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Hormonal therapy for primary dysmenorrhea

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HORMONAL THERAPY FOR PRIMARY DYSMENORRHEA

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TABLE OF CONTENTS

In the practice of gynecology one of the most difficult problems encountered is that of dysmenorrhea. In making a careful review of the literature one is impressed by the wide divergence of opinion which has existed in the past as to the incidence, the cause and the treatment of dysmenorrhea. With such a multiplicity of views on the subject, one naturally questions whether the underlying nature of the disturbance has really been uncovered as yet. Certainly the results of therapy have been far from consistent and, indeed, unsatisfactory. Time does not permit us to discuss at length the physical, economic and social effects of dysmenorrhea, and the loss of time and suffering which it causes. For so long now it has been classified by the medical profession as a minor gynecologic condition. Not so to the patient, however, for to the individual sufferer it is of major importance. Therefore any method of treatment which will give partial or timporary relief is gratefully received by these patients and should receive attentive consideration by the gynecologist.

A brief, but, adequate, classification of primary dysmenorrhea was offered by Kotz and Parker (1).

I. Dysmenorrhea caused by functional pathology

A. Nonendocrine causes

1. Pelvic congestion
2. Allergy
3. Neurosis

B. Endocrine causes

1. Ovarian dysfunction, Primary
2. Ovarian dysfunction, Secondary
   a. Hypopituitary function
   b. Hypothyroid function

Before any thorough discussion or understanding of the various methods of treatment can be expected, it is well to consider the numerous etiologic factors which contribute to primary dysmenorrhea. For years, the exact etiology of dysmenorrhea has remained unknown. Many theories have been advanced, but none has withstood scientific evaluation. Emil Novak (2) has done much pioneer work to set down an outline of the etiology of dysmenorrhea which is subscribed to today by most gynecologists:

A. Obstruction to the exit of menstrual blood. This can be due to stenosis of the cervical os, a long narrow cervix, or anteflexion of the uterus.

B. Hypoplasia of the uterus.

C. Constitutional factors. Patients with low pain thresholds are particularly susceptable to painful menstrual periods. Also such conditions as anemia, tuberculosis and diabetes may be factors in causing dysmenorrhea with the pain being

secondary to these conditions.

D. Psychogenic factors. To many gynecologists this would probably head the list. These are hard to evaluate, but there are cases which cannot be explained on this basis.

E. Endocrinopathies. The first thing to be considered is the role of hormones on uterine contractility:

1. The follicle hormone stimulates the uterus to contract, while the corpus luteum hormone inhibits uterine contractions.
2. Uterine contractions disappear after castration, but are restored by follicular hormone.
3. Uterine contractions stimulated by follicular hormone are inhibited experimentally by progesterone or the urine of pregnant women.

In conjunction with the various etiologic factors proposed by Novak, treatment over the years for dysmenorrhea has been very diversified. The gynecologists have attacked the problem on the basis of their conception of the exact etiology. Therefore, since the etiologic factors are numerous, so have been the methods of treatment. Before going into a detailed discussion of the hormonal treatment of this condition, I think it would be wise to

6. Rest. Both physical and mental fatigue are to be avoided.
7. Heat therapy to the painful area.
8. Dilatation of the cervix. Mechanical dilatation of the cervix and the use of stem pessaries were advocated by some with the idea of enhancing the egress of menstrual fluid.
9. Hypnosis.
10. Surgical. Presacral neurectomy was performed whereby the superior hypogastric plexus was resected. This was followed according to Cotte's original operation. Despite enthusiastic reports there were a substantial number of failures or recurrences.

In spite of the measures outlined above there were still many women who suffered from severe dysmenorrhea and were unable to obtain relief from any of these forms of treatment. In the absence of any pelvic pathology these were classed as primary, essential, idiopathic or functional dysmenorrhea. For these women an endocrine imbalance was suggested as being the major contributing factor and zealous investigations were conducted to determine the exact nature of this imbalance. With this in mind it is well to review, first of all, the physiology of the female genital system as it pertains to the menstrual cycle, and the affect of the specific hormones on

the menstrual cycle.

The anterior lobe of the pituitary gland figures strongly in this discussion as it is this gland which initially influences the ovaries, as well as many of the other glands of internal secretion in the body. The anterior pituitary liberates a gonadotropic hormone called the follicle stimulating hormone (FSH) which is responsible for the development and maturation of the Graafian follicle in the ovary. Another gonadotropic hormone is liberated by the anterior pituitary called the luteinizing hormone (LH) which is responsible for the formation of the corpus luteum after ovulation has occurred. During follicular growth, the follicle hormone or estrin is formed which causes vascularization and proliferation of the uterine endometrium and hyperplasia of the uterus along with stimulation or increase in the uterine contractions. After ovulation has taken place, the corpus luteum is formed in the ovary which produces a hormone called progestin. Progestin gives secretory growth to the endometrium, inhibits further follicle ripening and uterine contractions, and decreases the renal threshold for excretion of estrin. Knaus and Reynolds showed that castration caused complete quiescence of uterine muscle. Browne (7) and Israel (8) demonstrated that there was a hormone-like substance produced during pregnancy which

will cause follicle ripening and luteinization. If this substance doesn't remain fresh the estrogen-like action fades and the progestin-like action predominates with luteinization and follicle inhibition or arrest of follicle growth. Therefore, this gonadotropic principle present in the urine of pregnant women simulates progestin in quieting uterine contractions even in the absence of ovaries and thus has a direct affect on the uterus. With these facts in mind, it is easy to see how the endocrine theory of dysmenorrhea can be based on an imbalance of the normal estrogen-progestin ratio, and any condition upsetting this ratio must be strongly considered as a contributing factor in the production of painful menstruation.

A further breakdown of the endocrine etiology of dysmenorrhea presents more perplexing, contradictory and interesting problems. The whole question will be presented according to the views of the various pioneer investigators in this work who have correlated the type of treatment with their conception of the exact etiology.

One of the major concepts as to the origin of primary dysmenorrhea was that of increased and forceful uterine contractions. Novak (2) demonstrated that pain appeared one pr two days before menstruation began. It is at this time that the corpus luteum retrogresses and progestin is withdrawn. Therefore it was logical to assume that an abrupt withdrawl of the progesterone inhibiting effect

allowed full play of the follicle hormone with subsequent increased uterine contractions and pain. It was found that the follicle hormone was present in the blood in increasing amounts from the end of one menstrual period to the beginning of the next one. However, progestin formed by the corpus luteum after ovulation inhibits the effect folliculin has on the uterus. By withdrawing the progestin influence a quiescent uterus is whipped into marked activity by the action of an unopposed follicular hormone. Witherspoon (9) agreed with this idea and stated that, therefore, treatment should be aimed at counter-balancing excess of follicular hormone by substituting additional corpus luteum influence or withdrawing corpus luteum slowly so that follicular hormonal stimulation of the uterus appeared gradually. He administered follutein, the gonadotropin-like hormone, from the urine of pregnant women in the dosage of 250 rat units intramuscularly three or four days previous to the expected flow and one or two days during the flow. Seventeen cases were thus treated with satisfactory relief occurring in thirteen, partial relief in one and no relief in three. Israel (8) carried out a similar experiment in which he gave ten patients antuitrin-S, another anterior pituitary-like hormone, every other day in 200 rat unit doses for two or three months. Only four got complete relief, one for 14 months

and three during the treatment only, and six were unaffected. In comparing the results of these two studies it is obvious that they are not consistent or conclusive. To further clarify the role of uterine contractions as related to the problem of dysmenorrhea Randall and Odell (6) presented some of the work done by Kurarok on uterine contractions. Kurzrol demonstrated a difference in the uterine contractions during the proliferative and secretory phase of the endometrium. The proliferative phase had small rapid contractions, while the luteal or secretory phase had deeper and longer contractions in duration, which also lasted for the first two days of the menses. An accumulation of menstrual fluid within the uterine cavity stimulated luteal contractions with the result of pain for the first day or two of menstruation.

Prior to this time Elden and Wilson (10) had also discovered that the uterus was in a state of contractility and motility up to the 16th day of the cycle after which it became flaccid, sluggish and didn't react to pituitrin. However, on the day before the onset of the menses it reverted back to its preovulatory behavior. These authors studied 17 patients who received varying doses of progesterone ranging from 2/25 to one rabbit unit in either single or divided doses three to six days before the menses or the onset of pain. They discovered that if the

drug is given too early or too late it is without effect, and also that relief was obtained only during the months in which active treatment was carried out. Theri results showed that 47% got complete relief, 11.7% partial relief and 41.7% no relief at all. The relief obtained was explained on the basis of Schroders theory that sufficient relaxation of the uterine musculature was obtained to insure adequate circulation, thereby overcoming added congestion normally present at this time. The question may be asked as to what affect this type of treatment had on the subsequent menstrual periods. There was no delay in the onset of menstrual flow nor any change in the characteristics or duration of the period after small doses of this hormone was given.

Campbell and Hisaw (11) used a product of pure corpus luteum called corporin. Subcutaneous doses of five to eight rabbit units were given daily for five days prior to the onset of bleeding. Out of five patients studied one got no relief after five months of therapy, four got gradual relief which increased up to the third month. All that could still be said for this type of treatment was that it was temporary, and no assurance could be given that permanent relief would be obtained.

Previously between 1935 and 1940 progesterone therapy

had always been carried out by way of the parenteral route. Greenblatt (12) and Harding (13) demonstrated the use of an oral progestin-like substance called pregnenino-lone. This drug had been synthesized in 1938, was only slightly different from progesterone, had the same clinical effects as progesterone, and was very potent orally. The authors studied a series of 30 and 82 cases respectively. The average dosage administered varied from 5 to 15 mgm. per day and was given 2 to 22 days prior to the onset of the menses. The results were encouraging in that about 50% got satisfactory relief, 22% got partial relief and 28% got no relief. The duration of the relief, however, was variable and ranged from 6 to 12 months after therapy had been discontinued to relief only during active treatment. It was established that in order to be successful, treatment had to be given in the premenstrual period and had to be continued until bleeding occurred. Therefore, menstruated started during treatment, and was not a result of withdrawl of the drug. There was no interference with ovulation, and biopsies showed a pro-gestional endometrium with this oral progestin. However, the physiologic action that this drug exhibited and the results obtained still could not be accounted for.

Kotz and Parker (1), immediately following the work of Browne and Israel, confirmed the findings of earlier

investigators by supporting the theory that primary dysmenorrhea was due to ovarian failure which was secondary to anterior pituitary hypofunction in which there is an excess of follicle hormone and a deficiency of progesterone with subsequent excessive uterine contractions. They suggested that in order to bring about a normal estrin-progesterone ratio, the deficient hormone must be supplied or the pituitary must be stimulated to secrete normally. They used anterior pituitary-like hormones such as antuitrin-S and follutein, but it was questionable as to whether APL hormones actually stimulated the ovary to corpus luteum formation. Luteal hormones in the form of proluton or progestin were used two weeks before the onset of the menstrual period in the dosage of one international unit every other day up to the onset of menstruation. This was repeated for three consecutive months, but relief was not obtained until the third period. For stimulation of the pituitary gland something new was advocated -- X-ray. Twenty milliamperes, 200 KVP, 5 minutes, 60 inches distance with $\frac{1}{2}$ mm. copper and 1 mm aluminum filter to the right and left side of the pituitary every 3 weeks for 4 courses of treatment was used, but due to its destructive effects, this method was slow in being accepted by the medical profession.

It was discovered that a high concentration of estrin was necessary for the development of inhibition by the luteal hormone. At the beginning of pregnancy the uterus is under the influence of the corpus lutea and strong contractions with pain are controlled. However, from the third month on to term, the uterus is quiet, but is under the control of the placenta which contains a high concentration of estriol as shown by urinary excretions. Watson (14) conceived of the idea then, that an added supply of estrin in the normal cycle would favor the inhibiting effect of progesterone, and consequently, the administration of a placental extract with estriol in it was suggested. However, the results were not too gratifying as only 49 patients out of 150 received complete relief.

In spite of all the work that had been done with progesterone and progesterone-like substances up to this time no satisfactory conclusions could yet be drawn from this type of therapy. In the late 30's and early 40's a different form of therapy was being investigated, utilizing testosterone.. It was found that this androgenic product was closely related chemically to progesteerone and demonstrated a progestin-like action clinically. U. J. Salmon showed that testosterone

propionate depressed the anterior pituitary gonadotropic secretions with a subsequent decrease in estrogens, and Rubenstein (15, 16) and Abarbanel (15) showed that it inhibited ovulation. However, some believed that it favored luteinization and maintainence of the corpus luteum which lead to myometrial relaxation and relief of pain. Rubenstein and Abarbanel, in a series of 26 patients receiving 5 to 10 mgm per day intramuscularly for two or three injections in the week just prior to the expected onset of the menses, showed complete relief obtained in 16 patients, partial relief in 4 patients , no response in 4 cases and aggravated symptoms in 2 cases. Jacoby (17) in a similar investigation reported similar results with the same type of therapy. He showed that the male hormone, like progesterone, in large doses suppressed uterine contractions and in small doses reduced excessive contractions.

In 1950 William Filler (3, 18) brought forth the idea of using methyltestosterone in the preovulatory ½ of the cycle. He gave 10 mgm three times a day for 6 days before the estimated ovulation. Always before, with this type of therapy, the results were equivocal -- the pain was relieved, but many masculinizing effects resulted. With male hormone, it was interesting to note that there was a definite postovulatory increase of temperature, and

endometrial biopsies showed secretory endometrium. There was no evidence to indicate that ovulation had been suppressed as one patient became pregnant while taking the drug, and others became pregnant a few months after therapy was withdrawn. The pain was relieved only during the time that the drug was being administered, but returned again when therapy was discontinued. Recently a synthetic product, methyl andostenediol, has been used with no masculinizing effects, but its therapeutic value with relation to methyltestosterone is unknown. With these facts presented by Filler, still the mechanism by which methyltestosterone relieves dysmenorrhea is a mystery.

In spite of all the effort expended and the thorough investigations, a specific permanent type of treatment for dysmenorrhea was still to be found. The drugs thus far studied had afforded relief for some, but there were still many suffering from excruciating menstrual pain. In the 1940's a new approach to the whole problem of dysmenorrhea was formulated with the introduction of estrogenic therapy. Previously, a high estrogen concentration was believed to be the main contributing factor to dysmenorrhea, and attempts were made to decrease the high concentration or inhibit estrogen production in various ways. Now, estrogen therapy was being used to combat the condition which for so long had proved to be

distressing to many women.

The second major concept on which dysmenorrhea was based was that ovulation was a prerequisite for this condition to manifest itself. A large number of leading men adhered to this theory and set about attempting to prove this concept. In the following years many estrogenic substances were introduced by various workers. Brown and Bradbury (19), in a review of endocrinology, demonstrated that as a rule primary dysmenorrhea was associated with a normal ovulatory cycle. These patients usually have painless menstrual cycles if bleeding can be made anovulatory. Estrogenic therapy accomplished suppression of ovulation, and patients were relieved of cramps 6 to 10 months out of a year. Treatment was usually continued for 2 or 3 consecutive cycles, the patient was then allowed to have a normal (ovulatory and painful) cycle after which treatment was again resumed for another 2 or 3 months. By the majority of men working on this problem, it was generally agreed that the optimum time for instituting therapy was approximately 3 to 5 days after the onset of the menses. The dose of the drugs used varied as did the route of administration and the time element.

Sturgis and Albright (20) gave 1.7 mgm intramuscularly of estradiol benzoate every third day to 25 patients with the idea of suppressing ovulation and noting the optimum

time at which the drug should be given in order to accomplish this. They found also that if given within the first week after the onset of the menses, the following period was pain free, but the next period, when no estrin was given, was painful. This established the all or nothing phenomenon. To make their investigation more complete, these cases were followed by endometrial biopsies which showed secretory endometrium before any therapy was begun. This meant ovulation had occurred, and the following period was painful. However, after treatment was begun the endometrium was of the proliferative type, which meant no ovulation had occurred, and the following period was usually pain free. These men gave the drug in six injections -- one every third day -- and it was given only on alternate months. In connection with all this work, it was also demonstrated that estrins prevent maturation of the follicle by inhibiting FSH as a primary effect and suppress ovulation as a secondary effect. They also cause the endometrium to remain in the proliferative stage, and on cessation of treatment bleeding occurs 5 to 8 days later. However, in order to inhibit follicle maturation and FSH, the drugs have to be given early in the cycle as the growing follicle is dependent on the production of FSH from the 28th to the 21st day before menses. For that reason and with this regimen of administration, ovulation

cannot be suppressed for 2 consecutive months, because the second series of injections are given too late in the cycle. However, after a year or so of alternate month injections, there was an improvement in severity of pain even in the months when no estrin was given.

A couple of years later Sturgis (21) alone began working with an oral, synthetic estrogen called stilbesterol which had the same effect as the natural estrogens, but was more potent than any oral preparation of a natural estrogen. He compared his results of this drug with those of the use of estradiol benzoate. One or two mgm of stilbesterol was given daily for 10 to 24 days and withdrawl bleeding was gotten with 20 mgm stilbesterol orally as compared to 10 mgm of estradiol benzoate by injection. Cramps were relieved 59 times out of 79 courses of treatment. With this type of therapy Sturgis again proved that the drug had to be given at least 21 days before the next menstrual period and at least 7 days preceding ovulation in order to be effective. Therefore, it is essential that the patients ovulation variation be known before any correct timing as to when to give stilbesterol can be determined. If this isn't known, the drug may be given too late in the cycle so that maturation of the follicle is well under way and estrogens would have no effect on inhibiting the FSH.

Brown, Bradbury and Jennings (22) of Iowa carried on a similar experiment to Sturgis' original work with stilbesterol. However, they broke their patients up into 3 groups based on 3 general schedules. They also were able to obtain weekly endometrial biopsies for consecutive months before, during and after treatment. The first group of 5 patients were given a single 20 mgm dose early in the cycle. The next menstrual period was delayed to an interval of 34 to 37 days. Biopsy taken after treatment revealed secretory endometrial changes in 4 patients and there was no relief from the dysmenorrhea. A prolonged menstrual interval was associated with a delay in the onset of the secretory pattern. Therefore it was generally agreed that a single dose of estrogen given early in the menstrual cycle will delay, but not inhibit ovulation and will thereby increase the length of the cycle. The second group of patients were given prolonged treatment with diethylstilbesterol. This regimen was similar to Sturgis' and Albright's work with estradiol benzoate and stilbesterol. Starting at the end of a menstrual period 1 mgm of stilbesterol was given daily for 10 days, 2 mgm daily for the next 10 days and 3 mgm daily for the third 10 days. Bleeding occurred 3 days after the last 3 mgm dose and no dysmenorrhea resulted. This form of therapy was continued for 3 consecutive months, and in the third month of treatment,

endometrial biopsies revealed a proliferative endometrium. This demonstrated that prolonged or continuous treatment with estrogens would prevent ovulation and eliminate the luteal phase from the cycle. The third group of patients were given late treatment on the basis that estrogens maintained functional corpora lutea the same as in the rat. Three women were given 10 mgm of stilbesterol daily beginning in the postovulatory phase. However, there was no augmentation or prolongation of the luteal phase. Therefore, these observations offered no evidence that the human corpus luteum is affected in any way be estrogen as it is in experimental animals. Just what mechanisms come into play when estrogens exert their effect is not known for sure. Possible a single dose of estrogen early in the cycle can release enough hormone from the anterior pituitary before the Graafian follicle is mature enough to respond. The premature discharge of gonadotropin and a latent period for recovery of normal pituitary potency could account for prolonged cycles when estrogen is given soon after a menstrual period. Continuous or prolonged estrogen therapy would delay restoration of the pituitary hormone content so that anovulatory cycles would result. These authors also showed that progesterone protects the pituitary from depleting its hormone content under the influence of estrogen, so that the lack of estrogenic

effect during the luteal phase was due to the presence of progesterone.

Up to now no one had attempted to correlate the response to therapy with vaious dosage levels of estrogen. Hause, Goldzieher and Hamblen (23) attempted to do this by comparing various dosage levels of premarin and diethylstilbesterol. Therapy was given from the 5th to the 15th or 25th day of the cycle, and the total cycle dosage varied from 5 to 60 mgm of diethylstilbesterol and from 6.25 to 75 mgm of premarin. The results of this therapy can well be explained by Figure 1.

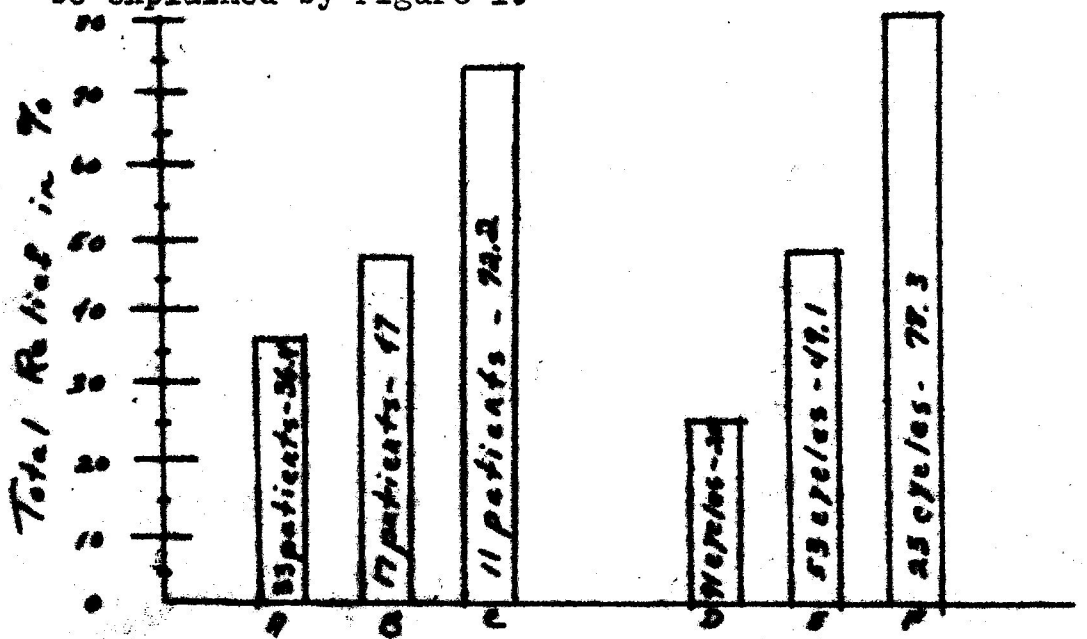

Figure 1. Dosage schedule

A. Less than 25 mgm premarin or 20 mgm diethylstilbesterol
B. 25 mgm premarin or 20 mgm diethylstilbesterol
C. 50 to 75 mgm premarin or 40 to 60 mgm diethylstilbesterol
D. Less than 25 mgm premarin or 20 mgm diethylstilbesterol
E. 25 mgm premarin or 20 mgm diethylstilbesterol
F. 75 mgm premarin or 60 mgm diethylstilbesterol

Of 32 endometrial biopsies taken at the end of treatment 21 were progestational, 20 of which were painful, and 11 were estrogenic, none being painful. Temperature records of 11 cycles were made, with 5 showing an ovulatory rise and associated with pain, while 6 showed an anovulatory curve and were pain free. From the results in Figure 1 it was obvious that the chances of obtaining relief in any cycle or any individual patient increased as the dose of estrogens was increased. This was the first time premarin had been used until Dignam, Wortham and Hamblen (24) came along and experimented with its use and value in combating dysmenorrhea. Their plan was to give a dose which would relieve pain and suppress ovulation at first, then decrease the dose until ovulation occurred, but no pain was experienced. Finally they wanted to withdraw medication entirely to determine whether or not the effect would be carried over into further cycles. Doses varied from equivalents of 0.3125 to 3.75 mgm of sodium estrone sulfate. Whenever a patient received 3.75 mgm daily from the 5th to the 24th day, pain was absent during the following menses. Doses above 0.625 mgm daily suppressed ovulation ½ of the time, while doses of 0.625 to 0.3125 mgm were never successful.

At the same time that Sturgis was working on diethylstilbesterol as a means of therapy for dysmenorrhea, he

had also joined Meigs (25) on some experimental work with estradiol dipropionate as another method of treating this condition. They followed the same theory as before -- if estrogen was given long enough and in sufficient doses it would suppress ovulation, prevent the formation of secretory endometrium, and cause endometrial proliferation from which bleeding occurred with estrogen withdrawl. The first effect was due to inhibition of FSH by estrogens thereby preventing maturation of the young follicle so that ovulation could not occur. They found that the failure to respond to treatment was due either to an inadequate dose or starting the medication too late in the cycle or both. These authors also agreed therapy must be started at least by the 6th day of the cycle and that one single 10 mgm injection gave more predictable results than two 5 mgm injections on the 6th and 16th day. Another regimen was formulated by these workers as far as timing the injections was concerned, whereby the first injection was given within the 6th day of the cycle, the second dose 10 days later and the third dose 2 weeks later. Bleeding occurred in the 2 week interval, and after this injections were given 10 days, 10 days and 14 days apart and then repeated again. After 3 months of therapy the patient was allowed to have an ovulatory cycle. In this way the patient was free from pain for 9 out of 12 months.

In the 1940's another drug, ethinyl estradiol was being investigated by Lyon (26) and MacGregor (27). This drug could be given orally, was very potent and removed at a slow rate by the liver with no signifacant toxicity. Lyon gave 0.05 mgm daily beginning 21 days prior to the next period and continued it for 24 days. Catamenia appeared about 6 days after the last dose of the drug. He then repeated it for another cycle, but discontimued treatment for the third cycle only to have pain recur. With estrogen therapy the cycles were prolonged, but the aftercoming untreated cycle was usually shorter. MacGregor's study was almost identical to that of Lyons, and only added further strength to the idea that an anovulatory cycle was painless in the majority of cases, and that the menstrual period is painless when estrogen and progesterone are in equilibrium and synergistic. Once again, it was established that to be effective estrogens had to be given in sufficient enough doses and had to be started early enough in the cycle.

Boynton and Winther (28) did some work with estriol glycuronide, but their results with this investigation were very unsatisfactory as far as the efficacy of this drug was concerned. They did demonstrate the value of controlled studies in any condition where psychogenic factors were so prevelant.

By way of comparison of various estrogenic substances Hirst, Hamblen and Cuyler (29) studied their effectiveness in relieving menstrual pain. Estradiol and diethyl-stilbesterol were given in largest doses with prompt relief in the greatest percentage of treated cycles. Estrone and estriol were given in the smallest doses and showed evidence of carry over and summation of effect in consecutive cycles of therapy. Besides this comparative work, Brown and Bradbury (30) wanted to demonstrate the potency of estrogens by the use of human vaginal smears. They showed estrone orally in daily doses for 10 days was as effective as stilbesterol, but intramuscularly in a single dose was only $\frac{1}{2}$ as potent as stilbesterol. In comparing estrone with estriol, an oral dosage of 1 mgm per day of estriol was without estrogenic effect, whereas estrone was. As an intravenous the natural estrogens, which are 90% estrone, compare favorably with stilbesterol.

In spite of all the work that has been done it is still obvious that the effects of estrogens are variable, since a given dose will suppress ovulation in a patient one month and not the next, or a given dose varies in its effects on different patients also.

To summarize the major concepts of this review it is seen that there are 2 causes of dysmenorrhea of functional pathological origin -- nonendocrine and

endocrine causes. The etiology of dysmenorrhea has been a major controversey among cynecologists for years, and for that reason methods of therapy have been varied. The methods of treatment have been correlated with the individual investigators concept of the etiologic factors involved.

The gonadotropic hormones from the anterior pituitary gland play a big role in the formulation of the endocrine theories as contributing factors in the production of dysmenorrhea. Increased and forceful contractions of the uterine musculature was the basis of many investigations on this problem. The appearance of menstrual pain occurred at a time when progesterone, with its inhibiting effect on uterine contractions, was withdrawn. This allowed full play of the estrogens with their stimulating effect on the uterine musculature, and pain followed. Therefore, many drugs were investigated which would bring about an equilibrium of estrogen-progesterone ratio.

Later it was recognized by many that ovulation was a prerequisite for dysmenorrhea. Consequently, it was found that estrogens, if given in sufficient enough dosages and at an early period in the menstrual cycle could suppress ovulation, eliminate the progestational phase of the endometrium and thereby relieve menstrual pain, without upsetting the subsequent ovarian cycles or causing undue

harm to the patient.

In conclusion and after thorough investigation of the whole problem, it is clear that nothing definite has, as yet, been arrived at as far as specific therapy for dysmenorrhea is concerned. All of the methods heretofore discussed have benefitted many, but there are still many who have not been reached by these various agents. Also there has been no demonstrable proof that any of the drugs have exhibited a permanent affect. Menstrual pain has been relieved only temporarily in the vast majority of cases, and since the carcinogenic action of the estrogens has been established, their indefinite administration as a means of suppressing ovulation has been contraindicated. However, many workers believe that the regular recurrence of a disabling complaint such as dysmenorrhea, no matter how normal the physiologic process with which it may be associated, justifies an attempt at relief from a psychological and economic view point. Much has been done to relieve temporarily the great amount of distress that this condition creates for so many women, but until a permanent agent can be discovered, dysmenorrhea will continue to be a perplexing problem facing the gynecologist.

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