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Etiology of primary dysmenorrhea

Rosalie Eva Brewer
University of Nebraska Medical Center

THE ETIOLOGY OF PRIMARY DYSMENORRHEA

Rosalie Breuer

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I. Introduction

Painful menstruation has been a trial to women throughout the ages, but only recently has it assumed significance in the defense of the nation, making it a problem of more than academic interest to the medical profession. With women workers performing a critical part of the work on the assembly line, woman-hours of labor lost can be measured in terms of tanks and planes. Estimates of the incidence of dysmenorrhea vary with the author, but range as high as fifty to eighty per cent of women during the menarche. (Schroeder, 1928; Graves, 1927). Goldwasser (1938) found that only 10.5% of high school girls suffer; Emge (1933) gave 11%. The incidence depends somewhat on the age group studied, for according to Clow (1927), dysmenorrhea is rare before thae age of eighteen. Hudgins (1941) quotes the estimates of various authors in a recent survey: Jacobi, 46%; Miller, 47%; Cullings, 60%; Blair Bell, 62%; Jeff Miller, 90%; Brown, 22%. Weiss and English (1943) reported that 52% of the student nurses studied had symptoms severe enough to keep them from work one or more days. Mazer and Israel (1940) stated that there is some discomfort with all

menstruation, and, although this may be questioned, rare indeed is the woman who has to be told what the nature of her labor pains will be.

If 50% is accepted as a mean of the values given, can it be assumed that half of all women suffer from a pathological condition of the menstrual function? Pain caused by anatomical malformation, by pelvic inflammation, or by local pathology is, of course, avoidable, but is it physiological for women to have periodic pain, possibly as a practice for labor? The biblical dictum that women must suffer has been accepted by the human race for so long that even to the present the advisability of giving relief for pain is questioned. Even more often is it outlined in scientific journals that dysmenorrhea is but a manifestation of psychic trauma. The question of the necessity of menstrual pain is a philosophical one, but the question of its origin is a medical problem.

II. Historical Review

Dysmenorrhea was recognized as a clinical and household entity in the earliest of medical writings. The Kahun Papyrus of about 1900 B.C. suggested that for relief bandaging of the abdomen with a mixture of crushed onion and pine sawdust was helpful. The Ebers Papyrus of a somewhat later date conatined a prescription for alleviating menstrual pain.. The Parsee women of India were segregated during menstruation which was considered a mildly dangerous state during which women were prone to cause domestic difficulties. (Browne, 1938) Trotula (1940 ed.) wrote during the eleventh century, "A woman who does not exercise much must necessarily be abundant in many menstrual periods in order that in this respect she may be in good health."

The ninteenth century saw the beginnings of clinical investigation. Probably it was McIntosh in 1832 who first suggested that mechanical obstruction was the cause of dysmenorrhea. Marion Sims (1835) laid down the maxim, "Nulla dysmenorrhea nisi obstructiva". He wrote, "There can be no dysmenorrha if the canal of the neck of the uterus be straight

and wide enough to permit the passage of blood." Tilt, (1851) however, listed a number of etiological factors in his textbook of gynecology: sub-acute ovaritis, ovarian peritonitis, "a neuralgic ovarian affection," undersized uterus, tubal inflammation, coarctation of the aorta, rheumatism and gout were among the causes. Hart stated in 1883 that menstrual pain was due to uterine spasm caused by anteflexion and defective uterine development.

Clifford Albutt in 1884 suggested that dysmenorrhea was a symptom of a neurotic constitution, and is quoted almost verbatim today. (Bauer, 1942) When Craigin published his Essentials of Gynecology in 1893, he leaned more toward the mechanical viewpoint, and divided the etiological factors into obstructive and congestive types. In 1903 Schultz presented his hypoplasia theory. He postulated that the cause of pain was the stagnation of blood in the uterine sinuses, and subsequent pressure pain because of insufficient musculature to force the blood out. The inadequate musculature was a sign of an infantile uterus and incomplete development. This launched a wave of therapy by estrogens for all patients, no matter

the size, shape, or position of their uteri.

Since that time there has been a trend toward the explanation of dysmenorrhea in terms of mechanisms rather than nomenclatures. The lists of clinical observations and more or less successful therapeutic measures grow longer by the week, but the causation of menstrual pain is far from being generally understood. The data available, however, make it possible to outline a scheme showing how a number of factors may contribute the development of dysmenorrhea.

III. Definition and Limitation

All the unpleasant symptoms which accompany menstruation fall into the category of dysmenorrhea. These may be divided into two groups: those which have their origin in the pelvis, and those which are extra-pelvic or systemic in nature.

Systemic	Pelvic
Headache	Abdominal pain
Nausea and vomiting	Bachache
Fainting	
Urticaria	
Acne	
Water retention; edema etc.	

The syndrome is termed primary where there is no demonstrable lesion of the genital tract, or secondary where there is known pathology of structure or function, either of the pelvic organs or systemically. This paper will be concerned with only one type of menstrual pain: the colicky, intermittent cramps which appear to be both abdominal and lumbar, beginning a number of hours before menstruation, and absent during the intermenstruum. This occurs in women who are in all obvious respects normal, and who have no associated pelvic or endocrine pathology.

IV. The Psychic Factor

The importance of the psychic factor in the etiology of primary dysmenorrhea has been much in dispute. According to Fluhmann, (1940) at least 50% of the patients are relieved temporarily or cured by a wide variety of therapeutic measures. This is interpreted as meaning that psychotherapy is the significant factor in the treatment. Boynton and Winther (1942) found that in a series of 100 college girls, 12% were cured by estriol glycuronide, 8% by placebos. Many different therapeutic regiemes show similar results, a fact which points to a definite psychosomatic relationship. Kunz (1934) voiced an opinion which is being more widely accepted daily when he wrote, "Every visceral function is subjected to influences exerted by the psyche and emotional states through the autonomic and endocrine systems".

Among the radicals are Novak and Harnik (1929) who say unequivocally that all cases of dysmenorrhea are explainable on a psychogenic basis. Their investigations indicate that psychic trauma, usually sexual, always lies at the bottom of the first attack of

dysmenorrhea, and that the recurrent monthly attacks are a result of anxiety and fear. It will be found, however, that almost all dysmenorrhea shows a gradual onset, and increases slowly in severity over a number of years. It begins in the high school age as mere annoyance and almost imperceptibly becomes incapacitating, although periods vary in intensity and occasionally there is only slight discomfort.

Weiss and English (1943) recognize a psychogenic type of menstrual pain. They find it in tomboys who are either resentful of their feminine role, or who are unwilling to give up their dependence upon their parents. Weiss and English (1943) cited cases in which dysmenorrhea began at the time girls came into contact with adult sexual problems.

In a study of the menstrual function in psychotic patients, Allen (1935) found that specific types of menstrual disorders are associated with the various psychoses, and that psychoneurotics invariably showed severe dysmenorrhea. Graves (1927) believes that most dysmenorrhea patients are psychoneurotics. In view of the fact that about 50% of all women suffer

from this disorder, is it to be said that half of all women are psychoneurotics? In comparison with what? The much quoted statement of Lord Moynihan becomes apropos: "...neurosis is another was of saying, 'I don't know' ".

V. Constitution, Threshold, Exercise, Posture.

One concept of dysmenorrhea is that uterine contractions, ordinarily not perceptible , are registered as pain in cases where the threshold has been lowered for some reason or other. The threshold may be low congenitally as in the case of Alvarez' (1942) "constitutional inadequates". Miller (1934) found that women whose menses were painless were on the average taller and showed more pronounced breast development than the dysmenorrheic group. Kapur (1940) noted that menstruation tends to be more painful in the asthenic type. Goldwasser (1938) stated that constitutional inferiors made up a large proportion of the dysmenorrhea group. Julius Bauer (1942) wrote dogmatically that primary dysmenorrhea is almost invariably a symptom of a neuropathic constitution, usually associated with signs of infantilism and asthenia.

The association of faulty posture, poor muscle tone, and painful menstruation has been stressed byt many authors. (Clow, 1927; Fluhman, 1939; Goldwasser, 1938; Mazer, 1940; Miller, 1930.) This relationship

has led to many attempts toward the alleviation of dysmenorrhea by posture correction and exercise. The results are not consistent. Goldwasser (1938) and Clow (1927) found marked improvement with regular exercise and other measures for the improvement of general health. Fluhman (1940) pointed out that the attention to rules of rest and hygiene is probably the significant factor. Mazer and Israel (1940) suggested that both dysmenorrhea and faulty posture are the result of loss of muscle tone in neurasthenic, visceroptotic women. In a highly controlled study by Miller (1934) it appeared that posture improved continuously during college training, but there was no improvement in the severity of dysmenorrhea. It was concluded that there is no cause and effect relationship, and that good posture has no advantage over poor posture as far as dysmenorrhea is concerned. Threshold seems to be a significant factor. With improvement of general health through proper rest, sleep, and diet as well as exercise, there will undoubtedly be better posture, muscle tone, as well as increased resistence to pain.

Several women medical students at the University

of Nebraska either began to notice menstrual pain for the first time during their freshman year, or found that it became much more pronounced the previously. The freshman year is notably associated with lack of sleep, worry, weight loss, and often improper diet. In the following yearswhen the strain is not so great, and there is more opportunity for sleep and mental repose, there is often decreased intensity of the dysmenorrhea. It may be pointed out that anyone who has suffered severe illness finds that ordinarily painless stimuli become extremely unpleasant in the debilitated state.

VI. Obstruction and Contraction

The similarity of menstrual cramps to labor pains has been responsible for a generalized assumption that uterine contractions were responsible for both. Kolisher wrote in 1909 that by bimanual examination he could feel clonic contractions of the uterus in patients with dysmenorrhea. He maintained that in these patients blood could be seen coming out of the cervix in jets, unlike the continuous flow in normal women. From the time of Marion Sims (1832) it was believed that obstruction of the neck of the cervix caused damming up of the discharge, and the blood, acting as a foreign body, stimulated uterine contractions. Novak (1915) described a large number of cases in which there was no stenosis and apinful menses were present. His findings were confirmed by Emge (1933), Blos (1929) and others. Lackner, Krohn, and Soskin (1937) showed that in many dysmenorrheic patients the cervix is soft, patulous, and with no evidence of stenosis.

It was now and again suggested that endometrial tissue and clots within the lumen initiated the contractions. Pullen (1942) demonstrated that only

a fraction of patients with pain pass clots or recognizable pieces of endometrium, and that 40% of normally menstruating women pass clots. Israel (1936) attempted to explain all pain on the basis of membranous dysmennorhea. He believed that expulsion of hyperplastic endometrium was the cause of the pain. Taylor (1942) stated that the discomfort was due not to the expulsion, but to the separation of the tissue from the uterine wall.

Witherspoon (1935) was fully convinced by his own observations and those of Reynolds (1930) and Knaus (1929) that the immediate cause of pelvic cramps was spasmodic uterine contractions. He was, however, without sufficient kymographic evidence to prove this convincingly. Wilson and Kurzrok in 1940 carried out extensive experimental work investigating the question. A bag was introduced into the uterus and the contractions recorded by means of a kymograph. These authors concluded that the amplitude of contractions had no association with pain, and that uterine motility was identical in painful and non-painful menstruation.

These investigators seem to have taken no note of the work of Adair and Davis (1934), and that of Moir (1934). Adair and Davis placed a bag in the uterus

following low cervical Caesarian section or therapeutic abortion. They found that pain was associated with increased frequency or amplitude of contractions. By using two bags simultaneously, they learned that the upper and lower segments do not contract at the same time. Contraction of the lower segment is more likely to be associated with pain than is contraction of the upper segment. The tonus of the upper segment is influenced by pitressin, pitocin, and pituitrin, while none of these affect the lower segment. They also discovered that uterine contractions prior to the onset of labor do not vary in frequency or amplitude. When painful contractions begin, the first change noted is in amplitude. This is followed by increased frequency of contraction. Pain does not occur until the contraction is well advanced. The pain begins at the upper third of the ascending curve, continues during the acme, and for about two thirds of the descending curve.

Moir (1936) working with intrauterine bags, measured pressures developed during contractions. He found that pressures of 120 mm of mercury were not uncommon, and usually formed the dividing line between painful and non-painful contractions. Only patients with dysmen-

orrhea showed strong uterine spasm, and all those with spasm suffered with pain. Pressures as high as 150 mm were occasionally recorded.

Bickers (1942) recently found the source of error in the work of Wilson and Kruzrok (1942). He discovered that in painful contractions the normal waves are superimposed on a high degree of tetany. Tetany was never observed in patients without dysmenorrhea. A base line was obtained on the kymographic tracing by relaxing the uterus with morphine after each record was obtained. Wilson and Kruzrok did not use a base line and hence observed only the contractions superimposed on the tetany. On the basis of this evidence it is not difficult to accept Bickers' statement that the dysmenorrheic uterus is the tetanic uterus.

VII. The Role of Calcium

The familiar effects of calcium on the neuro-muscular mechanism probably suggested its therapeutic use in dysmenorrhea. The uterus is dependent upon an optimal concentration of calcium ions for its muscular activity.(Best and Taylor, 1939). A deficiency of calcium ions decreases uterine motility, and decreases the activity of oxytocic drugs. (Spiegler and Schol, 1929). The administration of alkaline salts to reduce the concentration of ionized calcium would theoretically be of value in diminishing the irritability of the uterus. The rationale of calcium administration as a therapeutic measure in dysmenorrhea is to be questioned, but apparently it has little if any effect. (Boynton and Hartley, 1934). Nor is there any difference demonstrable in the serum calcium levels of patients with normal and painful menstruation. (Boynton and Greisheimer, 1931). Hartley (1931) learned in a series of 240 cases that women who had menstrual cramps usually showed tetanoid symptoms during their first pregnancy, and almost always during the following ones. It seems probable that a disturbance in the

calcium metabolism would aggravate an already disturbed uterine motility, but it appears unlikely that calcium is of primary importance in the problem of the etiology of dysmenorrhea.

VII. The Endocrine Picture

Why do some uteri contract more strongly than others? A number of factors must be considered in answering this question. Obviously the musculature must be strong enough to produce the high tension. Lack of muscular tone is probably one reason why the stretched muscles of multiparae do not frequently produce dysmenorrhea. The relationships of the endocrine glands, and the ratios of their secretions are of undoubted significance in the production of uterine contractions.

The normal menstrual cycle is controlled by an association of hormones. (Best and Taylor, 1932). The follicle-stimulating hormone of the anterior pituitary, acting upon the ovary, brings about maturation of the ovum and the secretion of estrogenic hormone which in turn depresses the formation of the follicle-stimulating hormone. Probably some change in quantity, either withdrawal or maximal concentration of estrogen, following rupture of the follicle causes liberation of luteinizing hormone by the anterior pituitary. (Allen, 1939). The resulting corpus luteum produces progesterone for a period, and then,

in the absence of fertilization, declines. (Reynolds and Allen, 1932). The withdrawal of progesterone is followed by menstruation.

Progesterone acts to inhibit uterine motility, and its withdrawal results in whipping the uterus into marked activity. (Reynolds, 1932; Brown and Venning, 1937). The uterus does not respond, however, unless it has been previously sensitized by estrogen. (Reynolds, 1930; Witherspoon, 1935) Hence both estrogen and progesterone are essential for the production of uterine contractions. (Novak, 1933) Pain in dysmenorrhea begins about the time the corpus luteum begins to disintegrate. (Novak and Reynolds, 1932) During the phase of activity of the corpus luteum from ovulation until just before menstruation, the normally stimulating effect of estrogen on uterine motility is inhibited by progesterone. (Novak, 1933) With the withdrawal of the influence of the corpus luteum hormone, there is an estrogen-produced excitation. (Reynolds, 1932) It has been further shown that normal ovulation is essential before true dysmenorrhea can be produced, and dysmenorrhea does

not occur in an anovulatory cycle accompanied by derangement of the hormonal system. (Novak, 1932; 1933)

The relief of dysmenorrhea by many different hormone preparations can be explained on the basis of these facts. Estrogens continually administered depress the anterior pituitary and prevent the secretion of follicle-stimulating hormone which is normally brought about during low estrogen states. A high estrogen titer appears to prevent ovulation and hence corpus luteum formation. The prescription of estrogens for the purpose of maturing the uterus, supposedly causing dysmenorrhea by its infantile state, is based upon unfounded supposition. Progesterone balance is essential for menstruation, and continued administration of this substance upsets the normal mechanism.

The exact derangement in the hormonal mechanism which causes uterins spasticityhas not been identified. Fluhman, (1938) in a study of blood estrogen curves, demonstrated that only one was abnormal in a series of 19 cases of dysmenorrhea. Browne (1935) suggests

that deficient progesterone formation, either primary from insufficient luteinizing hormone, or secondary through failure of the ovary to react to the luteinizing effect, might result in the uninhibited action of estrogen during the menstrual and pre-menstrual periods. Another type of inbalance might be seen in the overproduction of estrogen in the presence of a normal amount of progesterone, although Fluhman's work (1938) would seem to indicate that such is not frequently the case.

Phelps (1937) carried out a series of experiments in which the urine of women in labor, during normal menstruation, and with dysmenorrhea was injected into mature female rabbits. Kymographic tracings were made of the resulting uterine activity. Urine from painlessly menstruating women showed inhibitory activity; the degree of inhibition was inversely proportional to the amount of discomfort present. Urine from patients with frank dysmenorrhea showed marked increase in oxytocic activity and decrease in inhibitory function. The urine was 100% oxytocic during severe cramps in a large series of cases.

From these facts it was concluded that there is a disturbance in the hormonal physiology of women who suffer from dysmenorrhea. This disturbance gives rise to characteristic variations from the normal in the escretion of urinary substances which influence the activity of the rabbit uterus.

The interaction of the various endocrine secretions and their association with the nervous system introduce many variable factors into the equation. For, example, a number of research workers have treated dysmenorrhea with insulin. (Altshul, 1930; Okey, 1935; Tedstrom and Wilson, 1936) The "tonic" effect of insulin in increasing appetite and sugar metabolism is of certain value in elevating the threshold to pain, but its role in the endocrine picture is more obscure. Excess of estrogens can result in hypoglycemia, via the pituitary, while uterine contractions tend to elevate the blood sugar. (Tedstrom and Wilson, 1936) There is an increased sugar tolerance in 80% of menstruating women, although in some cases it is decreased. Patients having functional dysmenorrhea associated with low blood sugar levels are relieved by extra carbohydrate

feedings or intravenous glucose. (Tedstrom and Wilson, 1936) There seems to be a correlation between ovarian, pancreatic, and adrenal function. (Okey, 1935) The secretions of the ovaries, testes, and parathyroids appear to act with insulin to reduce blood sugar according to Tedstrom and Wilson. The thyroid shows increased activity during menstruation and may visibly enlarge. The adrenals are readily responsive to the psyche and have influence upon the activity of other glands. It has been found (Hartley, 1931) that .0005 mg of adrenalin per minute will induce hyperglycemia in the rabbit. The parathyroids are implicated in the calcium metabolism problem, and the question is rightly raised whether the parathyroids may be of great significance in the whole problem of spasticity. Although the endocrine problem cannot be blueprinted, there is no doubt that regulation through this channel must be approached with a much broader viewpoint than is customary.

IX. The Causation of Pain: Ischemia

In order for pain to be recognized, the afferent nervous pathways must be intact. Interruption of the pathway is the purpose of such treatments for dysmenorrhea as alcohol injection of the ganglia, or presacral sympathectomy. (Blos, 1929; Cotte, 1932) The origin of histologically demonstrated lesions in the ganglion cells of the sympathetic nerves supplying the uterus (Blotvogel and Poll, 1927) in many cases of dysmenorrhea have yet to be explained, but there is no other evidence suggesting that menstrual pain is on a neuritic basis. Assuming that the origin of the pain is in the myometrium, what is the direct stimulus giving rise to pain impulses?

It has been assumed, although referring chiefly to the gastrointestinal tract, that the only adequate stimulus for visceral pain fibers was tension; the result of distention and stretch applied to nerve terminals. (Best and Taylor, 1939) This may be true of the alimentary canal (although it is to be questioned in the case of gall bladder colic) but there is certainly another factor involved in some types of visceral pain. It is accepted in some quarters that ischemia and the resulting anoxia are the background

of phenomena such as angina pectoris and intermittent claudication. To what extent anoxia rather than tension causes smooth muscle pain as in ureteral colic is not determined, but the similarity of the pain to dysmenorrhea in certain respects suggests a relationship.

The pain of angina pectoris seems to depend upon the degree of myocardial anoxia. Anoxia produced by an oxygen deficient atmosphere brings about typical seizures in anginal patients, and individuals not normally troubled but showing electrocardiographic changes typical of angina pectoris. (Katz, 1934) Angina may occur even if coronary vessels are normal if oxygen supply to the myocardium is deficient as in anemia or a rarefied atmosphere. (Lewis and Grant, 1926)

Intermittent claudication is believed to represent periodic anoxia. Exercising a normal limb during an arrest in circulation causes pain identical with that of thromboangiitis obliterans. (Lewis and Harmer, 1927) Exercising the muscles of an anemic subject in whom there is no evidence of arterial disease similarly produces pain. This is seen in a normal person who exercises in an oxygen-poor atmosphere. (Pickering and Wayne, 1934)

In a study of the anoxia mechanism, Lewis and Grant (1925) concluded that oxygen lack itself might be further analyzed. Probably the pain is due not to want of oxygen, but to metabolic products of muscular activity which are ordinarily removed by oxidation, and which accumulate when oxygenation is inadequate. These pain stimulating substances are called collectively Factor P. Four significant feature are listed in the body of evidence:

1. Pain does not vary with individual contractions, but is a steady ache.
2. Experimentally, pain disappears within three seconds of the restoration of circulation, presumably as a result of the removal of Factor P. If the occlusion remains, the pain persists.
3. The time of onset of the pain is determined by the total amount of work done rather than the length of time of the exercise period.
4. When circulation is restored after exercise, then interrupted during further exercise, pain develops more quickly than the first time, supposedly because accumulated metabolic products have not been dissipated.

Katz and his associates who repeated this work believe that Factor P is acid in character and non-volatile.

Probably Moir (1934) first suggested that menstrual

pain is due to myometrial ischemia. The question arose as to the magnitude of pressure developed by the contracting uterus. He measured pressures of 150 mm of mercury, and found that 120 mm was the upper limit of painless contractions. Pressures of 100 mm are normal in the first stage of labor. It is justifiable to assume that if the patient's systolic blood pressure is great enough to force blood through the myometrium, menstrual pain will be slight or absent. Menstrual pain, then, is a function of blood pressure, inversely proportional. The mechanism is confirmed by the finding of Adair and Davis (1934) that individual spasms of pain are accompanied by coincident exaggeration of uterine contractions.

There may be association of anoxia with the rhythmic vascular contractions demonstrable during menstruation. Because of its accessibility, the endometrial circulation has been most carefully studied. It is found that just before menstruation one coiled artery after another clamps down, and for many minutes at a time, not a single blood corpuscle is seen to move. (Bartelmez, 1941) After a time the vessel

opens up and circulation is restored. For a period of four to twenty-four hours before menstruation begins, there is marked vasoconstriction associated with definite bluing of the endometrium. These characteristic changes are readily observed in bits of endometrium transplanted to the cornea in the rhesus monkey. (Markee, 1940) Generalized vasospasm is demonstrable pre-menstrually in the skin capillaries of human females. These spasms are rhythmic, and have about the same periodicity as the endometrial cycle. They are marked for a day or two preceeding the onset of the flow. Brewer (1937) reported a case in which the patient had an unusually prolonged period of vascular spasm in the skin vessels, accompanied by severe dysmenorrhea, which was assumed to be due to accompanying spasm in the uterine vessels.

Markee (1932) reported in a critical study of the vascular cycle of the uterus that each constriction could be divided into four periods:

Vasoconstriction.....5 - 15 sec.
Refractory period.....20 - 35 sec.
Resting period.....10 - 30 sec.
Latent period.....10 - 20 sec.

The uterine musculature has identical periods. The

vascular cycle in the corneal transplants may be independent of the uterine cycle.

It is interesting to note that adrenalin or fright will break through the refractory period. (Markee, 1932) Fright causes contraction of the vascular as well as the muscular structures, and is reflected in the endometrial transplants to the eye. Pain with fear and worry is a not uncommon observation among dysmenorrhea patients.

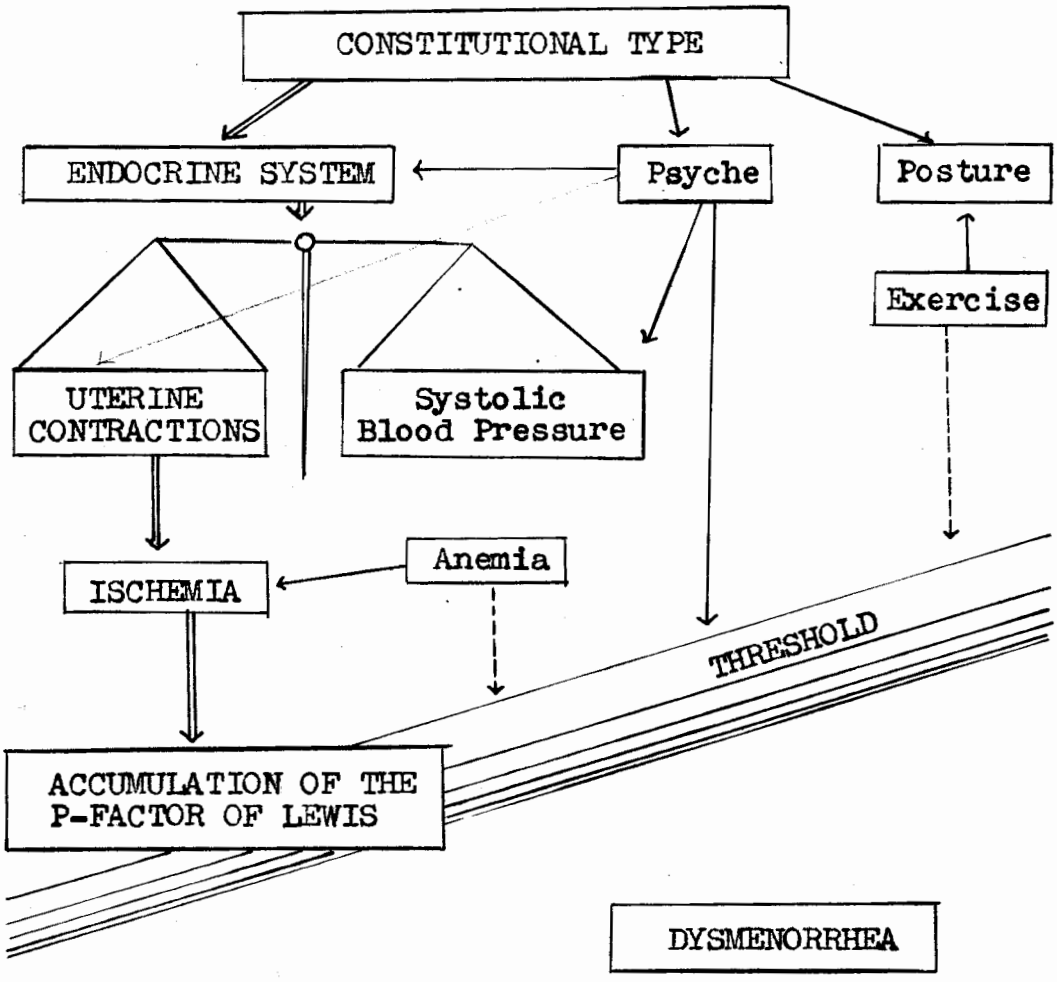
A humoral regulating mechanism suggests itself in that the uterine muscular cycle corresponds to the vascular cycle. One could postulate a vaso-pressor substance, acting on the smooth muscle of the vessel walls as well as on the myometrium.

X. Summary

Dysmenorrhea is a real pain, comparable in severity and causation to angina pectoris and to intermittent claudication. Ischemia is the common denominator of etiological factors, and brings about pain when a metabolic product, Factor P, is not oxidized in its normal mechanism, and stimulates sensory nerve endings. The classical causative agents of dysmenorrhea:

constitutional inferiority
psychic disturbances
posture
exercise
endocrine inbalance
anemia

all have a definite role in the etiology. The relationships may best be summarized by diagram:



Registration of pain on consciousness

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