (Fig. 19). All experiments with the evaporated extract and the infusion were negative. With the fluidextract the results were somewhat irregular, as in about an equal number of cases there was either no action or an immaterial increase or decrease in excursion. The variations at best were slight and within the limits of the natural variations. The strips usually contracted vigorously, but the less active ones gave the usual results.

CONCLUSIONS

The drugs employed with but one exception manifest their actions on the amplitude of the contractions rather than on the tone or the rate of contraction. The action is essentially the same on the pregnant and on the virgin uterus.

The following drugs lower the amplitude of the excursion, as their primary action: *Aletris farinosa*, *pulsatilla pratensis*, *Scrophularia nodosa* and *Ichthyomethia piscipula* are very active in the strengths used; *Valeriana officinalis* (the oil is very active) and *Cypripedium pubescens* somewhat less active; *Dioscorea villosa*, *Scutellaria lateriflora* and *Senecio aureus* least of all.

Caulophyllum thalictroides puts the strips into tonic contraction or tetanus.

Chamaelirium luteum, *Leonurus cardiaca*, *Passiflora incarnata*, *Mitchella repens*, *Viburnum opulus* and *V. prunifolium*, *Acer spicatum*, *Cnicus benedictus*, *Carduus marianus* and *Castanea dentata* are inactive.

The following infusions only are active and they are less active than the corresponding alcoholic preparations: *Leonurus*, *Scrophularia*, *Ichthyomethia* and *Cypripedium*.

We are glad to express our indebtedness to Prof. Sollmann for reviewing the manuscript.