

THE ACTION OF VARIOUS "FEMALE" REMEDIES ON THE EXCISED UTERUS OF THE GUINEA-PIG *

J. D. PILCHER, M.D.

W. R. DELZELL

AND

G. E. BURMAN

OMAHA

Among the drugs listed as unimportant, inactive or useless in the reports of the Council on Pharmacy and Chemistry of the American Medical Association are a number that have been reputed to possess certain "tonic" or "sedative" actions on the uterus. These drugs have never been studied pharmacologically; clinical observations on their usefulness are either entirely wanting or are inconclusive, and undoubtedly they would have fallen into disrepute long ago had they not been foisted on the medical profession in the form of a long list of proprietary preparations and on the public in the form of "patent" medicines.

These drugs, and specimens of the claims that have been made for some of them in medical literature or in proprietary medicine advertising, are as follows:

Black haw (*Viburnum prunifolium*): "sedative, antispasmodic, nervine and tonic . . . of value in all congested, inflamed and irritable conditions of the uterus, ovaries and adnexa." "Will certainly relieve dysmenorrhea."

Blue cohosh (*Caulophyllum thalictroides*): ". . . quite an efficient remedy to increase the force of uterine contractions . . . of service in the treatment of spasmodic dysmenorrhea."

Cramp bark (*Viburnum opulus*): "A uterine tonic and sedative of surprising potency." ". . . highly beneficial in the cramps of disordered menstruation, in the convulsions of pregnancy, in spasmodic contraction of the bladder and in cramps and spasms in general . . . anti-abortion and alterative to the reproductive system."

Lifefoot (*Senecio aureus*): "Regulates the functions of the uterus and allied organs, diminishing secretion when excessive or increasing it if scanty. It also exerts a tonic effect on the uterine adnexa, and is especially indicated in amenorrhea, menorrhagia and chlorosis."

Jamaica dogwood (*Ichthyomethia piscipula*, *Piscidia piscipula* or *Piscidia erythrina*): "Through its action on the muscular system it can supplement viburnum and neutralize hydrastis in spasmodic dysmenorrhea."

Pulsatilla (*Pulsatilla pratensis* or *Anemone pulsatilla*): "a curative in uterine colic and . . . a valuable remedy in inflammatory conditions of the uterus and ovaries . . . a valuable tonic stimulant to the uterine fibers."

St. Mary's thistle (*Silybum marianum*, *Mariana mariana*, *Carduus marianus*): ". . . there is no other remedy in the materia medica of equal value in the treatment of chronic uterine hemorrhage and

melenia, inasmuch as it not only checks the immediate flow, but by continued use remedies the causes on which it depends, regulating and restoring the natural portal circulation, and, where amenorrhea depends on such irregularity, it tends to restore the normal flow."

Skullcap (*Scutellaria lateriflora*): ". . . possesses tonic, nervine and antispasmodic properties in a high degree . . . of inestimable value in the treatment of amenorrhea, dysmenorrhea, menorrhagia and kindred disorders."

Unicorn root (*Aletris farinosa*): "Exerts a specific influence upon the uterus, imparting tonicity and vigor to that organ."

Valerian (*Valeriana officinalis*): "is antispasmodic and a gentle stimulant to the nervous and circulatory systems . . . is a valuable remedy in all forms of hysteria."

Wild yam (*Dioscorea villosa*): ". . . a powerful antispasmodic, relieving uterine pains, cramps, etc."

In addition, several drugs were examined for which few specific claims have been made, or none at all, but which are ingredients of various more or less extravagantly advertised "patent" or proprietary medicines. These are: blessed thistle (*Cnicus benedictus* or *Carduus benedictus*), false unicorn (*Chamaelirium luteum* or *Helonias dioica*), lady's-slipper (*Cypripedium pubescens*), motherwort (*Leonurus cardiaca*), passion flower (*Passiflora incarnata*) and squaw vine (*Mitchella repens*). Mountain maple (*Acer spicatum*) was examined because it is said to be substituted for cramp bark (*Viburnum opulus*), which is believed not to have been on the American market for a number of years. As a control chestnut bark (*Castanea dentata*), a drug that has no uterine action, was employed.

This paper is a summary of a preliminary pharmacologic investigation of these drugs on the isolated uterus of the guinea-pig. The guinea-pig was chosen, as the uterus of this animal is usually more active under experimental conditions than that of other animals.

METHODS

A strip of the uterus was attached to a muscle lever and immersed in a bath of well oxygenated Tyrode's fluid¹ and the contractions recorded on smoked paper. On immersion in the bath there is usually a latent period of from a quarter of an hour to an hour before the movements are initiated or become regular; frequently the strips do not become active. After the registration of a satisfactory control tracing, the drugs were added to the bath in the proportion of 1 or 2 parts of the drug to 1,000 of the bath.

The strip remained in the bath until there was evidence either of the activity or inactivity of the added drug. Before a drug was deemed inactive it was left in contact with the strip of uterus for about fifteen minutes, as a rule, but occasionally for an hour or even longer, before renewing the bath and adding a fresh drug. The active preparations, as a rule, caused a prompt change in the character of the tracing; usually they were allowed to act but a short time as it was found that prolonged action frequently destroyed the usefulness of the strips for other experiments. A few experiments were always made to show that the action of a given drug was persistent. The fluid extracts and

* From the Pharmacological Laboratory of the University of Nebraska, College of Medicine.

* This investigation was undertaken at the suggestion of the Therapeutic Research Committee of the American Medical Association; the Association assumed part of the expense of the investigation.

* The detailed results and tracings will appear elsewhere.

1. Tyrode's fluid contains the salts of the blood in isotonic quantities.

the freshly prepared infusions of each drug were employed.²

As the fluidextracts were alcoholic solutions, control experiments were made with equal amounts of alcohol, and these showed that the alcohol of the extract had no effect on the muscular strips in the concentrations used in these experiments; the fluidextracts, evaporated at about 45 C. (113 F.), manifested the same action as the fluidextracts themselves.

The interpretation of the activity of a drug was judged by the change in the character of the muscular contraction. Theoretically the action could be manifested in three ways, on the amplitude and rate of the excursion or on the muscular tone. Practically it was found that, with but one exception, the size of the excursion was the feature affected; the action on the rate was always secondary to this. In but a single instance was the tone primarily affected; secondarily, a number of drugs slightly decreased the muscular tone. When the contractions were altered the tendency was always toward a reduction in the amplitude of the excursions; in no instance did a drug appreciably increase the excursions.

RESULTS

The active drugs.—The following drugs lessened the amplitude of the excursions or, in the stronger solutions, caused their complete cessation: Unicorn root (*Aletris farinosa*), pulsatilla (*Pulsatilla pratensis*), Jamaica dogwood (*Ichthyomethia piscipula*), and figwort (*Scrophularia nodosa*); somewhat less active were valerian (*Valeriana officinalis*) and lady's-slipper (*Cypripedium pubescens*); the drugs possessing very weak actions were wild yam (*Dioscorea villosa*), life root (*Senecio aureus*) and skullcap (*Scutellaria lateriflora*). The infusions of figwort, Jamaica dogwood and lady's-slipper were active after the manner of the alcoholic preparations, but to a much lesser degree. The infusion of motherwort possessed very insignificant depressant properties, although the fluidextract was inactive. Blue cohosh (*Caulophyllum thalictroides*), even in the 1:2,000 solution, very promptly put the strips of uterus practically into a state of tonic contraction or tetanus. The action was very persistent and the normal muscular state was not resumed after the strips were placed in fresh Tyrode's solution. The infusion was quite inactive.

The inactive drugs.—The following were quite inactive or inert, both the fluidextract and the infusion: black haw (*Viburnum prunifolium*) the bark of both root and stem, cramp bark (*Viburnum opulus*), squaw vine (*Mitchella repens*), chestnut bark (*Castanea dentata*), false unicorn (*Chamaelirium luteum*), passion flower (*Passiflora incarnata*), blessed thistle

(*Cnicus benedictus*), St. Mary's thistle (*Silybum marianum* or *Carduus marianus*) and motherwort (*Leonurus cardiaca*); sodium valerianate was also inactive in solutions up to 1:1,000. The strips were allowed to remain in the solutions of these drugs in concentration up to 1:500 for some time (many of them for an hour) without evidence that the drugs changed the character of the tracings in any way. Control experiments showed that the strips were capable of being depressed or stimulated by these drugs so that there can be no question of their complete inactivity.

COMMENT ON RESULTS

The question arises, How far can the results of this work on the excised strips of uterus muscle be compared to the action in the intact animal and in the human uterus? There are no experimental data on the point at present, but judging by analogy to other drugs, notably pituitary extract and ergot, it may with perfect safety be assumed that the action would be the same on the uterus in situ as on the excised strips of uterus, provided the drug reached the uterus in a similar concentration; this refers to the action on the muscle directly and on the nerve endings; any action on the local circulation can be dismissed, as no known drug acts specifically on the circulation of any organ. The action on the human uterus would be the same, as a similar physiology implies a similar pharmacology. It is improbable, however, that the concentrations of the drug used in this work could be attained in the body in whatever way they were administered. From preliminary work on another form of smooth muscle (intestine) it seems highly probable that these drugs act in no sense specifically on the uterus but on smooth muscle in general, so that, even granted that they could be taken in sufficient dosage to exhibit their characteristic action on the uterus, it is more than probable that the action on the other forms of smooth muscle (intestine, blood vessels, etc.) would overbalance any favorable effect there might be on the uterus.

If the term "uterine tonic" implies a drug that increases the muscular tone of the uterus, with one possible exception (blue cohosh), the members of the group examined can be said to be absolutely void of any such action, for none of them increased the tone at all and many of them somewhat lessened the tone secondarily, although the majority were quite void of any action. Without question, then, the entire list of "uterine tonics," whose supposed activity depends on the presence of the drugs here reported, can be emphatically stated to be inactive; those containing blue cohosh may be a possible exception to the statement but, in view of the difference between the concentration likely to be attained in the body and that used in the experiment, it is highly improbable that this drug could manifest the same action in the body that it did on the excised uterine tissue. It is rather striking that some of the proprietary or "patent" nostrums are said to contain both cohosh and one or more of the depressant drugs; it is hardly worth while entering into a discussion of the result of mixing two or more preparations of this class with directly opposite physiologic actions.

The work shows further that the domestic use of teas made from these drugs, for any supposed action on the uterus, is quite irrational, for water either extracts but a very small part of any of the active principles of the drugs or, in the majority of them,

2. 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: blue cohosh (*Caulophyllum thalictroides*), false unicorn (*Chamaelirium luteum*), figwort (*Scrophularia nodosa* or *marylandica*), Jamaica dogwood (*Ichthyomethia piscipula*), lady's-slipper (*Cypripedium pubescens*), life root (*Senecio aureus*), motherwort (*Leonurus cardiaca*), mountain maple (*Acer spicatum*), passion flower (*Passiflora incarnata*), pulsatilla (*Pulsatilla pratensis*), skullcap (*Scutellaria lateriflora*), squaw vine (*Mitchella repens*), unicorn root (*Aletris farinosa*), valerian (*Valeriana officinalis*); by Prof. E. N. Gathercoal: black haw (*Viburnum prunifolium*), blessed thistle (*Cnicus benedictus*), and cramp bark (*Viburnum opulus*). A fluidextract was made by L. E. Warren of the American Medical Association Chemical Laboratory from each one of the following named authentic drugs: black haw (*Viburnum prunifolium*), bark of root; black haw, bark of stem; cramp bark (*Viburnum opulus*), and mountain maple (*Acer spicatum*); all other fluidextracts were made by different firms and their identity was not established, but, as the actions of two preparations of each drug was about the same, their identity is probably authentic.

none at all. The principles are probably of a resinous nature and therefore practically insoluble in water.

CONCLUSION

Not only are the drugs in this list unimportant, as they have been styled; they are also practically worthless. Their use is harmful as well as futile, since it tends to perpetuate therapeutic fallacies.

OPERATIVE TREATMENT FOR THREATENED GANGRENE OF THE FOOT

WITH SPECIAL REFERENCE TO REVERSAL OF
THE CIRCULATION *

J. SHELTON HORSLEY, M.D.

RICHMOND, VA.

Threatened or slow gangrene of the foot follows a diminution of the caliber of the blood vessels supplying the foot. This results from a disease which may be clearly systemic or which may manifest itself chiefly in the blood vessels of the lower extremities. Sudden occlusions, as by emboli, with consequent rapid gangrene, do not come under the title of this paper.

The diseases of the vessels which cause slow or threatened gangrene of the foot may be divided into four groups:

1. *Arteriosclerosis*.—This condition is caused by toxic products which may come from deranged metabolism, as in nephritis; from infectious diseases, as syphilis, or from general wear and tear, as in old age. It is found chiefly in the arteries. There is excessive thickening of the media or intima or of both.

2. *Intermittent Claudication*.—This disease was described by Charcot and occurs in the legs. It consists of a vasoconstrictor spasm in arteries that are already affected with arteriosclerosis. The spasm appears on exertion, when the tissues require an increase of blood, and causes painful cramps. During the cramps the legs are cold and pale or mottled. After rest the cramps may disappear, but pulsation of the tibial arteries is feeble or lacking.

3. *Raynaud's Disease*.—In this disease there is no organic pathologic condition, but the constriction of vessels is due to intense spasm of the small arterioles or venules just before they become capillaries. It may be of three types, a spasm of the arterioles alone, causing a bluish color; of the venules alone, making the affected parts red, or of both the arterioles and venules, causing a blanching. Any of these types may result in gangrene.

4. *Thrombo-Angiitis Obliterans*.—Leo Buerger of New York has made a careful study of this disease, which was formerly rather vaguely classified and was referred to clinically under various terms. The German writers considered it an obliterating endarteritis. Buerger has shown that thrombo-angiitis obliterans has many distinctive characteristics and that the occlusion of the vessels is not caused by a thickening of the intima, but by a thrombosis.¹ This disease occurs chiefly in the blood vessels of the lower extremity, though occasionally the upper extremity is affected. It begins, not in the arterioles or in the smallest arteries,

but in vessels of medium size, and then ascends. In the foot it is usual, according to Buerger, for the dorsalis pedis and plantar arteries to be involved first, and later the disease ascends to the tibials and sometimes to the popliteal artery. The deep veins are affected in about 40 per cent. of the cases. Occasionally a segment of apparently healthy blood vessel is found between diseased portions of the same vessel. Buerger has demonstrated that in the first stage of the disease the affected vessel shows signs of inflammatory change, and he seems to have proved quite clearly that thrombo-angiitis obliterans is due to some microbe or to a toxic material which, however, has not yet been isolated.

In the first stage there is a round cell infiltration of the media and adventitia of the vessel and usually of the tissue around the vessel. Soon after this, and sometimes almost accompanying it, a red clot forms in the vessel and practically always obliterates it. Then small foci appear in the clot, which Buerger refers to as "miliary abscesses." They are collections of pus cells and leukocytes that form in the thrombus, usually around its periphery. The leukocytes apparently come in from the media. Angioblasts then grow into the clot and the ordinary process of organization and canalization occurs in the thrombus as elsewhere in the body except in these small foci. Here the angioblasts seem to lose their power of producing blood vessels and terminate around the edge of these pus foci as endothelial cells or penetrate the foci and either fray out or produce giant cells. A little later the giant cells arrange themselves around the periphery of the focus, the leukocytes disintegrate, and the resemblance to a tubercle is marked. After this the degenerated products are absorbed and the focus becomes connective tissue. Then all traces of acute inflammatory process disappear. The leukocytes and wandering cells in the media and adventitia and perivascular tissue disappear and the obliterated or canalized vessel is left as the final product.

This is the life history of the disease as traced by Buerger. It begins with every evidence of acute inflammatory reaction, is followed by an apparently specific process in the tubercle-like formation, and ends in organization and canalization of the thrombus. The disease is sometimes extensive and often ends abruptly in a clot which projects into the lumen of a vessel that appears to be normal. It may progress in stages, so that, while the vessels in the foot may show the old type of organized and canalized thrombus, farther up in the leg the tubercle stage may be seen, and still farther in the upper tibials the acute inflammatory reaction with a red clot, pus foci, and infiltration of the blood vessel wall and perivascular tissue may appear.

Thrombo-angiitis obliterans occurs between the ages of 20 and 35 and rarely after 40. It is found chiefly in males. Most of the patients are Russian Jews, or descendants of Russian Jews, or Jews from the country around Poland, the eastern part of Austria-Hungary or eastern Germany. Koga, however, has found this disease among the Japanese, and the patient whose case is reported in this paper had no Jewish ancestry and was born and raised in Virginia. The symptoms depend largely on the extent of the disease. Buerger has found that the superficial veins are often involved and may give no symptoms in themselves. There may be vasomotor symptoms such as flushing of the leg or foot when it hangs down, followed by blanching when it is elevated. Ordinarily the foot is cold and of a dark bluish or purplish color. Often pain in

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1. Buerger: *Am. Jour. Med. Sc.*, October, 1908, p. 567; *ibid.*, February, 1915, p. 210; *Surg., Gynec. and Obst.*, November, 1914, p. 582; *Jour. Med. Research*, November, 1914, p. 181; *Arch. Diagnosis*, October, 1915.