A Comparative Review of Eclectic Female Regulators

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Abstract

Botanical medicines have been used for centuries to regulate abnormal menstrual patterns, especially after childbirth. However, the clinical development of New World medicinal herbs, formulas and dosages, have evolved dramatically over the past 150 years. Uterine tonics, sedatives, phytoestrogens and their clinical applications are discussed here, based primarily on the writings of the Eclectic Medical Doctors of the late 19th and early 20th centuries and subsequent scientific research findings.

RESEARCH REVIEW

BACKGROUND

Menstrual Variation

Changes in typical menstrual patterns commonly occur in women. These variations can be especially distracting if the discomfort before menses or the pain during the period becomes severe or if the menstrual flow is absent, irregular, or excessive. The interplay of activity, health, age, stress, mental and emotional demands, travel, and nutrition all play a role in these changes. Following child-bearing the period of adjustment can become prolonged for some individuals as hormonal cycles are reestablished. Botanical remedies are often employed in an attempt to restore the functional pattern that is normal for a particular woman. The biological effects of these plants need to be understood as thoroughly as possible for their most effective use.

Eclectics and Botanical Medicine

The use of herbs as female regulators or restoratives has been common for ages throughout the world. Indigenous peoples of the New World employed herbs for such purposes as well. However, their practices were often not well documented and typically existed in a cultural context outside of Western medical understanding. With the development in the 19th century of Thomsonian folk applications and professional physiomedical and eclectic medicine, the native American herbs were popularized and incorporated into clinical practice for treating health problems, including those of the female reproductive system. Refining the medical use of many of these plant remedies occurred over the last 150 years, but much of the understanding of their activity and indications was established in the first half of this period. As a result of their investigations, contributions to the knowledge about American plant remedies were made by numerous doctors, mostly in the eclectic profession, through letters and articles advocating these remedies that were published in professional journals. The updated *materia medicas* by the eclectic medical doctors Harvey W. Felter (1) and Finley Ellingwood (2) published around 1920 utilized the new discoveries and expanding information. Their descriptions of native botanical medicines were based on their decades of professional experience and the clinical prescribing of others like them. Since then, published reports in the American literature on most botanical medicines have been greatly reduced. Much of what has been passed on by herbal writers in simplified form was borrowed from these earlier authors and practitioners.

A number of Old World herbs had long been employed by doctors and others for treating conditions of concern to women. The

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introduction of these New World plants into medicine did not occur without a certain amount of controversy as to their pharmacological activity and the accurate identity of medicinal species, as well as the appropriate forms and dosages. This has been documented by both standard pharmacology journals and the *Eclectic Medical Journal.* With the help of the recent indexing of the entire *E.M.J.* by Eclectic Institute, Inc., the identification and therapeutic applications of some of the more common women's remedies will be reviewed in this article. The eclectic *materia medicas* have also been used as important references, along with a collection of later formulas taken mostly from the *Eclectic Medical Gleaner.* (3) These clinical findings are then compared with contemporaneous medical and pharmacognostic research together with more recent studies on these plants and their components, especially their pharmacological activities as shown by laboratory research. Many of the doses given by the eclectic authors were for Specific Medicines produced by the Lloyd Brothers Pharmacists which are no longer manufactured. Only the doses of forms still available today have been included in this article. Updating the information provided by the eclectics and others about these plants should help us to better understand their mechanisms of action; they can then be more confidently selected, and their application can be more specific and effective.

EXCLUDED CONDITIONS AND TOXIC REMEDIES

In the process of reviewing nearly a dozen female regulators, certain topics such as menopause were excluded so as to focus on typical menstrual difficulties in women of reproductive age. Conditions involving sexual function or the external genitalia and the local or external use of herbs will not be considered. Herb use during pregnancy has a greater potential risk and requires a separate thorough discussion. (See Appendix A of *The Toxicology of Botanical Medicines,* rev. 2nd ed., by F. Brinker, Ecl. Med. Pub., Sandy, Ore., 1996.) Likewise, oxytocic herbs and their potent alkaloids such as sparteine from *Cytisus scoparius* and *Claviceps purpurea* with its ergometrine, ergotamine, and ergotoxine which are utilized primarily in labor and delivery or postpartum care (1,4) are not covered here.

Certain potentially toxic botanical medicines used by the eclectics for women's problems and other conditions will not be discussed. Some of these were prescribed in safe, small doses alone or in combinations as synergists according to guiding constitutional symptoms. Such remedies include *Ignatia amara, Gelsemium sempervirens, Atropa belladonna, Bryonia alba,* and *Rhus toxicodendron.* (1,2,3) Other plants and their potent volatile oils considered as active uterine stimulants were employed in higher doses that could be toxic. (1,2) Studies on the "emmenagogue oils" from *Hedeoma pulegioides* (pennyroyal), *Juniperus sabina* (savin), *Tanacetum vulgare* (tansy), *Ruta graveolens* (rue) and *Thymus vulgaris* (thyme), as well as turpentine and apiol, showed that low doses had no effect and high doses had a depressant effect on cat and human uterine muscles *in vitro.* Therefore their emmenagogue action seems to be due to reflex uterine contractions from renal and gastrointestinal irritation and inflammation caused by the oils rather than from uterine-specific effects. (5,6) A plant that had been a popular uterine tonic is *Senecio aureus* (life root). (1,2) However, it will be passed over since it has been shown to contain several pyrrolizidine alkaloids. (7) These *S. aureus* pyrrolizidines have the type of chemical structure associated with similar alkaloids from other *Senecio* species which cause hepatic toxicity and should be avoided. (8)

REPUTED UTERINE TONICS

UTERINE TONICS VERSUS OXYTOCICS

Uterine tonics are described as agents that add tone and strength to the uterus to perform its natural functions. (2) These tonics can act as indirect emmenagogues when they help produce or increase the menstrual flow. However, not all emmenagogues are uterine tonics. Uterine sedatives can also act as indirect emmenagogues where there is excessive uterine contraction. (1,2) Other emmenagogues have a direct oxytocic effect that increases the expulsive power of the uterus by stimulating a strong, short-term muscular contraction of the womb. For example, *Gossypium* (cotton root) is a uterine stimulant that induces or increases uterine contractions. (1)

Oxytocics such as *Gossypium* are also often employed to control acute uterine hemorrhage, especially after childbirth. (1) Fresh *Gossypium* root bark is noted for its hemostatic powers to prevent hemorrhage from uterine fibroids, menorrhagia, and metrorrhagia. (2) Apart from its uterine stimulant effect an extract of *Gossypium* root bark was also shown to produce an accelerated coagulation of blood, increase the serum prothrombin, and constrict blood vessels in animal tests. (9)

Some uterine tonics have a mild uterine stimulant activity initially and have been used for excessive menstrual flow when uterine contractile power is weak. However, their effects are not limited to the acute problem but help address the underlying condition. Since their contractile effects are not as powerful or as immediate as oxytocics, uterine tonics are typically used for chronic conditions and applied over a longer period of time. Other so-called uterine tonics can have an antispasmodic and/or hormonal effect as part of their influence.

CAULOPHYLLUM AND CIMICIFUGA

For *Caulophyllum thalictroides* the common name blue cohosh has become the most familiar, but the term false cohosh has also been applied in the past. The Algonkin name "cohosh" means "it is rough" and was originally applied by the Canadian Montagnais to the bristly fruit of *Ribes lacustre.* This designation was further applied by whites to smooth plants besides *Caulophyllum* including *Cimicifuga racemosa* and *Actea spp.* Some of *Caulophyllum*'s other names such as papoose root and squaw root indicate its importance to indigenous American women. (10) Members of the Fox, Menominee, and Potawatomi tribes used an infusion or decoction of *Caulophyllum* root to control profuse menstruation. Ojibwa women used it for painful menstruation and some Cherokees took it to relieve inflammation of the womb. (11)

The first written report on *Caulophyllum* was in 1828 by Durand. Early classifications of the root's activity were as an oxytocic and emmenagogue. Circa 1900 the indications for its use included uterine pain, weight and fullness in the

pelvis, and pain extending into the legs. It was seen as a direct emmenagogue, acting specifically on the uterine muscle or mucous membrane and not indirectly as a tonic. However, *Caulophyllum* was also applied to chronic uterine disease where there was irritation and was considered ideal for leucorrhea. *Caulophyllum* was considered a superior remedy for uterine subinvolution, prolapse, anteversion, or retroversion. It was also utilized for acute and chronic ovarian disorders. It was believed unsurpassed for dysmenorrhea and amenorrhea. (12) For rheumatic dysmenorrhea with severe, irregular, spasmodic pains which cause the woman to cry out, the indicated dose of tincture was 10 drops every half hour. (13) The later eclectic *materia medicas* concur with these indications and agree that *Caulophyllum* is similar to *Cimicifuga* as a specific for chronic inflammatory conditions of the uterus and ovaries, particularly where there is congestion with irritation. (1,2) Felter and Eli Jones also advocated the Lloyd Bros. product leontin, considered the emmenagogue principle, for amenorrhea, especially in young girls. (1,13) The dose for *Caulophyllum* fluid extract was 5-10 minims used over a considerable period of time for best results. (2)

An early study on *Caulophyllum* showed that weak dilutions of the fluid extract increased the tone of strips of excised uterus from guinea-pigs. About one third remained in tonic contraction from 20 to over 60 minutes. (14) Chemical analysis of the roots and rhizomes showed that the glycoside leontin was a saponin which was renamed caulosaponin. A similar saponin found in smaller quantities was named caulophyllosaponin. (15) On the rat, rabbit and guinea-pig uteri a crystalline glycoside from *Caulophyllum* was shown to increase the degree and rate of contraction for about 90 minutes *in vitro* and *in situ* in rats. Larger doses *in vitro* and *in situ* in rats increased the tone and rate but decreased the degree of contractions for about 45 minutes. Injected in rats *in vivo* a small increase in uterine tone was observed. (16) The glycosides produced an irritating effect on other organs. (15,16) The hot water extract and saponin-containing fraction of the roots and rhizomes had a stimulant effect on rat uterine muscle *in vitro*. The most concentrated saponin exerted a uterotonic effect. Three saponins in this fraction yielded hederagenin as the aglycone. (17) Caulosapogenin, the caulosaponin agly-cone from ethanol extracts of *Caulophyllum* roots and rhizomes, is identical with hederagenin. (18) The alkaloid caulophylline discovered in *Caulophyllum* by John Uri Lloyd was shown by its purification to be identical to methyl cytisine. (15) This alkaloid is similar in its peripheral effects to nicotine but is less powerful and much less toxic. (19,20) Other alkaloids in smaller amounts include baptifoline, anagyrine and magnoflorine. (21) The total alkaloid bases had a mild uterotonic effect *in vitro* in rats. (17)

Cimicifuga racemosa is commonly known as black cohosh, but it was also called squaw root by Barton in 1801 who noted that Indians valued it highly and used it for the diseases of women. (10) The Cherokees used an infusion of the root to stimulate menstruation and as an anodyne for rheumatic pains. The Iroquois also made an infusion of the root, but it was taken for rheumatism and to promote milk flow in women. (11)

Cimicifuga was introduced to the medical profession in 1832 by the eclectic pioneer, Dr. John King, whose writings established *Cimicifuga* as a valuable medicine. It came into general use about 1850, becoming one of the most popular eclectic remedies. *Cimicifuga* was commonly known to this profession under the name Macrotys. (10) Dr. King believed that a high concentration of alcohol (90%) was important for making the most effective extract. Extracts were only of value when made from recently dried roots. (22) The consensus among eclectic doctors was that *Cimicifuga* was specific for muscular pains of a rheumatoid character: heavy, tensive, aching, dull, sore, and stiff. This applied to skeletal muscles as well as dysmenorrhea with uterine congestion and radiating rheumatoid pains. (1,2,22-28) It was also viewed as an antispasmodic and sensory nerve sedative. (1,2) Felter states that the indications for salicylate use were also usually present. (1,25) *Cimicifuga* was highly regarded for the treatment of amenorrhea. (1,2,23,26-29) It was also employed as a uterine tonic to treat subinvolution, for malposition after restoring the position of the uterus (1,24,26,29), and for leucorrhea. (1,2) It was indicated for the pain of ovarian neuralgia. The dose of *Cimicifuga* tincture is 1/2-1 dram and for the fluid extract it is 5-30 minims. (2) Large doses can produce a severe, frontal headache with a full or bursting sensation which passes after administration is stopped. Larger toxic doses can cause sensory and circulatory depression. (1,25,27,29)

Early research showed that *Cimicifuga* produced a fall in blood pressure and stimulated the nonpregnant uterus of the guinea-pig and cat (30,31) but depressed the pregnant uterus. (30) Following the marked primary contraction of the uterus, the fluid extract of *Cimicifuga* produced a rapid relaxation and depression of this organ *in vitro*. It also produced a mild central depression in rats. (31) Acteina, a resinous component of *Cimicifuga* (once called *Actaea*), is hypotensive in rabbits and cats but not in dogs or humans, though it does act as a peripheral vasodilator in the latter two. (32,33,34) This demonstrates that biological effects cannot always be directly extrapolated between species. (33) Of perhaps greater significance is the presence of salicylic acid in *Cimicifuga* which helps explain its benefits in myalgias and neuralgias. (35)

Summary - Though the traditional uses of *Caulophyllum* and *Cimicifuga* as uterine tonics are similar in many respects, there are some definite differences. *Caulophyllum* apparently has more uterine stimulant activity, while *Cimicifuga* has a sedative and antispasmodic component to its influence. In addition, much of *Cimicifuga*'s value in uterine and skeletal pain appears to be due at least in part to its salicylate content. Another distinction involves the hormonal dimension of *Cimicifuga*'s activity which will be discussed in the section on phytoestrogens.

HELONIAS AND ALETRIS

The confusion between these two uterine tonics and their uses has been long-standing and begins with their common names. Both have been designated by various authors as unicorn root, false unicorn root, blazing star, star grass, and starwort. (1,2,10,36,37) *Chamaelirium luteum* is the correct modern scientific name for helonias (*Helonias dioica*), the name under which the

Ed. Note: 1 dram = 4 mls.; 1 minim = 1 drop; 15 minims = 1 cc.; 1 grain = 60-65 mg.

roots and rhizomes of this plant were listed in the National Formulary and the Homeopathic Pharmacopeia of the United States. (36,38) *Chamaelirium* grows in low areas from New England to Georgia and westward. The medicinal parts are actually easy to distinguish from *Aletris*. If the *Chamaelirium* rhizome is cut across, fibrous rootlets are readily visible that pierce the cortex through large foramina and are movable like threads in a needle's eye. A number of other characteristics of the plant and rhizome help identify *Chamaelirium*. It has a peculiar odor and a strong bitter taste. (10,36) The specific applications of *Chamaelirium* by the Indians are not recorded, though they used it as a medicine. (36,38,39)

The reputation of *Chamaelirium* as a remedy was said to have suffered from having *Aletris* roots mixed with it. (40) The early eclectics used it as a restorative, particularly for women with fatigue and despondency, since its tonic effects improved digestion. *Chamaelirium* was found effective in cases of amenorrhea. It is also used for leucorrhea. (2,39,40,41) It was applied to menorrhagia due to uterine atony and where there was a tendency to uterine malpositions. (2,39) The indications for *Chamaelirium* as a uterine tonic were fullness or heaviness and congestion in the pelvis with lumbar pains, restlessness, mental irritability, and weakness. (1,40,41) It was used for pains that extend down the thighs and back of the legs and in dysmenorrhea with a bearing-down pain as though the uterus would prolapse. (40) The dose of the powder is 10-30 grains (1) and of the fluid extract is from 5-30 minims. (2)

In a single test on the guinea-pig uterus *in vitro* *Chamaelirium* was inactive. (42) Early chemical analysis of its rhizomes and roots discovered the presence of sterols (38) and saponins. (43) The dried root was shown to yield 0.0013% of the steroidal sapogenin diosgenin. (44)

Aletris farinosa is another native American herb indigenous to the eastern U.S. which was formerly official in the National Formulary. (37) It is commonly called stargrass. Its root (rhizome) has neither an odor nor a bitter taste, yet much *Chamaelirium* has been sold as *Aletris*. (10) This led to an empirical understanding that their properties were interchangeable. (10,37) If early identification is accepted, its root was used by the Micmac Indians as an emmenagogue, by the Cherokees to strengthen the womb, and by the Rappahannock tribe as an infusion for female troubles. (11)

Felter believed that its use as a female remedy was due to the confusion of identifying *Aletris* with *Chamaelirium*. He valued it only as a digestive tonic. (1) Yet others found genuine *Aletris* to be a useful uterine tonic and emmenagogue. It was considered especially helpful in anemic women who were constipated or had leucorrhea, an engorged or prolapsed uterus, or any pelvic discomfort. (2,45) It was also used for too frequent menstruation with dysmenorrhea from labor-like pains. It was a remedy in cases of general pelvic weight and debility of the uterus leading to sterility. (45) Ellingwood thought that uterine weakness from too frequent childbearing or overwork was benefited by *Aletris*. For retroversion or anteversion from enfeebled tissues its influence was said to be conspicuous. It was taken in amenorrhea or dysmenorrhea where there was uterine engorgement as well as for deficient menstruation with protracted intervals. In sterility it helped to improve the function of the ovaries. The dose of the fluid extract was 10-15 minims. (2)

Research on *Aletris* has produced some interesting results. In tests of the fluid extract on an excised guinea-pig uterus *Aletris* was found to reduce the amplitude of uterine contractions. (14,42) Further pharmacological studies showed that a buffered dilution of dealcoholized *Aletris* fluid extract, despite some evidence of inhibition at high concentrations, mostly had either a slight stimulation or no effect on an isolated guinea-pig uterus. Of 22 tests on the rabbit uterus *in vitro* 12 had no effect, 5 inhibited uterine activity, and 5 stimulated activity. However, 3 of the latter were followed by inhibition. These effects were independent of the concentrations used. When *Aletris* solution was given i.v. to 19 live rabbits, it produced uterine stimulation in 8, caused slight stimulation followed by slight sedation in 6, and induced a definite sedation of uterine activity in 5. Weak dilutions depressed the activity of the isolated rat uterus including antagonizing contractions induced by pitocin. In 17 *in vivo* tests on cats under mild anaesthesia, 7 produced definite uterine depression while in the others the effect was slight or negligible. On decerebrated cats 5 tests out of 5 depressed uterine contractions. In 5 of 8 cats with induced estrus the uterus was sedated by *Aletris*, but 2 showed slight stimulation and 1 had no change. While guinea-pig and rabbit tests were quite inconstant, evidence from the *in vitro* rat and *in vivo* cat experiments suggest that *Aletris* acts mostly as a uterine sedative. (37) Several analyses of *Aletris* roots and rhizomes have shown that they contain the steroidal sapogenin diosgenin ranging in yield from 0.17-0.29%. (46,47)

Summary - The comparative value of these two female regulators is difficult to assess. While commonalities existed, universal agreement on their distinctive uses was not found among the opinions of eclectic doctors. Was this solely because of the confusion of their identities, or was *Aletris* unreliable in its effects on humans? Clearly, here is a case that illustrates the difficulty of applying animal research to human treatment. While the data on *Chamaelirium* is clearly insufficient to draw conclusions, the findings on *Aletris* were so inconsistent between and within animal test species as to be relatively worthless. Reliance on clinical assessments would give *Chamaelirium* the edge as a uterine tonic with *Aletris* used more a digestive tonic. A fascinating feature in this interspecies confusion is that both of these remedies are sources of the steroid precursor diosgenin, though the concentration in *Aletris* is about 20 times greater. The significance of their sapogenin content will be discussed in the section on phytoestrogens.

UTERINE SEDATIVES

UTERINE SEDATIVES AS SPECIFIC ANTISPASMODICS AND MILD NERVE SEDATIVES

Uterine sedatives are agents that primarily lessen or decrease uterine contractions. Some act as antiabortifacients. (2) Uterine sedatives do not depress general muscle tone or render the uterus incapable of contracting. While they are mainly smooth muscle antispasmodics or motor depressants, many function as cerebral sedatives or anodynes. (1,2) However, popular uterine sedatives do not overly affect nervous activity. For example, *Valeriana officinalis* (valerian) acts both as an antispasmodic and cerebral

sedative. (1) Though *Valeriana* has been shown to inhibit uterine contractions (14,42), its cerebral effects are more pronounced. Consequently, it has not commonly been used as a uterine sedative. Many uterine sedative remedies are mild cerebral sedatives. Certain of these botanical medicines have been used as anaphrodisiacs to reduce excessive sexual impulses. (1,2) Another aspect of the influence of some uterine sedatives is their antiseptic activity which can help reduce irritation produced by infectious agents. The different combinations of activities make certain herbs more alike and others less alike. Comparing the botanical medicines which are most similar will help to distinguish their specific usefulness.

Dioscorea and Piscidia

Dioscorea villosa is the only wild species of its family to be found in the United States. The other members are found growing naturally in Central and South America. (48) It is usually known as wild yam or colic root though its long, slender rhizome is the actual part used. The heart-shaped leaves of this vine are covered with a thick pubescence on their underside. It has at times been adulterated with the large, knotty rhizome of its smooth-leafed variety *glabra* which eclectic physicians insisted did not possess the medicinal properties. (10) The only recorded use of *Dioscorea* root by early native Americans was as an analgesic to relieve pain at childbirth. (11)

The eclectics believed that *Dioscorea* root loses its therapeutic value after a year, so it was gathered fresh each year, carefully dried, and extracted with water or alcohol. (10) Early eclectic use of *Dioscorea* indicated that it acted by overcoming irritation of mucous membranes and the attendant pain resulting from spasmodic contractions of underlying muscle fibers. Its use as an anodyne and antispasmodic applied to dysmenorrhea arising from spasmodic irritation within the uterine neck. (49) Later it was applied to uterine cramps, neuralgic dysmenorrhea, and ovarian neuralgia. (1,2,50) Though considered a nerve sedative, *Dioscorea* serves more as an antispasmodic than an anodyne. (1) Specific indications for its use include paroxysmal pain due to contraction of nonstriated musculature of tubular organs (colic) caused by irritation and gradually relieved by pressure. It acts best for dysmenorrhea when given in hot water. (1,2,50,51) The dose of the powder was from 5-60 grains. A dose of 2-6 fluid ounces of a decoction made by boiling 1 ounce of dried *Dioscorea* rhizome in 1 pint of water was also used. (1)

Dioscorea villosa fluid extract was tested on the excised guinea-pig uterus and found to have no (14) or a slight effect in reducing the amplitude of contractions. (42) *Dioscorea* has long been known to contain a saponin-like substance (1,2,50), and this was found to be the sapogenin diosgenin. (48) If diosgenin were the active antispasmodic component, one would expect to see other *Dioscorea* species used preferentially, since some contain up to 5 times more of this compound than *D. villosa* which yields 0.5-1.2%. (52,53) However, diosgenin does have potential hormonal effects which add to the overall influence of *Dioscorea.*

Piscidia erythrina is an eclectic remedy that lacks a recorded history of use by either early native Americans of this country or the early eclectic physicians. It was formerly known as *Ichthyomethia piscipula* while the most familiar common name in the United States has been Jamaican dogwood. While found mostly in the West Indies, it also grows in southern Florida, Texas and Mexico and northern South America. Caribbean natives used the bark both to stun fish and as an analgesic. Colonial doctors reported on its narcotic and anesthetic properties. (56)

Piscidia was not used to a great extent by eclectics, but it was found effective for painful spasms, pelvic pain, dysmenorrhea, and ovarian neuralgias. As a nerve sedative it overcame reflex irritability and excitation and functioned as a motor depressant. Besides its antispasmodic and anodyne activities, *Piscidia*'s sedative and hypnotic effects were utilized. (1,2) *Piscidia* was inactive in small doses. The dosage range for the fluid extract was 1/2 to 2 drams (2) or 5-60 drops. The dose for the root bark was 5-60 grains. (1)

Piscidia fluid extract was very active in reducing the amplitude of contractions of an isolated guinea-pig uterus compared to *Dioscorea.* (42) The motor depressant activity of *Piscidia* as demonstrated in dogs *in vivo* was recommended as a means of standardizing the fluid extract, since concentration of the crystalline component piscidin did not correlate with the degree of activity. (55) *Piscidia* was shown to contain the fish toxin rotenone. (56) Weak dilutions of the fluid extract acted as a strong uterine sedative *in vitro* on isolated rat uteri, while stronger dilutions reduced spasms after uterine exposure to pitocin. During *in vivo* tests uterine contractions of the cat were reduced and uterine motility of a monkey was inhibited by the fluid extract given i.v. Using 95% alcohol as a solvent on the bark produced a more potent extract than the fluid extract with 38.5% ethanol. All parts of the *Piscidia* tree provide uterine sedative activity, but the root bark is the most potent, especially when it is fresh. *Piscidia* not only had a low toxicity, but it was a much more potent uterine sedative than *Viburnum prunifolium* when their effects were compared *in vitro* on a rat uterus. (57) A methanolic extract of the bark inhibited oxytocin-induced contractions of the rat uterus in a dose-dependent manner. Two isoflavone components in significant concentrations in the extract demonstrated spasmolytic activity. These were piscidone and tetrahydroxy-methoxy-diisoprenyl-isoflavone, which was equivalent to papaverine and twice as potent as piscidone. (58) An extract of *Piscidia* also produced sedation of the central nervous system in addition to antispasmodic and anti-inflammatory effects. (59)

Summary — Of these two remedies *Dioscorea* was the preferred antispasmodic by the early eclectic doctors, probably since it was more commercially available at that time. *Piscidia* has demonstrated greater uterine sedative activity in the lab, but its sedative actions on overall mental and motor functions make its effects less specific. Where general excitability is involved, *Piscidia* would seem to be preferred, while *Dioscorea* has potential hormonal influence due to its relatively high diosgenin content.

Pulsatilla and Humulus

The species *Anemone pulsatilla* (formerly called *Pulsatilla vulgaris*) and *Anemone pratensis* (formerly *Pulsatilla pratensis*) are both recognized as legitimate sources of the remedy known as pulsatilla, also called pasque flower or wind flower. These species grow in Europe and eastern Asia. The American species

Anemone patens (formerly *Pulsatilla nuttalliana*), commonly known as American pulsatilla, was considered by the eclectics as interchangeable with the European species as a medicine and was designated by the United States Pharmacopeia in the past as an acceptable substitute. (10)

Coming from Europe, *Anemone* did not originate as a medicine with the eclectics. (1) However, it was one of the major eclectic remedies for leucorrheal discharge with pain in the loins (1,2) from acute endometritis (60) and endocervicitis. (61) For subacute or persistent functional leucorrhea with a bland, milky flow *Anemone* was used for a considerable length of time. (62,63) Ovarian neuralgia and congestive ovaritis with tensive, tearing pains were treated with larger doses. (1,2,62) While inflammation was a common symptom treated with *Anemone*, it was of greater value for nervous conditions such as dejection, brooding, fearfulness, apprehension, general "nervousness," and mental unrest with a tendency to weep easily (1,2,62,63), especially when associated with amenorrhea. It produced antispasmodic and nerve-soothing effects (2) and helped to give sleep in nervous exhaustion. (1) Since it lessened sexual excitement, *Anemone* was used in cases of sexual overindulgence and habitual masturbation. *Anemone* was used where there was general weakness and helped correct amenorrhea or irregular menstruation in women who were pale, chilly, anemic, and had a poor appetite and little interest in life. (1,2,62) It was helpful in chronic uterine disorders with anxiety about the reproductive organs and their function. (2,63) It treated dull pain during menstruation, described as nagging, aching, or congestive, but not cramping. (62) For dysmenorrhea from uterine colic it was given between and during the menstrual periods. (1,63) When emotional causes made the menses scanty or late or for nervous headaches during the period, *Anemone* relieved the pain and promoted the menstrual discharge. (1,2,63) The fresh herb was used to make alcoholic extracts. (2,10) The extracts were frequently renewed and not kept longer than one year. (10) The dose of the tincture was from 5-30 minims and the fluid extract was used at 1/2-2 minims per dose. (2) Large doses produced sensory and motor paralysis and toxic doses led to stupor, coma, or convulsions. Applied topically the fresh plant was irritant and could cause blistering. (1,10)

In its action on the isolated guinea-pig uterus, *A. pratensis* was very active in reducing the amplitude of contractions. (42) The alcoholic extract of *A. pulsatilla* was shown to have both a sedative and analgesic activity. (64) The tincture of *A. pulsatilla* contains protoanemonin and anemonin. (65) Both protoanemonin and its dimer, anemonin, participate in the sedating effect as shown in rats *in vivo*. (66) *A. pulsatilla* has shown antibiotic activity (67) *in vitro* as a distillate against *Streptococcus* and *Candida albicans*. (68) Anemonin is not irritating but is bacteriostatic and bactericidal *in vitro* against pathogenic *Staphylococcus* and *Streptococcus*. (69) Protoanemonin is active against gram-negative *Escherichia, Neisseria, Klebsiella, Pseudomonas, Vibrio, Proteus, Salmonella, and Shigella* species, gram-positive *Staphylococcus, Streptococcus, Diplococcus, Corynebacterium, Bacillus,* and *Clostridium* species, acid-fast *Mycobacterium* species, and the fungus *Cryptococcus, Microsporum, Trichophyton, Coccidioides,* and *Candida* species *in vitro*. (70,71,72) Protoanemonin is the component that causes blistering. (73) Besides protoanemonin, *A. pulsatilla* tincture contains ranunculin (74), a glucoside which yields protoanemonin in alkaline solution or by enzyme action. (75) Ranunculin is also a component of *A. pratensis*. (76)

Humulus lupulus has grown in the wild from Europe to America to Asia. Known as hops, the strobiles or flower cones are the part used. *Humulus* is usually cultivated for use in brewing and as a medicine. (10) Among American tribes the Cherokee used hops to alleviate pain, produce sleep, and for female complaints where the womb is debilitated. The Mohegans used the blossoms for pain and, along with the Shinnecocks, for nervous tension. (11)

The eclectics used *Humulus* as a sedative for nervous excitement and in wakefulness from anxiety and worry. It was also used to inhibit sexual excitement and desire. The dosage of the tincture was from 1-2 drams. Lupulin, the active granular powder from off the strobules, was used in doses of 5-10 (2) or 5-20 grains. Lupulin was also taken to allay nervousness and irritation and induce sleep when insomnia was caused by worry or a headache. It was given for uterine pain due to nervous debility including dysmenorrhea. *Humulus* was considered to be both sedative and antispasmodic. (1)

Humulus was shown to be useful in the treatment of dysmenorrhea, especially when taken prior to the onset of the pains. (77) An alcoholic extract of *Humulus* had a strong spasmolytic effect on contractions of the rat uterus induced by a variety of chemicals and neurotransmitters. It acted more through the muscles than the nerves. (78) Water and alcohol extracts of hops inhibit oxytocin-induced contractions of uteri from mice and rats *in vitro*. (79) The alcoholic extract also showed sedative and anti-inflammatory effects in lab animals. (80) The sedative-hypnotic effect of *Humulus* is partially due to 2-methyl-3-buten-2-ol, but this compound is not responsible for the muscle relaxing effect. (81,82) Conversion of *Humulus* alpha-acids (humulones) and beta-acids (lupulones) to 2-methyl-3-buten-2-ol occurs during storage. (83) Humulon and lupulon and other hop bitter resins were shown to have antibiotic activity against gram-positive (*Staphylococcus, Streptococcus, Diplococcus,* and *Corynebacterium* species) and acid-fast (*Mycobacterium* species) bacteria (84,85) and antifungal activity on various fungi. (86) Antigonadotropic substances that prevented weight gain in gonadotropin-primed rat ovaries were obtained from dried powder of the hop cone. (87)

Summary — The use of *Anemone* for uterine disorders is based primarily on its sedative and analgesic effects and secondarily on its antibacterial activity. The mind, pain, and infections can all produce an influence on the complex interactions affecting a woman's hormonal cycle. Its sedative activity may be responsible for its anaphrodisiac effect. In addition, *Anemone* has a uterine sedative component that makes it specifically applicable as a female regulator. The risk of toxic side effects and the use of other botanicals makes its current application less widespread than formerly. Though *Humulus* has similar activities (e.g., uterine spasmolytic, sedative, antibacterial/antifungal), its stronger hypnotic effect limits its usage. Whether the

antigonadotropic activity of hops compounds contributes to the reported anaphrodisiac effect of *Humulus* or whether this effect is simply a consequence of its sedative activity remains in question. *Humulus* could be considered more often for conditions in which *A. pulsatilla* was given in the past.

THE VIBURNUM SPECIES

The story of the use of *Viburnum* species is once again a tale of confusion and subsequent disregard for these extremely valuable remedies. There was much misidentification and substitution among species prior to 1940 that led to their being discredited. *Viburnum prunifolium* under the name of black haw was the first to draw the attention of white physicians. (88) The Cherokees had used an infusion to prevent recurrent spasms, and the Delaware tribe used the root bark as a tonic for female generative organs. (11) In the South where it grows, plantation owners used *v. prunifolium* to overcome threatened miscarriages and abortions induced by slaves with cotton root bark. This brought *v. prunifolium* to medical attention. The dried bark of the root or stem was made an official drug in the United States Pharmacopeia VII. *V. cassinoides,* often adulterated with black choke cherry (*Aronia melanocarpa*), was widely substituted for black haw. (88) In the U.S.P. VIII and IX *V. lentago* bark was recognized as an official source of black haw but then dropped (1,89), and the species *V. rufidulum* was later made an official substitute in the National Formulary. (88) Pharmacognostic distinctions between these *Viburnum* species were made in the early 1930s. (89,90) Prior to this it was common for ordinary haw trees to be used to adulterate black haw. (91)

Though the eclectics were not the first to introduce *V. prunifolium* to medical practice, they popularized it through their extensive use. (1,91) It was used as the base for many proprietary compounds advertised for female reproductive complaints. (2) With the uterus as the center of its influence, it was given to sooth excessive uterine and nerve irritability. (2,91,92,93) It was considered a mild sedative but decidedly antispasmodic. Used as a uterine sedative more than any other botanical medicine, it relieved expulsive, cramp-like pains of dysmenorrhea (1,2,93,94) along with pain in the thighs and low back. (93) Where these severe bearing-down, intermittent pains were accompanied by profuse bleeding, it also controlled the menorrhagia. It was also effective in metrorrhagia and in cases of amenorrhea where young girls with uterine cramps are pale and anemic. (1,2,91,93) *V. prunifolium* was given in cases of uterine displacement. (2) It was used in chronic uterine inflammation where there was congestion and leucorrhea and for ovarian irritation and congestion. (1) It was believed to influence functional ovarian activity in previously sterile women. (2) *V. prunifolium* was also used as a gastrointestinal tonic to treat dysmenorrhea due to debility. (1,2) The bark of the root was the part that eclectics used. (1,92,93) The fluid extract was taken in doses of 1/2-1 dram. (2) A dram or less of the tincture was usually employed, but half an ounce would be used in urgent cases. (90) The dose of the powdered root bark was 5-60 grains. (1)

Using a verified source of *V. prunifolium* a study tested the dealcoholized fluid extract on a patient and succeeded in causing a definite relaxation of the uterus. Strips of this same human uterus removed for therapeutic reasons were tested *in vitro* and the same *V. prunifolium* extract was found to relax the uterine muscle in a dose-dependent manner. (95) A fluid extract of authentic *V. prunifolium* was made and an active glycoside was isolated which relaxed the uterine horns from 15 rats and strips from 11 human uteri *in vitro.* (96) A glycosidal constituent was initially identified as salicin, the compound found in poplar and willow barks (97,98), but this component was later determined to have been arbutin. (99) The components scopoletin and esculetin from *V. prunifolium* have shown antispasmodic activity that was 1/20 and 1/8 that of papaverine, respectively. (99) The antispasmodic activity of scopoletin was demonstrated on the rat uterus both *in vitro* and *in vivo.* (100) A volatile oil containing acids was extracted from the root bark and also found to have uterine sedative activity. (101) The major portion of the acid from the root bark was identified as isovaleric acid. (102) The potency of the whole root and its powder was 0.05% that of papaverine. (103) In tests comparing the uterine relaxant activity of 8 *Viburnum* species 4 species had no effect, but the species *V. carlcephalum* and *V. chenaulti* showed activity equal to and twice that of *V. prunifolium,* respectively. (104)

Viburnum opulus var. *americanum* is the species known commonly as cramp bark that grows in the northern states and Canada. (105) The Iroquois used a decoction of the branches for a fallen womb after birth. (11) Its description was first published in 1768 and the first report of its use as a medicine was by the eclectics Wooster Beech in 1833 (105) and Elisha Smith in 1844. When the demand was limited the authentic bark was more commercially available. (106) When the dried bark was made official in the U.S.P. VII and VIII of 1894 and 1905, the description given was of the bark of mountain maple (*Acer spicatum*). The correct description was given for it in the N.F. IV in 1916. (105,106) Still, however, in 1918 a study of the cramp bark sold in the commercial market as *V. opulus* showed that out of 50 specimens, 48 were mountain maple. (106) The substitution of this inert bark for *V. opulus* renders the early research done on cramp bark unreliable. (105,106) The southern species *V. alnifolium* was frequently substituted for *V. opulus.* Even though it was shown to produce the typical uterine sedative activity, it contained a toxic constituent which made it an undesirable replacement. (107)

The eclectics used *V. opulus* for spasmodic dysmenorrhea much the same as *V. prunifolium* (94), but *V. opulus* was believed to have a stronger antispasmodic effect. (1,2) It was used as a sensory nerve sedative particularly for bearing-down or expulsive pain. (1) Tincture made with the recently dried bark was taken in painful conditions of the uterus and ovaries not due to inflammation. (108) The pains that are irregular and spasmodic, beginning in the back and extending through to the loins and down the thighs, are especially benefitted. For this type it is taken every hour or so. The fluid extract was given in doses of 10 to 30 minims. (2)

The extract of *V. opulus* was shown *in vitro* on rat uteri to be 4 times more potent than *V. prunifolium* at relaxing uterine contractions. (104) The alcoholic extract and an aqueous solution of *V. opulus* dried bark produced a sedative action on the uterus, while its

volatile oil containing a number of acids was strongly depressant to the uterus. (101) The root bark of *V. opulus* contained more oil and scopoletin than *V. prunifolium* root bark. The scopoletin had antispasmodic effects *in vitro* and *in vivo* on the rat uterus. (100) Besides scopoletin an isovaleryl ester compound in *V. opulus* bark was shown to have strong musculotropic antispasmodic activity on the rat uterus *in vitro.* (109) This antispasmodic compound was also found in the oil. It was named viopudial and shown to be a sesquiterpene dialdehyde. (110)

Summary — The confusion that existed over the identity and value of medicinal *Viburnum* species is no longer a problem. The similarities between the active *Viburnum* species can be explained by the constituents they hold in common. Both *V. prunifolium* and *V. opulus* are effective uterine antispasmodics. However, each is unique in its make-up. *V. prunifolium* contains the antispasmodic component esculetin, while *V. opulus* yields the more potent viopudial. While they are not entirely interchangeable, both have demonstrated uterine sedative activity.

PHYTOESTROGEN COMPONENTS

PHYTOESTROGEN ACTIVITIES AND THEIR USE DURING LACTATION

Phytoestrogens are compounds from plants that are capable of producing estrus in animals. They consist mostly of sterols, coumestans, and isoflavones. Some estrogenic plants have been shown to induce ovulation, though the mechanism remains to be shown. (111) Phytoestrogens compete with estradiol for estrogen binding sites in the reproductive tracts of animals *in vivo* (112,113,114) and in human breast cancer cells *in vitro.* (115) Estrogenic effects include the increase in the growth and weight of the uterus. Using uterine weight increases in mice to measure potency, sterols were shown to be the most potent, while coumestans are much stronger than isoflavones. (116) The estrogenic isoflavones in descending order of relative strength are genistein, daidzein, biochanin A, and formononetin. (114,116) The coumestans and isoflavones are found mostly in the Leguminosae (pea) family (111) including the forage plants *Medicago sativa* (alfalfa) which is highest in coumestrol and *Trifolium pratense* (red clover) which is highest in formononetin and biochanin A. (117) Alfalfa extract and the isoflavone genistein both improved lactation in the hamster after parturition. (118) *Medicago* was used by eclectics to increase the secretion of milk in nursing mothers. (2)

Other plants contain components similar to the powerful nonsteroidal synthetic estrogen diethylstilbesterol (DES) in structure and effect. These are *Foeniculum vulgare* (fennel) and *Pimpinella anisum* (anise) which contain the phytoestrogens anethole and its polymers in their essential oils. (119,120) *Foeniculum* and *Pimpinella* seed oils produced vaginal cornification and increased uterine weight in ovariectomized rats (120,121) and anise seed oil antagonized the effects of progesterone. (121) Ancient and medieval practitioners as well as eclectics gave *Foeniculum* for amenorrhea and suppressed lactation and considered *Pimpinella* to be a galactogogue. (1,119) Knowledge of phytoestrogens and their activity was unavailable during the eclectic era, but the clinical practice of eclectic physicians led them to empirically utilize these effects nonetheless. To better understand this, the uterine tonic and sedative herbs previously discussed will be examined in light of their phytoestrogen content.

PLANT STEROLS

A fat-soluble extract of *Humulus lupulus* was analyzed and found to contain small amounts of estradiol. (122) The nonsteroidal beta acids (lupulones) in hops are also believed to have a phytoestrogen effect because they bear a chemical resemblance to DES. (123) One study using vaginal smears of ovariectomized rats and uterine weight gain of immature mice showed hops to have 200 times the amount of phytoestrogen activity as red clover. (124) While some studies concurred in this finding, still others could find no estrogenic activity in mice or rats from hops, its essential oil, or its bitter alpha acids (humulones) or beta acids. (125, 126) While these phytoestrogen claims are disputed, water-soluble glycoproteins obtained from hops flower cones are antigonadotropic and suppress progesterone production by luteal cells in rats. (87,127)

The most ubiquitous of all sterol phytoestrogens is beta-sitosterol, though in most plants its low concentration renders its effects insignificant. (111,128) Beta-sitosterol is a relatively potent phytoestrogen in mice even in small amounts. In terms of estradiol equivalents it ranges from 2.5×10^{-3} to 7.7×10^{-2} which is more potent than coumestrol (128,129), while coumestrol is about 35 times again as active genistein. (116) Beta-sitosterol has been isolated from extracts of *Piscidia erythrina* (56), *Anemone pratensis* (76), and *Viburnum prunifolium.* (99) It has also been shown to have potent anti-inflammatory activity similar to hydrocortisone and antipyretic activity similar to acetylsalicylic acid. (130)

A SAPOGENIN CONVERSION CONTROVERSY

Diosgenin is a steroidal sapogenin whose discovery and extraction from *Dioscorea* species led to the efficient commercial production of progesterone. This involved a five-stage process for degrading the side chain, the first step resulting in conversion of diosgenin to estrone. Testosterone can be produced from progesterone with 3 additional steps. Adrenocortical hormones are also readily produced from diosgenin. (131) (It seems that the identification of diosgenin with the commercial manufacturing of progesterone has led some prescribers to believe that this conversion will preferentially occur *in vivo* in humans when diosgenin is given as a steroidal precursor.) When diosgenin was fed to a dog it was transformed in the gut to smilagenin (132), a steroidal sapogenin found in a number of *Agave* and *Yucca* species. (53,54, 133) The caecal flora of rats also transform diosgenin to smilagenin *in vitro.* Diosgenin is poorly absorbed when given orally to rats, dogs, squirrel monkeys, and humans. What is absorbed is distributed to the liver and the adrenals where it undergoes extensive biotransformation. Humans receiving oral diosgenin for 4 weeks had even less unchanged diosgenin in their serum than dogs. (134)

When diosgenin was given orally to female rats it produced an increase in uterine weight, vaginal opening, and vaginal cornification, indicating clearly its estrogenic activity. It was about 1/11 the potency of the synthetic estrogen neoclinestrol. (135) Diosgenin further

demonstrated its estrogenic activity by stimulating the growth of mammary epithelium when injected in ovariectomized mice. The absence of alveolar development showed a lack of progestogenic action. Exogenous estrogen augmented the estrogenic effect of diosgenin. (136) Furthermore, the alcoholic extracts of both *Aletris* and *Chamaelirium* produced estrogenic activity in rat bioassays (137) and they each contain diosgenin. (44, 46,47) Therefore, it may be concluded that, at least in rodents, the *in vivo* biotransformation of diosgenin results in products with estrogenic, not progestogenic, activity.

CIMICIFUGA—AN ISOFLAVONE AND MORE

Extracts of the roots of *Cimicifuga racemosa* injected in female mice and rats increased the weight of the uterus. The weight of the ovaries and the number of corpora lutea were also increased. Menses were produced in juvenile amenorrhea and in climacteric rats. (138) In ovariectomized rats an extract of *Cimicifuga* reduced the amount of luteinizing hormone (LH) in the serum (139,140) but did not affect follicle stimulating hormone (FSH) or prolactin levels. (139) By an estrogen receptor assay using the rat uterus *in vitro* at least three different endocrine-active compounds were detected. The isoflavone formononetine was identified as one of the estrogen receptor competitors, but it did not reduce serum LH. (140) Formononetine is the least potent estrogenic isoflavone in terms of binding estrogen receptors (114,115) and increasing uterine weight in mice. (116,141) Formononetine has shown very little, or no, estrogen activity in some studies. (115,141,142) However, in guinea-pigs it has been demonstrated that formononetin is converted to equol which has a potency nearly equivalent to genistein. (114,143) The other two estrogenic compounds in *Cimicifuga* presumably are responsible for reducing serum LH levels. Hydrolysis of glucosides in the extract led to a significant loss of the LH reduction effect. (139)

VARIABLE EFFECTS OF PHYTOESTROGENS

In high concentrations phytoestrogens can exert a significant estrogenic effect in animals. In lower concentrations they can act as antiestrogens by competing for estrogen-receptor proteins with the more active endogenous estrogens and by influencing the neuroendocrine centers of the brain that control the menstrual cycle. (123,143) This activity is due in large part to biotransformational products of the compounds found in the plants. (132,134,143) In humans it can be assumed that their effect in low-estrogen conditions such as menopause would be estrogenic, whereas in hyperestrogenism the competition for the receptor would actually result in lowering the overall estrogen effect. The relatively small amounts of these compounds in whole plant parts or extracts suggests that they would act as anti-estrogens when used during the reproductive years unless extracts were taken regularly in extremely high doses. In either case they can influence the estrogen-sensitive tissues and affect conditions associated with the reproductive organs. Whether this influence extends in some way to sensitizing uterine muscle to the uterine tonic or sedative activity is a matter for more research. It is interesting to note that three of the four uterine tonic herbs and five of the six uterine sedatives discussed contain substances with some hormonal activity.

CLINICAL APPLICATIONS

SINGLE REMEDIES VERSUS COMBINATIONS

The lists of conditions for which many of the primary uterine antispasmodics and other female regulators were used are remarkably similar (Table I). The most important concern regarding these botanical medicines is how their properties can be most effectively utilized. In this regard the eclectics developed distinctive indications for most of these remedies. However, in practice they were very often combined in formulas to cover a number of different conditions. In examining their application for several menstrual difficulties, their individual and combined effects can be better evaluated.

AMENORRHEA

A wide variety of underlying conditions can be responsible for secondary amenorrhea. After ruling out pregnancy, possible concerns in these cases are constitutional conditions, psychogenic factors, and endocrinopathies. Disturbances in nutrition or metabolism (e.g., anemia or obesity) can undermine hypothalamic-pituitary controls. Emotional and mental states affecting the autonomic nervous system, hypothalamus, or higher cerebral centers can also alter endocrine functions. Ovarian failure often involves cystic conditions of the corpus luteum or ovaries. This includes polycystic ovarian syndrome which has a steady state of estrogen feedback and persistently elevated LH and diminished FSH levels. These types of amenorrhea problems are typically treated by regulating the diet, counseling, or hormonal therapy. (144) (Such cases may call for digestive tonic herbs, mildly sedative botanicals, or cyclic application of phytoestrogens.) Some of the favorite eclectic remedies for amenorrhea were *Chamaelirium, Viburnum prunifolium, A. pulsatilla,* and *Cimicifuga.* (2,145) When acute amenorrhea was associated with inflammatory conditions of the uterus, combined extracts of *Caulophyllum* and *Cimicifuga* were given. If it was associated with spasmodic activity due to nervous irritability, an antispasmodic such as *Dioscorea* extract was indicated. In chronic conditions a strong tonic such as *Chamaelirium* was used, and then an emmenagogue was given when the menses seemed imminent. (146) While each of these prescriptions contain phytoestrogens, *Cimicifuga* provides salicylates for inflammation, *Dioscorea* is spasmolytic, and *Chamaelirium* serves as a digestive tonic.

Several combinations were recommended by eclectic doctors for amenorrhea. In cases of a functional delay in menstruation one part of *Cimicifuga* was combined with almost two parts of *Caulophyllum* and given every two hours. (3) The intention here was apparently to initiate uterine contractions. (1,2) A formula for "suppression" of the menses combined equal parts of *Cimicifuga* and *Viburnum prunifolium* to be taken every two hours. (3) The need to relax and soothe irritation in a condition with congestion and discomfort is one interpretation of this proposed prescription. (1,2) Another formula for amenorrhea as well as dysmenorrhea used one part *Cimicifuga* to one part *Chamaelirium* and one half part *A. pulsatilla.* This was also given every two hours. (3) While these allay discomfort and are useful general tonics for the entire system (1,2), they are also sources of 3 different

phytoestrogenic compounds. *Cimicifuga* seems to be the most popular phytoestrogenic plant and a specific for polycystic ovarian syndrome based on its hormonal activity. The only nonestrogenic remedy recommended for amenorrhea was *Caulophyllum* which is employed for its uterine stimulant, emmenagogue effect.

DYSMENORRHEA

The primary types of painful menstruation usually encountered are either prior to menses due to congestion that subsides as the flow progresses, labor-like pains from the passage of blood clots, membranous dysmenorrhea, or menstrual colic. Secondary dysmenorrhea can be due to pelvic lesions such as endometriosis or chronic infections. Obstruction from uterine displacement, estrogen excess or deficiency, and psychogenic factors are believed to potentially play a role in primary dysmenorrhea. The influence of progesterone in inducing high levels of prostaglandins F_2 and E_2 has also been implicated. It can often be difficult to establish the principal cause. In addition to constitutional concerns such as an optimal diet and adequate rest, psychotherapy or hormone therapy is sometimes used for primary dysmenorrhea. Acetylsalicylic acid may be used beginning prior to the period to inhibit prostaglandin synthesis. Analgesics can help to relieve the symptoms. (144)

The greater variance in symptoms of this condition allowed the eclectics to differentiate more specifically between the appropriate remedies. In addition to very potent synergists and botanical medicines such as *Atropa belladonna,* the commonly recommended remedies for dysmenorrhea included extracts of *Caulophyllum, Cimicifuga, Chamaelirium, Dioscorea, A. pulsatilla,* and *Viburnum.* (147) *Caulophyllum* was used for chronic rheumatic dysmenorrhea or for severe, irregular uterine pains. (13) It was best for young women who are thin, weak, and anemic with anorexia, irritability, and thin, acrid leucorrhea. (148) *Cimicifuga* was indicated when there was a congestive headache (1) and uterine congestion with bearing-down pains, rheumatic soreness, and backaches. (1,2,148,149) It was used when the throbbing muscular pains were increased by uterine contractions. (24) *Chamaelirium* was taken in dysmenorrhea associated with fullness and bearing-down sensations in the pelvis, and stringy, viscous leucorrhea (1,148) and in cases where uterine atony led to menorrhagia. (39) Additionally, the general condition of the patient is flabby and relaxed and there is often mental irritability and loss of libido. (40,148) *Dioscorea* was typically given every three hours for spasmodic or neuralgic dysmenorrhea when the pains are colicky in character. (1,2,50,149) *A. pulsatilla* was used mainly for dysmenorrhea from neurosis. This includes nervous symptoms such as melancholy and worry apart from menstrual difficulties with additional anxiety and fear in regard to the outcome of the menses. It is given during the interval between periods or just before they begin. (1,148, 149) *Viburnum opulus* was given

TABLE I

SOME CONDITIONS FOR WHICH FEMALE REGULATORS WERE USED BY ECLECTIC DOCTORS

Uterotropic Botanical Medicines	Uterine Prolapse/ Displacement	Dysmenorrhea	Amenorrhea	Ovarian Pain/ Inflammation	"Hysteria"	Endometritis/ Leucorrhea
Aletris farinosa Stargrass	+ (2,45) *	+ (2,45)	+ (2)		+ (45)	+ (2,45)
Anemone pulsatilla or *A. pratensis* Pulsatilla		+ (1,3,62,63, 147,148,149)	+ (1,2,3,62,145)	+ (1,2,62)	+ (1,2)	+ (1,2,60,63)
Caulophyllum thalictroides Blue cohosh	+ (12)	+ (1,2,12, 13,147,148)	+ (1,2,3,12,146)	+ (1,2)	+ (2,12)	+ (1,12,148)
Chamaelirium luteum Helonias	+ (2,39)	+ (3,41,147,148)	+ (2,3,39,40, 41,145,146)			+ (2,40,41,148)
Cimicifuga racemosa Black cohosh	+ (1,24,26,29)	+ (1,2,3,22-28, 147,148,149)	+ (1,2,3,23,26-29,145,146)	+ (1,2)	+ (1,2)	+ (1,2,29)
Dioscorea villosa Wild yam		+ (1,2,49, 50,147,149)	+ (146)	+ (1,2,50)		
Humulus lupulus Hops		+ (1)			+ (2)	
Piscidia erythrina Jam. dogwood		+ (1,2)		+ (1,2)	+ (2)	
Viburnum opulus Cramp bark		+ (1,2,94, 147,149)		+ (108)	+ (1)	
Viburnum prunifolium Black haw	+ (2)	+ (1,2,93,94,147)	+ (1,2,3, 91,93,145)	+ (1)	+ (2,91)	+ (1)

* + = references giving these uses

TABLE II

PHARMACOLOGICAL ACTIVITIES OF THE BOTANICAL EXTRACTS AND THEIR ACTIVE COMPONENTS AS DETERMINED BY LABORATORY TESTS

Uterotropic Botanical Medicines	Uterine Tonic/ Stimulant	Uterine Sedative/ Spasmolytic	Estrogenic	Anodyne/ Anti-inflammatory	Hypnotic/ Central Sedative	Antibiotic/ Antifungal
Aletris farinosa Stargrass	+ and - (37)*	+ and - (14,37,42)	+ (46,47,135, 136,137)			
Anemone pulsatilla or *A. pratensis* Pulsatilla		+ (42)	+ (76,128, 129)	+ (64,76,130)	+ (64,66)	+ (67,68,69, 70,71,12)
Caulophyllum thalictroides Blue cohosh	+ (14,16,17, 42)					
Chamaelirium luteum Helonias	- (14,42)	- (14,42)	+ (44,135, 136,137)			
Cimicifuga racemosa Black cohosh	+ and - (30,31)	+ and - (30,31)	+ (114,140, 143)	+ (35)	+ (31)	
Dioscorea villosa Wild yam		+ and - (14,42)	+ (48,135, 136)			
Humulus lupulus Hops		+ (78,79)	+ and - (122,123, 124,125,126)	+ (80)	+ (80.81,82)	+ (84,85,86)
Piscidia erythrina Jam. dogwood		+ (42,57,58)		+ (39)	+ (59)	
Viburnum opulus Cramp bark		+ (100,101, 104,109)				
Viburnum prunifolium Black haw		+ (95,96,100, 101,104)	+ (99,128, 129)	+ (99,130)		

* + = references demonstrated the activity *in vitro* or *in vivo* or indicate plant contained active component
- = references failed to show the activity in certain tests

for spasmodic dysmenorrhea every two hours when it feels as if something is being expelled. (1,2,94,149) *Viburnum prunifolium* was used for dysmenorrhea as a general tonic when there was debility, but it was especially useful when the uterus was engorged and suffered severe, intermittent, cramping pains. This was often accompanied by profuse bleeding. (1,93) Simply understood, the uterine tonic remedies were given to strengthen the expulsive power of the uterus when there was congestion and weakness, while the uterine sedatives would help relieve tension or relax painful uterine spasms.

Often the leading indicated remedies were combined, and the results were found to be superior to using them singly. (148) For example, to combat dysmenorrhea before it occurred, four parts of *Viburnum prunifolium* was mixed with one part *Cimicifuga* and one part *A. pulsatilla* and given every three hours for one week before the expected period. (3,94) *Viburnum opulus* and *Dioscorea* were combined with other remedies to be used every three hours for three days before and during the period. (3) The mixing of uterine tonic and sedative remedies may seem antagonistic unless it is understood that they each work to subdue an extreme of muscular activity, i.e., laxity or spasticity. Their primary functions are not as uterine stimulants or depressant muscle relaxers. This is intended to be a nonspecific, preventive approach. The salicylates in *Cimicifuga* given before the period would also help reduce prostaglandin influence, while the central sedative effects of *A. pulsatilla* could improve relaxation. The antispasmodic effects of *Dioscorea* and *V. opulus* would certainly help reduce the painful spasms. The phytoestrogen influence in cases of dysmenorrhea is uncertain. Since estrogen is known to sensitize the uterus to the contractile effects of oxytocin (144), phytoestrogens may compete with it and help to reduce the tendency for strong contractions from other stimuli.

PREMENSTRUAL TENSION

Prior to the onset of menstruation, from 70-90% of women experience symptoms for 7-10 days associated with this portion of their cycle. For about 20-40% these symptoms can be temporarily incapacitating, and about half of these women seek medical intervention. Known as the premenstrual syndrome (PMS), the most common symptoms are anxiety and irritability, headaches, bloating, breast tenderness, generalized edema and weight gain, or fatigue, depression, crying spells and insomnia, and increased appetite, constipation and craving for sweet or salty foods. The combinations of these and other symptoms differ from one woman to another. No one hypothesis has adequately explained this variable constellation

of symptoms, so different theories have been proposed. Several factors may possibly contribute to each case. Included in the possible etiology are excessive estrogen, progesterone deficiency, prolactin elevation, or extreme hormone sensitivity, as well as high levels of the 2-series prostaglandins, vitamin B_6 (pyridoxine) deficiency, and hypoglycemia. These may in turn lead to the sodium and fluid retention, digestive disturbances, cerebral fluctuations in catecholamines, alpha-melanocyte-stimulating hormone and endorphins, and emotional instability. These theories help explain the limited empirical success of treatment regimens using drugs (progesterone, nonsteroidal anti-inflammatory drugs such as prostaglandin inhibitors, diuretics, sedatives or antidepressants) and support therapy (avoidance of methylxanthine-containing beverages, luteal phase salt restriction, balanced diet, counseling). (144, 150,151) The use of supplements (pyridoxine, niacin, ascorbic acid, zinc, magnesium, and essential fatty acids, especially gamma-linolenic acid) to promote the production of 1-series prostaglandins in preference over the 2-series and to attenuate hormone sensitivity has achieved some significant success. (152,153)

The eclectics described what we know as premenstrual tension as a type of hysteria which was understood in their day as a nervous condition with loss of emotional control and associated with functional disturbances often perceived as hypochondriacal. The term hysteria was taken from the Greek word for uterus, *hystera,* since this condition was recognized most frequently in women. *Caulophyllum* was seen as **the** remedy for the hysteria that appears at or near menstruation. (12) It was used where there was constant ovarian irritation or breast pain accompanied by general irritation. (2) The mechanistic explanation for *Caulophyllum*'s beneficial influence is not apparent from research. On the other hand the estrogen-competing and luteal-inhibiting compounds in *Cimicifuga* can be seen as reducing the estrogenic effect (139,140), while its salicylate content (35) could inhibit prostaglandin production. *Cimicifuga* also has mild sedative properties. (31) It was given for hysterical conditions of the menstrual epoch, especially for hypochondria or melancholia at these times. *Cimicifuga* was indicated for restlessness and nervous excitement. (20) *Cimicifuga* was also used to treat painful breasts, congestive headaches due to uterine disease, and spasmodic conditions associated with hysterica. When the patient was despondent, or for pain before and at the beginning of the menses until the discharge flows freely, *Cimicifuga* was combined with *A. pulsatilla.* (1) The use of the other tonics was minimal in such cases. *Chamaelirium* was given to women who were despondent or irritable from suffering uterine wrongs (41), and *Aletris* was used in some cases of hysteria where the women were tired, anemic, and constipated. (45) The estrogenic effects of these two plant extracts (137) due to the diosgenin (135,136) that they contain (44, 46,47) may compete with and reduce the activity of endogenous estrogen if these remedies are given in small amounts.

As might be expected, the uterine sedative herbs were often used for this condition. *Piscidia* was employed when hysteria was perceived to be due to uterine and ovarian disorders. (2) Besides its beta-sitosterol content (56) possibly competing with endogenous estrogen, its sedative activity helps explain its usefulness. (55,59) *A. pulsatilla* was used for hysteria when there was despondency and general nervous irritation due to chronic uterine disorders. (2) It was especially indicated in mild forms where menstruation was suppressed and the patient was weak and would weep frequently. *Anemone* was also given for chilliness and headaches when the menses were suppressed. *A. pulsatilla* was a remedy for insomnia due to nervous exhaustion and for constipation in hysterical females. (1) The sedative effect of its alcoholic extract (64) due to its anemonin and protoanemonin (65,66) is most likely responsible for this use. The presence of beta-sitosterol in *Anemone* could also have an effect. *Humulus* is another sedative plant extract (80) that was used to soothe nervous excitement in hysteria. Its application for insomnia in hysterical patients (2) is explained by the presence of its sedative/hypnotic principle 2-methyl-3-buten-2-ol. (81,82,83) *Viburnum prunifolium* was given to sensitive ladies when irritable nervous tendencies before or during menses resulted in sympathetic disturbances of the heart, stomach, and nervous systems. (2) It was indicated in hysterias where there was uterine irritability (91), but its influence was mild. It worked best when combined with *Cimicifuga.* (2) *Viburnum prunifolium's* beta-sitosterol content (99) might be beneficial in a small way. *Viburnum opulus* also was said to allay uterine irritation that tended to excite hysteria. (1)

SELECTING THE APPROPRIATE REMEDY

Examining these three conditions illustrates the primary effects and usefulness of these female regulators. In amenorrhea and premenstrual tension the hormonal influence is significant, but associated constitutional tendencies, mental and emotional dispositions, and physical symptoms aid in the selection of the most appropriate remedy. Thus, all women with a similar problem are not treated as though they were cut from the same cloth. Attention must be paid to individual factors. This seems also to be true in dysmenorrhea where the causes and symptoms can likewise vary. It is important in selecting a remedy to keep associated symptoms and systemic conditions in mind. One advantage of using botanical medicine consists in the mixing and matching of remedies to the individual and not the disease category. This aspect of the art of prescribing can be further enhanced by understanding the different pharmacological activities behind each therapeutic agent (Table II).

COMMENTS AND CONCLUSIONS

THE NEED FOR CONTINUING ASSESSMENTS

The efficacy of traditional botanical therapeutics is often challenged by the medical establishment in the absence of controlled clinical trials using extracts with a standardized concentration of the active constituent. Some botanical practitioners believe a subjective understanding derived from clinical experience is all that is required. Medical science demands that activity must be quantified in the laboratory and repeatedly demonstrated in the clinic as proof before acknowledging an advantage is to be gained through the use of any medicine. In gathering the available data on certain herbs, the comparison between limited laboratory studies and reported

clinical applications and successes provides a critical step in bridging the gap and assessing their relative value. Further studies and reassessments must certainly follow to avoid complacency and insure a growth in understanding.

EMPIRICAL AND RATIONAL PRESCRIBING

The traditional medical use of these female regulators is based on folk and clinical empiricism in the light of a scientific understanding of their activity. These tenets remain important for appreciating their usefulness. As Felter stated in his preface (1), "Though the pharmacological ... action of drugs is neither followed nor relied upon in eclectic therapy for the purpose of prescribing drugs ... we believe ... that the student ... have access to a summary of the accepted views of pharmacologists, and that he may know the tissues acted upon and the kind and extent of action when a drug is administered." The eclectics relied mostly upon the presenting signs and symptoms of each patient (calling them "specific indications") in determining their prescriptions, rather than correlating the action of a remedy with the pathology of a particular diagnosis. The eclectic doctors after decades of prescribing experience felt assured that the remedies worked when the indications were appropriate, but they were not always certain or correct about how they worked. As they developed the art of prescribing, so must the advancement of its science be a concern in our day. Methods of assessing patient complaints have changed since the days when botanical remedies were common in medical practice. The descriptive eclectic terminology is no longer entirely adequate for our current knowledge of either medicines or pathologies, e.g., hysteria vs. premenstrual syndrome. This calls for a refinement in the rationale of prescribing.

There can be a tendency to rely on information from the past in a way which limits knowledge and progress. In a certain way familiar herbal remedies are like old friends. They are known and relied upon in many ways, but a careful analysis of their different attributes can help in appreciating their behavior in certain circumstances even more. By recognizing inherent strengths and limitations, our understanding grows and our expectations become more appropriate. Information regarding isolated constituents and their activity may not make a great practical difference in certain cases, but it is preferable to make important decisions on the basis of verified results rather than assumptions when possible. This may require a re-examination of therapeutic rationale. For example, diosgenin-containing remedies are used to help combat symptoms of estrogen excess. Knowing that diosgenin probably acts by competing with endogenous estrogen rather than by promoting progesterone production helps in considering its application for other conditions.

THE VALUE OF IN VITRO AND ANIMAL RESEARCH

In vitro research and animal studies cannot be the entire basis for establishing the usefulness of a particular extract or compound. Making judgments about a therapeutic agent based solely on its activity in animals or on their isolated organs is presumptive at best. These findings are only validated when compared with evidence derived from its use by someone with years of experience at clinical assessment. The eclectic authors were this type of expert. When there is a correlation of activity demonstrated by research with apparent clinical effectiveness in treating a recognizable condition, the lab results are supportive evidence. Without prior clinical or folk applications that are related to the lab findings, the research is no more than suggestive. For example, finding evidence of antibacterial activity *in vitro* for a substance does not confer antibiotic status on the agent. If that substance had prior successful use for certain infections, the *in vitro* tests can help to establish the possible scope of its efficacy. Even then, its specific activity must be established *in vivo*. The animal testing provides a closer comparison to its real use, but this method can also be inadequate and at times exceedingly cruel.

How important are the negative findings from laboratory research? A remedy's usefulness is ultimately validated in the clinic and not the lab. The complexity of a human system's response to the multiplicity of active components found in each plant extract cannot simply be reduced to the sum of effects of isolated components on isolated tissues or organs *in vitro*. The effect of an extract in resolving a pathological condition may or may not be demonstrated on normal tissues or organs. Negative laboratory findings do not necessarily indicate a lack of efficacy, but merely the failure to demonstrate a specific activity using a particular model. For example, the use of *Echinacea* for infections was called into question when a strong antibacterial activity could not be demonstrated. However, it was later shown that *Echinacea* did enhance the body's own immune response used to fight infections. Failures in testing can also be called into question since animals are used as subjects in place of humans. Diverse animal species react differently in their physiologic responses to a pharmacologic agent; in fact, individuals within a species do. The significance of the tremendous psychological differences inherent between humans and other species must be taken into account. In evaluating a remedy whose activity can be surmised from its therapeutic effects, a confirmation of this activity from lab tests carries more weight than a negative test. The former supports or verifies what has been observed, whereas the latter merely fails to confirm it under limited dissimilar conditions.

The dangers in assessing traditional remedies range from either accepting them with blind faith or requiring the same degree of scrutiny given to new synthetically-created pharmaceutical substances. Neither the clinic nor the lab exists in a vacuum. It is appropriate to learn what is of value from all contributing disciplines to be able to make the best decisions in selecting a medicine. For botanical medicines this could involve history, botany, pharmacognosy, chemical analysis, pharmacology, pharmacy, posology, toxicology, physiology, psychology, clinical diagnosis, pathology, and other studies that pertain to the interaction between doctor, remedy, and patient. A major value to be derived from these collective findings is the incentive to develop appropriate clinical trials and publish the findings. To accurately evaluate traditional botanical medicines clinically the tests should not simply be on patients with a common diagnosis but should include other parameters of assessing patients. The basis for these selected parameters should be the "specific indications" recognized through clinical experience. These take into account the combined

activities of the remedy being studied and not simply one effect of one constituent.

SUMMARY

The direct action of botanical agents on the female reproductive system is centered on the uterus. The main effects of these medicines are to produce tonic and/or clonic contractions, to relax spasms, and to exert hormonal influence by binding to estrogen receptors. Auxiliary actions of different remedies help to distinguish their overall influence and allow for the specific selection of the most appropriate remedy in most cases. Combining several of these medicines broadens their impact and provides a general balancing that can be used as a preventive measure for chronic conditions.

The findings derived from laboratory research are useful for understanding the clinical indications that guide the prescribing of female regulators. Clinically, *Caulophyllum* and *Chamaelirium* had reputations as reliable tonics, whereas *Dioscorea* and *Viburnum prunifolium* were favored uterine sedatives. On the basis of the research *Caulophyllum* has demonstrated the most uterine tonic and stimulant activity, and viewed strictly as a uterine spasmolytic *Viburnum opulus* has an even greater effect than *V. prunifolium*. Not only has *Aletris* had an identity crisis in clinical practice, but research has shown its effect to vary between being a uterine tonic and a uterine sedative. The salicylates in *Cimicifuga* contribute to its influence. *Cimicifuga* and *Anemone* were important remedies for clinical conditions involving hormonal imbalance. While *Cimicifuga* has demonstrated hormonal activity in the lab, *Anemone*'s tranquilizing effect seems to be its greatest value. Compared to *Aletris* and *Chamaelirium, Dioscorea* would qualify as the leading source of estrogenic diosgenin among these female regulators. The sedative and hypnotic activities of *Piscidia* and *Humulus* combine with their uterine antispasmodic activity to make them useful for PMS irritability and insomnia as well as for the discomfort from painful menstrual cramps.

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