

OVARIAN HORMONE THERAPY IN FUNCTIONAL MENOMETRORRHAGIA

Preliminary Report

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This brief preliminary report is presented at the present time because of the gratifying results obtained from the use of cyclic estradiol benzoate and progesterone therapy in ten cases of functional menometrorrhagia. Clinical investigation is still in progress, and a more detailed record will be submitted subsequently. This method of therapy has been effective in certain stubborn cases where other methods have failed.

Browne¹ has reported the successful treatment of metropathia hemorrhagica with premenstrual progesterone following curettage. The endometria of those cases which we have treated have not shown the changes found in metropathia hemorrhagica. It has been our impression from previous experience that cyclic use of the sex sterols has proved more effective in our cases. This is still to be verified.

Our application of estrone, or estradiol benzoate, and progesterone therapy has been limited to those cases of menorrhagia and/or metrorrhagia which are "functional" in character as determined by careful history, examination, assays and endometrial biopsies. Indirectly responsible organic disease and endocrine aberrations, such as hypothyroidism, must be excluded first.

Our original conception of the cyclic use of sex sterols in the treatment of functional menometrorrhagia developed as a consequence of finding low urinary assays for estrogenic substances in such a case early in 1938. This has been confirmed by assays in other cases, and has been correlated with endometrial biopsies. We felt that the condition was due to hypo-ovarianism and that the logical treatment would be an attempt to reproduce in the endometrium those changes which would occur there normally. Various commercial estrogens and progesterone preparations are highly potent, and have been shown to be capable of producing normal premenstrual endometria in human castrates².

Since that time, Hamblen^{3, 4} has advanced an interesting theory in support of the use of estrogens and progesterone in menometrorrhagia, and has reported a series of cases treated successfully by both the oral and the intramuscular routes. He feels that refractivity on the part of either the ovary or the endometrium, or both, may be a primary factor in many cases of functional menometrorrhagia. Under such circumstances he reasons, it is logical to employ the hormones of the ovary cyclically since this therapy, by its retrograde action on the pituitary, might be effective in overcoming ovarian refractivity. Moreover, the

stimulating action of these products on the endometrium might favorably influence its refractivity.

Our use of estrone, or estradiol benzoate and progesterone, has been designed to produce the desired effect with the minimal quantity of the hormonal preparations necessary for good results. On the basis of our studies, the following mode of therapy should prove effective in many instances, and may be modified in the direction of greater or lesser dosage as required by the individual case. It has been effective when large doses of APL have failed.

Treatment may be initiated at any time, even during an episode of metrorrhagia, since estrogen injections usually are sufficient to stop hemorrhage. Injections are then given on the basis of a twenty-eight day cycle, 2,000 rat units of estradiol benzoate, or 10,000 international units of estrone, being given two or three times weekly during the first three weeks. During the fourth week, two to five international units of progesterone are given on the fifth and third days before the onset of the calculated menstrual period. Therapy is then withheld for three or four days, after which the course is initiated again without regard for the presence or absence of bleeding, and is repeated on the above-mentioned twenty-eight day basis. Estrogen sometimes may be given with the two injections of progesterone, but it is likely to delay the onset of bleeding. When a fairly definite cycle is present or has been established it usually has been our custom to give the estrogen and progesterone only during the two weeks preceding menstruation in total divided dosage of 4,000 to 8,000 rat units of estradiol benzoate and two to ten international units of progesterone. With this method, estradiol benzoate and progesterone probably should be given concurrently during the fourth week on the fifth and third days premenstrually. After four to six months of such cyclic usage, therapy should be withheld for a time to determine whether or not a normal rhythm and flow have been re-established.

We do not recommend this method of treatment to the exclusion of other more commonly employed procedures. Pregnancy urine and placental preparations, testicular hormone, pregnant mare's serum derivatives, and even roentgen therapy and surgery have certain applications. Moccasin snake venom is sometimes an emergency measure. Curettage is helpful from the diagnostic standpoint and may be effective in controlling hemorrhage. It is preferable to do a curettage before beginning therapy with hormones, especially in women over thirty years of age, where malignancy has to be considered more seriously than in younger women. Thyroid may be used empirically with benefit in many cases, and may be especially helpful if the metabolism is low.

Our dosage has been considerably less than that employed by Hamblen³ and the progesterone particularly has been far below the

OVARIAN HORMONE THERAPY ESTRONE - PROGESTERONE IN MENOMETRORRHAGIA

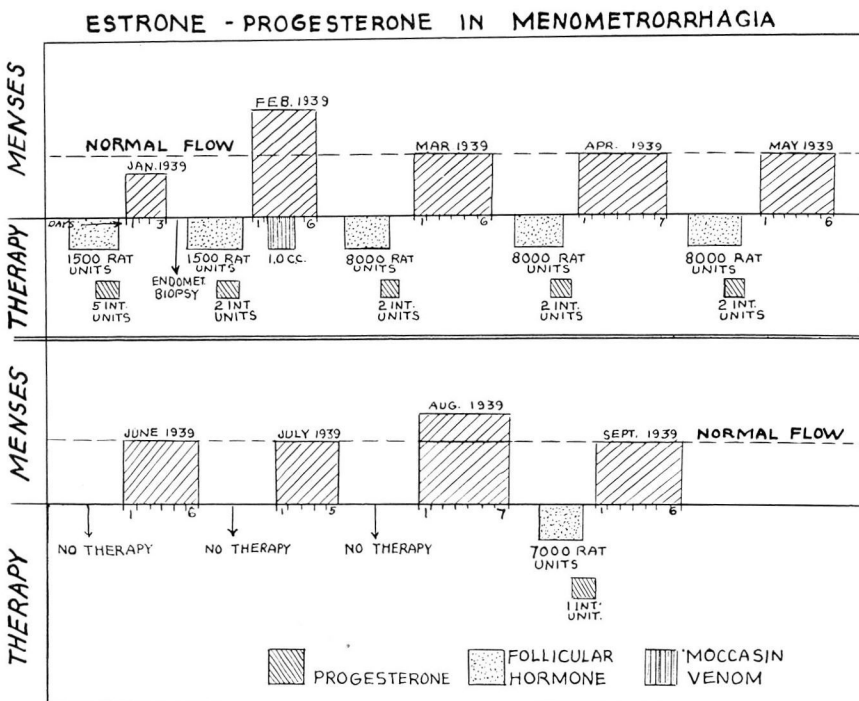
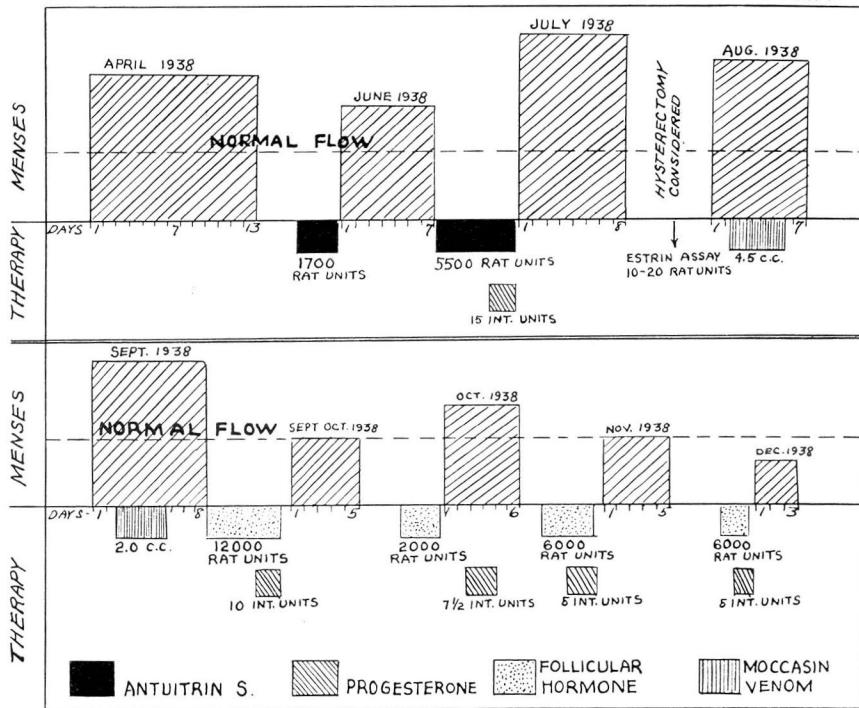


FIGURE 1A AND 1B

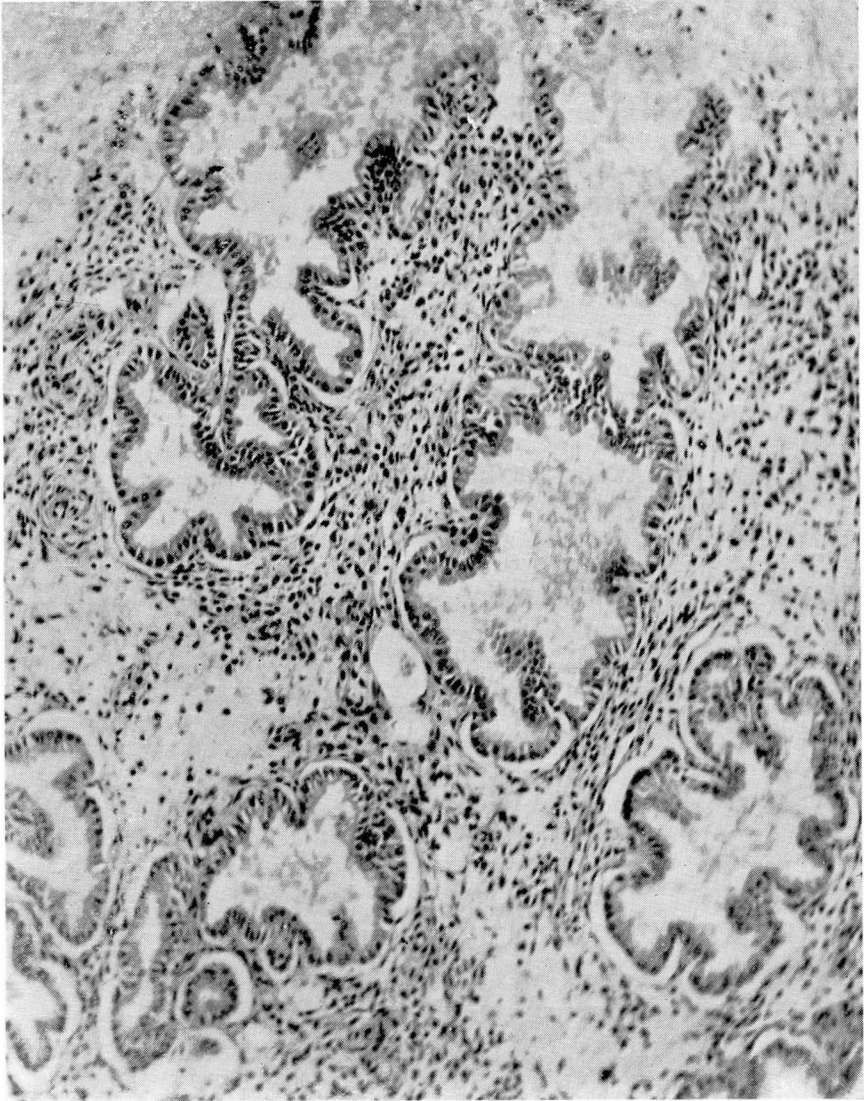


FIGURE 2: Endometrial section, Date: March 29, 1938.

minimal requirements for castrates, as outlined by Kaufmann². Nonetheless, in approximately twelve cases, our results have been distinctly favorable, with but two exceptions. The following case is fairly typical:

CASE REPORT

A twenty-seven year old woman was seen originally in March, 1938, relative to her menorrhagia. This was the first case in which we employed cyclic follicular and luteal hormonal therapy. The idea originated with the finding of a low assay for estrogenic substances in the urine, indicative of hypo-ovarianism. The patient

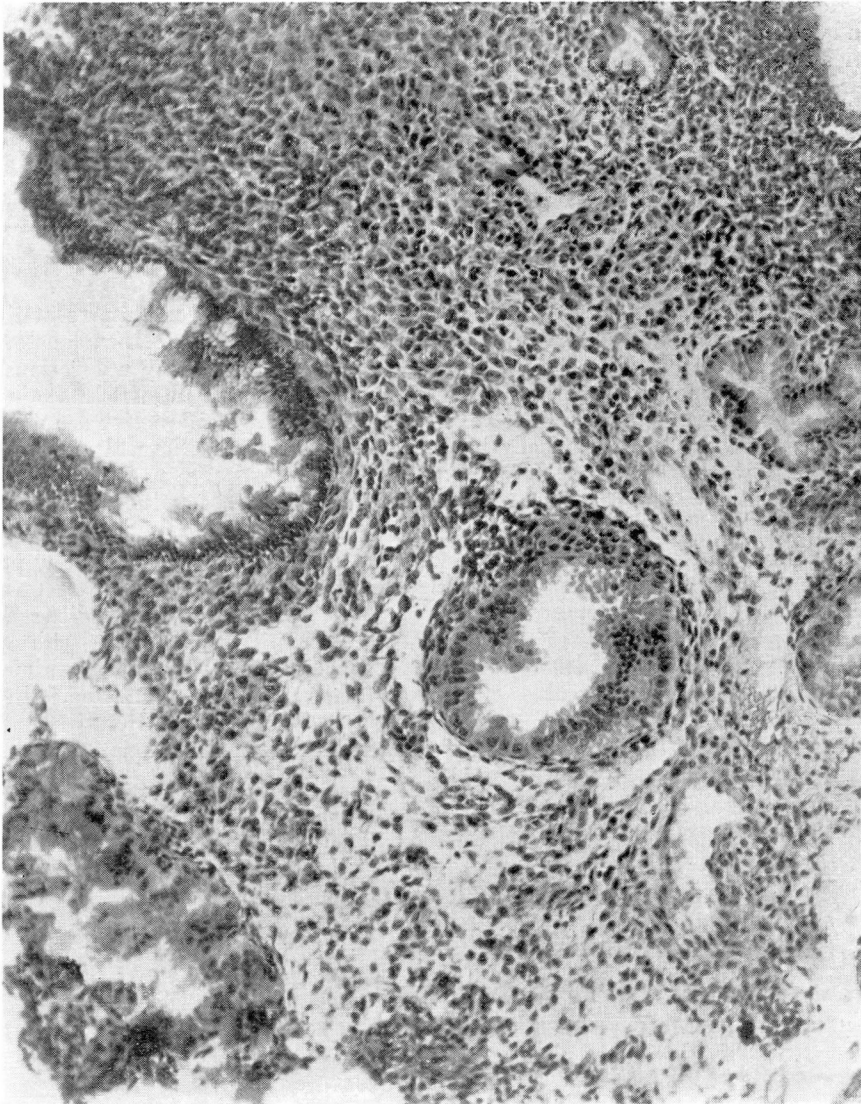


FIGURE 3: Endometrial section, Date: January 17, 1939.

had had regular but excessive and prolonged bleeding for a number of years. Large doses of antuitrin-S in February, 1935, and of APL in October, 1935, had proved ineffective. Removal of an ovarian cyst in July, 1936, was followed by a decrease in the duration of periods to eight or nine days, but the flow continued to be excessive. She had no unusual premenstrual symptoms but there was a rather profuse leukorrhea, which was exaggerated before and after the menstrual flow.

General physical examination revealed normal findings. The pelvic examination was negative.

Routine laboratory investigation, including urinalysis, blood counts, serology, and determination of the blood sugar level showed no significant findings, except for a hypochromic anemia which has been treated by iron medication. An assay for estrogenic substances was distinctly low, showing less than ten rat units in a twenty-four hour specimen of urine collected at approximately the midcycle. A subsequent assay showed ten to twenty rat units. The method used for these assays is that described by McCullagh and Guillet⁵.

An endometrial biopsy two days before the onset of the menstrual period showed marked thickening with enlarged tortuous glands, lined by cuboidal and columnar epithelial cells, with infoldings into the lumina. There was marked edema and diffuse hemorrhage into the stroma.

The following charts represent her response to treatment over a representative period. (Figs. 1a and 1b). To a great extent, these charts are self-explanatory. It will be noted that antuitrin-S was not effective. Hysterectomy was seriously considered at one point. Completely normal bleeding was ultimately attained by the use of 8,000 rat units of estradiol benzoate and two international units of progesterone, employed cyclically in the manner described. Several months of normal flow resulted without therapy. The only untoward symptoms noted as a consequence of treatment were a sensation of pelvic fullness and mild cramping pain.

Figures 2 and 3 are photomicrographs of endometria collected on the day preceding or on the first day of bleeding, representing the findings before treatment and those following five months of therapy. There is relatively little difference in the two and each shows progesterone effect. This is in accordance with our opinion and that of others that such functional bleeding may occur from almost any type of endometrium, and is very common from that showing a mixed follicular and luteal hormone response. Bleeding from a purely proliferative endometrium, in our experience, has been somewhat less common than anticipated.

The fact that there is so little difference in the two specimens suggests that some factor³ other than endometrial change, as a result of treatment, is responsible for the good results which were obtained.

SUMMARY

A method of treatment for functional menometrorrhagia with cyclic estrogens and progesterone is presented. A typical case is discussed. The results are satisfactory, and the method is tentatively recommended. Further confirmatory investigation is in progress.

REFERENCES

1. Browne, J. S. L.: (abstract) Some effects of sex hormones on certain abnormalities of corpus luteum function, *Canad. M. A. J.*, 39:84-85, (July) 1938.
2. Kaufmann, C.: Umwandlung der Uterusschleimhaut einer kastrierten Frau aus dem atropischen Stadium in das sekretorischen Funktion durch Ovarialhormone, *Zentralbl. f. Gynäk.*, 56:2058-2061, (August) 1932.
3. Hamblen, E. C.: Therapeutic use of the sex sterols in functional menometrorrhagia, *Endocrinology*, 24:13-28, (January) 1939.
4. Hamblen, E. C., Powell, N. B., Cuyler, W. Kenneth, and Pattee, C. J.: Oral use of pregnenolone in functional menometrorrhagia, *Endocrinology*, 26:201-207, (February) 1940.
5. McCullagh, D. R. and Guillet, R.: Summary of some laboratory methods in endocrinology, *Cleveland Clin. Quart.*, 6:95-104, (April) 1939.