Specific Procedures for the Elimination of the Menopause*

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There is general agreement that gonadal failure has remained the only endocrine alteration demonstrated to be characteristic of a woman's old age.1 Masters2 considers the ovaries to be the Achilles' heel of her body. The aging ovary appears phylogenetically unable to respond to even very high levels of follicle-stimulating hormone (FSH). Morphologically it becomes small and hard and all its ova disappear within 2 to 3 years after the menopause. The unpalatable truth must be faced that all postmenopausal women are castrates. There is a variation in degree but not in fact. Many women actually spend more of their lives without functioning ovaries than with them. It is in this rapid failure of gonadal function that women differ markedly from men; their aging process is distorted. Granting that the cessation of ovulation is opportune, certainly the progressive disappearance of the gonadal hormones at this relatively early time of a woman's life is a misfortune.

Solez3 suggests that the decreased activity of the gonads is associated with increased corticotrophic and adrenal cortical activity. He indicates that in Cushing's syndrome we have a condition which occurs explosively, while in the aging female similar changes occur over a period of decades. There is good functioning capacity of catabolism mediating glands in contrast to a progressive loss of capacity of the glands with anabolic activity. The scales are unbalanced; there is catabolic dominance. Fortunately, appropriate remedies to balance them are now available.

The advent of the new oral, highly potent progestogens has attracted considerable attention to the area of progesterone therapy. However, a large and important sphere of their usefulness so far has passed almost unnoticed. Certain progestogens, allied with estrogens and intelligently administered, can compensate for nature's inexplicable accident, the menopause. Crystalline progesterone is absorbed very poorly by mouth; it is irritating by hypodermic. Therefore, it is not practicable for long-term use.

In this communication we present the steps and techniques which enable us to help partly or completely castrated women to avoid or overcome their misfortunes.

It has been shown, both from a clinical and laboratory standpoint, that estrogen deficiency is associated with the following:
- Negative nitrogen balance.4,5
- Hypertension.6,7
- Hypercholesteremia with cerebral and coronary atherosclerosis.8-12
- Osteoporosis.13,14
- Impairment of carbohydrate metabolism.15,16
- Hyperactivity of the anterior pituitary gland with pluriglandular imbalance.17,18
- Regression of secondary sex characteristics.
- Regression of sex organs with senile vaginitis.

It is only a matter of when and to what extent each woman will become a victim of this deficiency. Obviously placebos have no place in the definitive treatment of these pathologic changes.

We believe the menopause and the menopausal state to be a disease so insidiously blended with chronic aging that there is a tendency for it to be overlooked and neglected.

The symptoms of the menopause are notoriously bewildering. They may be a direct result of physical and psychic difficulties brought about by the deficiency state or they may be due to unrelated causes. When these are jumbled together the physician is faced with a difficult, often unrewarding problem. This accounts for a frequent disinclination to handle such cases, the hit-or-miss treatment sometimes instituted and the frequently poor results. The dilemma is solved and success

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achieved by treating primarily and principally the vaginal smear, not the symptoms.

MATERIAL

The human material for this study consists of 304 white women found to be estrogen-deficient according to the Papanicolaou smear and treated by methods herein presented. The youngest patient was 40 years of age; the oldest was 73 years; the average was 50.8 years. The average duration of treatment was 7.8 years. The age group 50 to 59 included the largest number of patients.

Our armamentarium consists of 3 preparations: Conjugated estrogens, equine, 1.25 mg. and 0.625 mg. tablets, Premarin®—a-Estradiol benzoate 1.50 mg., in oil for intramuscular injection—medroxyprogesterone acetate (17α-hydroxy-6α-methyl progesterone acetate) 10 mg. tablets, Provera®.

METHODS

Since the selection of the method of treatment is the sine qua non of our project, it seems advisable to define the categories into which our patients fall in the interest of conciseness we have telescoped identification of characteristics with their appropriate treatment and have labeled these A, B, C and D.

Before instituting treatment 3 steps are essential: (1) complete examination, (2) vaginal smear and (3) selection of appropriate method of treatment.

Step 1. Complete examination. This examination is essential. Fibroids, ovarian cysts, cystic mastitis and malignancies will be discussed later.

Step 2. Vaginal smear. (See “The Value of the Vaginal Cytologic Smear for Estimating Hormonal Function” under Comment). The recommended routine is as follows: Using a small cotton tipped applicator, thinly smear the distal half of a slide with secretion from the mid-portion of the lateral wall of the vagina, this being the best site for the evaluation of hormonal function. Next, cover the inner half of the slide with material obtained by dipping an Ayre wooden spatula in the secretion directly below the cervix and then rotating it lightly around the cervical os. This part of the slide is for Papanicolaou classification. Place the slide immediately in a fixative for the subsequent staining processing.

Request the cytologist, apart from malignancy screening, to report only the percentages of superficial, intermediate and parabasal cells arranged in that order for convenience and counted from at least 3 random fields. This simple and easily comprehended colposcytogram is a measure of the growth and maturation of the vaginal epithelium. When expressed in reversed order, it is known as the Maturation Index. We use it to measure the degree of estrogen activity, particularly in menopausal and postmenopausal women. Require the cytologist not to mention the Karyopynotic* and Eosinophilic*** Indices and the more sophisticated and often confusing terms such as precorneulated, basophilic and

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*We are grateful to Dr. John B. Jewell of Ayerst Laboratories for supplies of Premarin, brand of conjugated estrogens, and to Drs. J. William Hendrix and Samuel S. Stubble of the Upjohn Company for supplies of Provera, brand of medroxyprogesterone acetate.

**The Karyopynotic Index—the percentage of pyknotic nuclei in the superficial cells—is the most accurate and refined method for general use when superficial and intermediate cells predominate. It is unsuitable for determining the degree of estrogen deficiency in the older postmenopausal woman because of the diminution in number or absence of superficial cells and the large number of parabasal cells frequently encountered.

***The Eosinophilic Index—the proportion of superficial cells with eosinophilic staining—is unsuitable for the same reasons as for the Karyopynotic Index and, in addition, is easily influenced by inflammation, infections and changes in the pH of the vagina, factors almost always present in postmenopausal women.
navicular cells, histocytes, and so forth. The following is a representative report of a healthy woman 20 years of age.

Report:
(a) Smear contains occasional lymphocytes but no bacteria.
(b) Mature superficial squamous cells represent 85% of the total; intermediates 15%; no parabasals seen.
(c) Estrogen effect high.
(d) No abnormal forms present, Pap. 1 (Fig. 1).

The principal therapeutic aim is to approximate and maintain the respective cell per-

Table I
RECOMMENDED MAINTENANCE CELL PERCENTAGES AND ESTROGEN ACTIVITY FOR DIFFERENT AGE GROUPS

<table>
<thead>
<tr>
<th>Age group</th>
<th>Superficial squamous cells</th>
<th>% Intermediate cells</th>
<th>% Parabasal cells</th>
<th>Estrogen activity</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-44</td>
<td>85</td>
<td>15</td>
<td>0</td>
<td>High</td>
<td>Satisfactory for most women in this age group. Usually those in the professions, arts, public life, etc. require a higher level of estrogen activity than those leading a less active life.</td>
</tr>
<tr>
<td>45-54</td>
<td>80-85</td>
<td>20-15</td>
<td>0</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>55-64</td>
<td>70-75</td>
<td>30-25</td>
<td>0</td>
<td>High medium</td>
<td></td>
</tr>
<tr>
<td>65-670</td>
<td>35-30</td>
<td>0-5</td>
<td>Medium (maximum)</td>
<td></td>
<td>Each patient in this group must be individualized depending on the extent of pathology.</td>
</tr>
</tbody>
</table>

- All the suggested estrogen titers prime the endometrium satisfactorily. Estrogen levels are not critical and latitude may be exercised. The estrogen activity levels of the patients in the last two groups are in accord with decreased tissue and pluriglandular metabolism associated with the aging process.

- A good cytogram always indicates an adequate presence of estrogen for utilization at tissue level.

Step 3. Selection of appropriate method of treatment (a good smear report is the goal).

Method A. For the younger hypogonadal as well as the premenopausal woman if menstruation is regular.
Method B. For the hypogonadal and perimenopausal woman who skips and/or has irregular menstruation.
Method C. For the postmenopausal woman who has not bled for 1 or more years.
Method D. For the older postmenopausal woman with advanced pathologic findings (a modification of Method C).

Methods A and B are essentially preventive while C and D are restorative. The dosages specified in the 4 methods of treatment are the result of experience in treating over 2,000 estrogen-deficient women.

Method A: For the younger hypogonadal as well as the premenopausal woman if menstruation is regular. The following is a representative pretreatment smear.
(a) Smear reveals occasional lymphocytes and bacteria.
(b) Mature superficial squamous cells represent 70% of the total; intermediates, 28%; parabasals, 2%.

70-28-2
Fig. 2. Schematic representation of the cell population of the vaginal mucosa of the average hypogonadal and premenopausal woman whose menstruation is regular. Of interest is the decline in the percentage of superficial cells and the appearance of parabasal cells.

Fig. 3. Schema of the vaginal epithelial cells of the average hypogonadal and perimenopausal woman who menstruates irregularly. The percentage of the most mature component has decreased while the percentages of the less mature have increased.

Menstruation becomes irregular, change to Method B.

Method B: For the hypogonadal and perimenopausal woman who skips and/or has irregular menstruation. The following is a representative pretreatment smear.

(a) Smear reveals numerous lymphocytes and bacteria.

(b) Mature superficial squamous cells represent 55% of the total; intermediates, 38%; parabasals, 7%.

(c) Estrogen effect low medium.

(d) No suspicious forms present, Pap. I (Fig. 3).

Treatment. One 1.25 mg. tablet of conjugated estrogens daily on and from day 5 of the menstrual cycle to and including day 25. If 2 or more months have elapsed since menstruation, an artificial cycle of 28 days is used.

One half 10 mg. tablet (5 mg.) of medroxyprogesterone acetate daily on and from day 14 to and including day 25.

Menstruation can be expected on day 27 or 28. If bleeding should inadvertently occur during the proliferative phase, for example on day 9, interrupt the treatment and consider that day as day one. Resume medication on day 5. Inadvertent bleeding is unlikely during the secretory phase (day 14 onwards). If it should occur, double the dose of medroxyprogesterone acetate for the remainder of the cycle. This will control it. Repeat smear every 6 months,†,‡ on day 12, 13 or 14, and adjust the estrogen intake whenever necessary.

This group of women usually has sweats and flushes, headaches, insomnia, fatigue and depression, although on physical examination the pelvic organs are essentially negative. As indicated by successive smears, regulate the conjugated estrogens to increase the superficial cells close to 85% and to eliminate the parabasal cells. One 1.25 mg. tablet of conjugated estrogens daily from day 5 to day 25 is the average dose. More or less estrogen may be needed. Increase or decrease the estrogen intake using the half strength tablet (0.625 mg.). Whatever the dose, it must be administered daily from day 5 to day 25 without interruption.

About 20% of women have a satisfactory cytogram and estrogen activity for as long as 3 years after the menses cease or become irregular. Only the medroxyprogesterone acetate

†If the suppression of ovulation is desired, administer the medroxyprogesterone acetate daily on and from day 5 to and including day 25 simultaneously with the conjugated estrogens. This will cause certain progestational changes in the smear.

‡In the younger hypogonadal female, this cyclic treatment may restore ovulation but this is unlikely after age 43.
should be administered in these cases until the inevitable decline in estrogen production occurs.

At about age 50 and sometimes sooner, most of these patients can be transferred advantageously to Method C.

Method C: For the menopausal woman who has not bled for 1 or more years and for those previously treated by Method B. The following is a representative pretreatment smear.

(a) Smear reveals numerous leukocytes and bacteria, cocci and a few red blood cells.

(b) Superficial squamous cells represent 35% of the total; intermediates, 51%; parabasals, 14%.*

(c) Estrogen effect low.

(d) No suspicious forms present. Pap. I (Fig. 4).

Treatment. One 1.25 mg. tablet of conjugated estrogens daily for 42 consecutive days (see Comment).

One 10 mg. tablet of medroxyprogesterone acetate daily on and from day 31 to and including day 42.

Discontinue both tablets at that time and expect menstruation 2 to 3 days later. Resume the conjugated estrogens on the fifth day of the bleeding phase. Approximately 7 yearly bleedings result. Repeat the smear every 6 months, about day 30 of the cycle, and adjust the estrogen intake if necessary.

A woman, typical of this group (age 57), 7 years postmenopausal, usually has many symptoms such as insomnia, depression, extreme fatigue, low backache, pruritis vulvae and some dyspareunia. The blood pressure is likely to be elevated. A dowager's hump is apparent, also flabby breasts and Heberden's nodes. The vulva and the vaginal mucosa are moderately atrophic.

If the repeat smears are not satisfactory, increase the conjugated estrogens to 1½ or more tablets daily. Women vary considerably in the amount of estrogen they require and in the rate of its metabolizing. After age 55, a slightly lower standard of smear excellence is often permissible (Table I).

Method D: For the older postmenopausal woman with advanced pathologic findings (a modification of Method C). The following is a representative pretreatment smear.

(a) This streaky smear shows numerous white and red blood cells, abundant nuclear debris and is loaded with bacteria and cocci. A few trichomonas are seen.

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(a) This streaky smear shows numerous white and red blood cells, abundant nuclear debris and is loaded with bacteria and cocci. A few trichomonas are seen.
(b) Superficial squamous cells are absent; intermediate cells are 30%; parabasals, 70%.
0-30-70

(c) Estrogen effect none.

(d) No suspicious forms present, Pap I (Fig. 5).

Treatment. Similar to Method C, except that two 1.25 mg. tablets daily of conjugated estrogens are used for the first 2 cycles. In addition, a-Estradiol benzoate 1.50 mg. is injected intramuscularly weekly during the first 2 cycles. After 2 cycles this method reverts to, and is identical with, Method C.

This method is suggested for women in advanced stages of estrogen deprivation with pathologic findings such as arteriosclerosis with a high total serum cholesterol, concentration of B-lipoproteins and C/F ratio. At about age 65 these women can be expected to exhibit some degree of osteoporosis, senile vaginitis and menopausal negativism. The parenteral injections materially hasten the restoration of diseased areas and have a strong psychic effect, an important aid to these distressed patients. This method is also suitable for trial in involutional melancholia. The initial high level of estrogen activity established in Method D is continued for 2 cycles or until tissue changes have been satisfactorily reversed. Maintenance should then be in accord with levels recommended in Table I.

Breakthrough Bleeding—Methods C and D. Spotting or bleeding during postmenopausal cyclic therapy is avoided by keeping the estrogen intake even, or by increasing it slowly during the proliferative phase. Sudden drops in the body level of estrogen result in a lack of endometrial support with areas of focal necrosis and resultant bleeding. The following suggestions are offered if bleeding occurs.

1. In the proliferative phase, such as on day 18, double the dose of conjugated estrogens for the remainder of the cycle. If the patient is already receiving a double dose (2.50 mg.) increase it by only 1.25 mg. If this fails to control bleeding in 3 days, start the secretory phase ahead of time (10 mg. of medroxyprogesterone acetate daily for 12 days). This will stop the bleeding.

2. Bleeding in the secretory phase is less likely. Usually it is the result of forgotten medication. It is quickly controlled by doubling the dose of medroxyprogesterone acetate for the remainder of the cycle.

Failure to control bleeding or its unexpected recurrences demand curettage.

Postponement, Advancement or Abandonment of Induced Menstruation—Methods C and D. For many reasons, including that of convenience, it may be desirable to postpone bleeding. One plan is to begin the 12 days of the progestogen later in the cycle, the conjugated estrogens being continued. A second plan is to begin the progestogen on schedule but to continue it, and its accompanying estrogen, for a longer period. The first plan is to be preferred.

Advancement of bleeding is achieved by commencing the progestogen earlier in the cycle. Such advancement should be limited to a few days in order not to interfere with adequate priming of the endometrium. Whenever menstruation becomes absurd because of age, or for other reasons, an androgen should be substituted for the progestogen. This is common geriatric practice today.

RESULTS

Three hundred and four perimenopausal and postmenopausal women, treated by an appropriate method, were shielded properly against pathologic conditions known to be associated with estrogen deficiency.

One hundred and thirty-nine of these women, treated by Methods A and B, never experienced the menopause.

The remaining 165, 1 or more years postmenopausal, some with long-standing pathologic changes, received the specific treatment needed to reverse these changes as far as practicable. Eighty-seven patients in this last group, treated by Methods C and D, resumed cyclic bleeding, in one case 22 years after her last menstruation. There were approximately 1,450 restored menstrual cycles up to January 1, 1963. There was 1 unexplained failure in a 54 year old woman in spite of perfect priming and daily 30 mg. doses of the progestogen (Table II).

Satisfactory vaginal smears were achieved in a relatively short time. Sixty-seven percent of the women represented had attained recommended cell percentages and levels of estrogen activity at the time of their first posttreatment smear. The remaining 33%, prin-
TABLE II
RESULTS OF TREATMENT OF 304 ESTROGEN-DEFICIENT WOMEN

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen activity increased to recommended levels (Table I)*</td>
<td>304</td>
</tr>
<tr>
<td>Postmenopausal estrogen-progestogen induced cyclic bleedings to Jan. 1, 1963</td>
<td>1,450 (app.)</td>
</tr>
<tr>
<td>Reactions or side-effects necessitating discontinuance of therapy</td>
<td>0</td>
</tr>
<tr>
<td>Surgical intervention during treatment with Methods A and B</td>
<td>6</td>
</tr>
<tr>
<td>Surgical intervention during treatment with Methods C and D</td>
<td>0</td>
</tr>
<tr>
<td>Malignancies of breasts and/or genitals</td>
<td>0</td>
</tr>
<tr>
<td>Deaths‡</td>
<td>2</td>
</tr>
</tbody>
</table>

*Comparison of pretreatment and post-treatment smears.
‡Both from unrelated causes.

principally those treated by Methods C and D, required an average of 3 post-treatment smears, 6 months apart, before the long-standing estrogen deficiency was remedied.

The results with medroxyprogesterone acetate are highly predictable, requiring little variation in dosage.

Our results with the 304 women under discussion, as well as hundreds of others of different ages, indicate that the body tissues are indifferent as to whether or not ovarian hormones are endogenous or exogenous. Tolerance for these hormones does not increase with usage.

There were no breast or genital malignancies in the 2,604 patient years of exposure to exogenous estrogen although 20 was a reasonable expectation.

Fig. 6. Endometrial biopsies taken from the same patient during the same cycle. She was 47 years of age, her last natural bleeding having occurred 1 year previously. This was the fourth induced cycle. She was primed by 1.25 mg. of conjugated estrogens (Premarin) per day for 30 consecutive days. She also received 10 mg. of medroxyprogesterone acetate (Provera) per day for the last 7 days. (A). Taken on the seventh day of estrogen administration. It shows a typical proliferative effect. There is no hyperplasia from the previous cycle or cycles (x 92).
Fig. 6 (B). Taken on the seventh day of medroxyprogesterone acetate administration. It is compatible with an early to early maximum secretory phase of the natural cycle (x 92).

Fig. 6 (C). Taken on the fourteenth day after starting medroxyprogesterone acetate. It is compatible with the late menstrual phase of the natural cycle and shows no significant difference from other late menstrual phases of young women (x 92).
COMMENT

It is of interest to note that the atrophic endometrium can be regenerated even 20 or more years after the menopause. The following brief case report illustrates this.

E. O., aged 53 (a registered nurse) never bled after a bilateral oophorectomy in 1938. She developed advanced osteoporosis of the spine. Started on cyclic therapy July 1960, 22 years after castration, she responded at the end of the third cycle and has menstruated regularly since on double doses of conjugated estrogens (2.50 mg.) and medroxyprogesterone acetate (20 mg.).

A 42 day cycle rather than one of 28 days is used in Method C because, although the opposing effect of progesterone or its derivatives is needed, progesterone is desirable fewer days per year than in youth. Its metabolic effects are essentially catabolic and cause increased urinary excretion of nitrogen and phosphorus. Some of the anabolic potential of estrogen is, therefore, combated. Our continuing studies indicate that longer cycles will be satisfactory. Longer cycles result also in fewer yearly bleedings, a welcome decrease in the nuisance factor.

Medroxyprogesterone Acetate. The action of the 19-norsteroids on the endometrium is atypical. If such curettages are dated according to the criteria of Noyes and Hertig, a prompt accelerated progestational action is noted. In a few days one obtains a picture of a much later day. An arrest of glandular development and secretory activity soon is followed by glandular regression accompanied by stromal stimulation.

We have not found medroxyprogesterone acetate to have this galloping effect. Probably because it is a derivative of progesterone, its action more closely resembles the parent substance. Endometrial biopsies from primed postmenopausal women taking 10 mg. daily, obtained from the seventh to the twelfth day of the secretory phase (Methods C and D), are not distinguishable from those of the young untreated adult (Figs. 6 and 7).

Miscellaneous Pathology. Fibroids, per se, are not a contraindication to menopausal treatment although they may enlarge as a result of estrogen stimulation. Whether or not subsequent surgery is necessary depends on the symptoms they produce and the frequency of

Fig. 7. Endometrial biopsy taken at the end of 12 days of medroxyprogesterone acetate administration. She was 49 years of age, her last natural bleeding having occurred 4 years previously. This was the first induced cycle. She was primed by 1.25 rug. of conjugated estrogens daily for 42 consecutive days. She also received 10 mg. of medroxyprogesterone acetate per day for the last 12 days. Specimen was removed on day 43. We observe a maximum secretory phase similar to that of the young female (x 92).
unexpected bleeding. "Bleeding by plan" is reassuring. Unexplained bleeding is an inevitable source of concern to doctor and patient and makes prompt counter-measures advisable. Unexplained bleeding also interferes with treatment.

Fibrocystic disease of the breast is not a contraindication. There is usually improvement when a progestogen is used.

Ovarian tumors should be removed with all adnexal tissue, and usually with the total uterus, before commencing postmenopausal cyclic treatment.

Plastic operations for urinary incontinence, cystocele, prolapse and so forth should be postponed if possible until several months of treatment have elapsed. Local infection thereby will be reduced and tissues will heal more rapidly.

Bilateral Oophorectomy with or without Hysterectomy. In this study we are not concerned with the removal of the uterus, per se. Whether or not the ovaries have been removed is of greatest importance. If they have been removed, the patient is severely hypogonadal and must be treated vigorously. If the ovaries are present, as after a simple vaginal hysterectomy, she is subject to the same endocrine problems as any other woman. The hysterectomized woman without ovaries, or with ovaries which are failing, even though she cannot have an endometrial response, needs exogenous progesterone or its derivatives in addition to estrogen because these steroids have widespread systemic metabolic effects as well as important conditioning properties which affect the periolobular and alveolar tissues of the breasts. Their use also helps to avoid excessive stimulation of the ductal system.

The Value of the Vaginal Cytologic Smear for Estimating Hormonal Function. Nesbitt and colleagues state: "It is often possible to perceive the slightest changes in the vaginal epithelium due to hormonal inadequacy before these deficiencies are detectable by quantitative analysis." Quantitative analyses, obtained by a precise biochemical method such as that of Brown, Kellar and Matthew, require special laboratories, are expensive and time-consuming and therefore are not practical for the majority of women.

Rakoff believes that smear methods permit semi-quantitative determinations of body estrogen if certain interfering factors are not present. We have found the Maturation Count to be quantitatively valuable in the absence of progesterone, severe vaginal and cervical infections or the administration of other hormones. It is, in fact, at times superior to bioassays because of errors inherent in such methods.

Repeated tests in hundreds of young, untreated women serving as controls have shown the 20 year old female to have an average Maturation Count of 85-15-0 at the time of ovulation (data to be published). These percentages indicate peak estrinism corresponding, according to Rakoff, to an approximate urinary estrogen excretion of 200 M.U. per 24 hours (Allen-Doisy assay). With the progress of age, there is a decline in the percentage of superficial cells and a corresponding increase of parabasals. At 80 years of age the count could be completely reversed and read 0-15-85, corresponding to a urinary excretion of less than 20 M.U. per 24 hours. In the intervening years, there are infinite variations between these extremes.

A temporary improvement in the Karyopyknotic and Eosinophilic Indices occasionally noted at the time of the menopause and mentioned from time to time in medical literature, is not due to an increase in estrogen production. It is the result of the loss of progesterone's regressive effect on the epithelium.

Regressive vaginal changes due to age definitely are reversible with therapy. There is some loss of diagnostic sensitivity of the atrophic vagina, but after about 2 months of high estrogen exposure there is a remarkable rejuvenation of the mucosa and it again becomes a very satisfactory indicator. A few examples of cellular shifts resulting from treatment are shown in Table III.

The Importance of a Progestogen for a Healthy Endometrium. The solitary, continuous administration of estrogen to postmenopausal women is seldom advisable. Continuous bombardment of the endometrium may lead to spotting and irregular bleeding requir—

*The cytologic signs of progesterone effect are frequently confusing: desquamation of plaques of twisted intermediate basophilic cells with vesicular nuclei. The vaginal smear is not suitable for quantitative estimates of body progesterone.
ing surgical intervention. In the past, our incidence of dilatation and curettage in such cases was as high as 1 per 46.6 patient years. To date, no intervention has been needed in those postmenopausal women who resumed menstruation as a result of the administration of medroxyprogesterone acetate. Even if estrogen alone is administered cyclically (21 days on, 7 off or in longer cycles) and expected withdrawal bleeding occurs, there is no assurance that all the proliferative, or possibly hyperplastic, endometrium is being cast off.

**SUMMARY AND CONCLUSIONS**

1. Through evolutionary accident the female gonads undergo premature regressive changes and have a shorter life span than the other glands of internal secretion. The menopausal woman is, therefore, not normal; she suffers from a deficiency disease with serious sequelae and needs treatment.

2. Four specific methods are presented for the elimination of the menopause and the menopausal state.

3. Conjugated estrogens and medroxypro-

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Table III

**SHIFTS IN CELL PERCENTAGES OF THE COLPOCYTOGRAM DURING TREATMENT**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pretreatment cytogram</th>
<th>1st Post-treatment cytogram</th>
<th>Method of treatment</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>D.R. 40</td>
<td>S I P†</td>
<td>S I P†</td>
<td>70-28-2</td>
<td>A</td>
</tr>
<tr>
<td>A.S. 48</td>
<td>50-50-0</td>
<td>70-30-0</td>
<td>Jan. 30, 1961</td>
<td>A</td>
</tr>
<tr>
<td>M.F. 54</td>
<td>5-75-20</td>
<td>85-15-0</td>
<td>July 20, 1961</td>
<td>C</td>
</tr>
<tr>
<td>E.L. 67</td>
<td>5-85-10</td>
<td>85-15-0</td>
<td>July 20, 1961</td>
<td>D</td>
</tr>
</tbody>
</table>

*These pretreatment cytograms show more impairment of the cell population of the vaginal mucosa than the representative examples given in the text.
†The conjugated estrogens were subsequently increased to 18 tablets monthly to achieve satisfactory cell percentages.
‡The conjugated estrogens were subsequently increased to 21 tablets monthly to achieve satisfactory cell percentages.

A progestogen also helps to prevent breakthrough bleeding and the necessity for large increases in estrogen intake.

**Estrogen—Breast and Genital Cancer.** There is no convincing proof that estrogen has ever induced cancer in the human being. Studies, the most recent, even indicate that estrogen and progesterone are prophylactic to cancer of the breast and genitalia to an unknown degree. No breast or genital cancers occurred during the treatment of the 304 cases herein reported.

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were the criteria used. This cytohormonal assay is the only practical guide in the management of the menopause.

5. There were no breast or genital malignancies in 2,604 years of patient exposure to exogenous estrogen, although 20 was the expected incidence.

Acknowledgment: We are deeply grateful to Dr. Henry T. Haggstrom, Attending Cytologist Methodist Hospital, and to Dr. Edmund R. Marino, Brooklyn, for the cytologic studies in this work.

Deceased, December 1961.

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