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Estradiol Pellet Implantation in the Management of Menopause

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INTRODUCTION

Menopause, the cessation of menses, starts as ovarian follicles fail to respond to increasing levels of endogenous gonadotropins. The postmenopausal ovary, on histologic study, reveals the complete absence of or the presence of some primordial follicles.[15,27] Attempts at ovarian stimulation with exogenous gonadotropins are also without effect.[2] Zondek[38] reported large amounts of gonadotropins in the serum and urine of postmenopausal women that were confirmed later by bioassay,[25] immunoassay[36] and radioimmunoassay.[32] Unless estrogen therapy is instituted, the gonadotropins remain elevated until the sixth and seventh decade, after which the levels begin to decline.[31]

In vitro studies of postmenopausal ovaries reveal that the steroids secreted are primarily weak androgens—that is, Δ^4 androstenedione (Δ^4A) and dehydroepiandrosterone (DHA).[6,24,30] Greenblatt and co-workers[15] and Grodin and co-workers[19] demonstrated that Δ^4A was the primary steroid produced by the postmenopausal ovary. Serum estradiol is at one-third to one-half the level found in adult women during reproductive life (Table I).[15] Human chorionic gonadotropin (hCG) administered intravenously increases ovarian and peripheral Δ^4A and testosterone (T) titers in serum with minimal or no effect on estradiol (E_2) (Figure 1).

A myriad of symptoms gradually follows the decrease or loss of ovarian steroid production but does so more rapidly in the surgically castrated (Table II). The resulting syndrome may come from a combination of autonomic nervous system, psychogenic and metabolic disturbances.[18] The rate of withdrawal of sex steroids undoubtedly plays a role in the development of symptoms as well as in the degree of vaginal regression as indicated by vaginal cytology.

The most common symptoms are vasomotor disturbances, especially hot flashes and sweats. Emotional stress may increase their frequency and severity.[18] Interestingly, tranquilizers and autonomic depressant agents such as Bellergal, though capable of suppressing daytime hot flashes, are ineffective during sleep (Figure 2). Very small doses of estrogens

TABLE I

MEAN ± VALUES OF SERUM ESTRADIOL (E_2), Δ^4-ANDROSTENEDIONE (Δ^4A) AND TESTOSTERONE (T) LEVELS IN 11 MENOPAUSAL AND 10 NORMAL WOMEN

	Peripheral			Ovarian		
	E_2 (pg/ml)	Δ^4-A (ng/ml)	T (ng/ml)	E_2 (pg/ml)	Δ^4-A (ng/ml)	T (ng/ml)
Normal	41 ± 15* 58 ± 11†	1.47	0.28 ± 0.4	83.1	1.72	0.87
Menopausal	21.26 ± 2.18	1.09 ± 0.10	0.53 ± 0.06	30.52 ± 2.49	2.12 ± 0.17	0.91 ± 0.13

From: Greenblatt: Ovarian and adrenal steroid production in the postmenopausal woman. Obstet Gynecol 47:383, 1976.
*Follicular phase.
†Luteal phase.

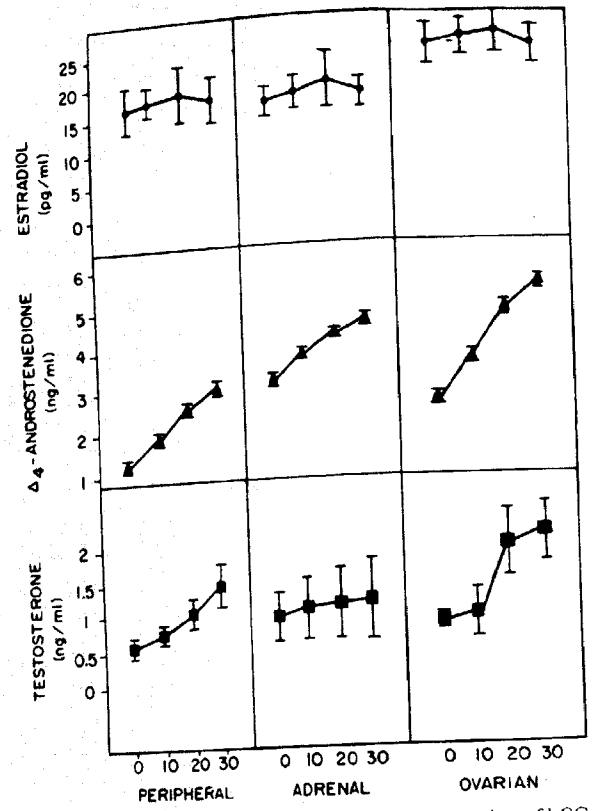

FIG. 1. Effect of 5,000 I.U. intravenous administration of hCG on levels of testosterone, Δ^4-androstenedione and estradiol in four postmenopausal patients (mean ± SE). Blood samples obtained by catheterization of left ovarian and left adrenal veins. From: Greenblatt: Ovarian and adrenal steroid production in the postmenopausal woman. Obstet Gynecol 47:383, 1976.

may eliminate hot flashes without lowering serum FSH and LH levels to any marked degree. On the other hand, estrogens in adequate dosage do lower gonadotropin levels, as shown in Figure 3. Gonadal dysgenesis is not associated with hot flashes despite elevated FSH and LH values; hence it appears that gonadotropins are not responsible for this phenomenon. However, such patients experience hot flashes when estrogens are administered for several years and then discontinued, which suggests that hypothalamic sensitization is a requisite.[18] Antigonadotropin therapy, as a rule, does not afford relief for hot flashes.[8,17] Dysfunction of the autonomic nervous system may also be manifest by globus hystericus, tension headaches, gastrointestinal disorders, formication and generalized paresthesias.

Common psychogenic problems such as increased anxiety and apprehension, depression, crying spells, loss of energy and changes in libido may occur. The hormone deficiency state is not primarily responsible for the psychogenic disturbances: this state merely aggravates latent psychoneurotic tendencies.

The metabolic complications[11] in the climacteric may be subtle, and several years may elapse before symptoms develop. Some patients develop senile vaginitis and its attending discomforts, and others present with gradual bone loss, eventuating often in compression fractures of the vertebral bodies.

Who Should be Treated and by What Means

The current opinion is that only those with hot flashes and atrophic vaginitis should receive estrogen therapy. The American College of Obstetricians and Gynecologists has recently suggested therapy that in the case of ". . . severe vasomotor instability and atrophic urethritis and vaginitis, . . . therapy should be designed to maintain the patient's health with the smallest effective dose." Osteoporosis, emotional stability and decreased tissue tone were suggested as possible indications for therapy.[1]

We concur and include symptoms and signs shown in Table II. Furthermore, we believe that the very presence of a castrate smear, even in the absence of symptoms, is reason for hormone replacement therapy. However, all complaints arising in the climacteric should not be labelled "menopausal," and therapy should be instituted after careful evaluation to eliminate other serious disorders. No more than

TABLE II

SYMPTOMS OF THE CLIMACTERIC CLASSED ACCORDING TO CAUSES—I.E., AUTONOMIC NERVOUS SYSTEM IMBALANCE, PSYCHOGENIC AND METABOLIC CAUSES

Autonomic N. S.	Psychogenic	Metabolic
Hot flashes	Apprehension	Demineralization
Formication	Depression	Myalgia
Globus hystericus	Insomnia	Skin atrophy
Perspiration	Nervousness	Atrophic vaginitis
Spasms	←headaches→	Incontinence
Palpitations	←Increase in→ sexual responsiveness	Arthritism
G.I. disorders	←Decrease in→ sexual responsiveness	Change in lipid metabolism

From: Greenblatt RB: Menopause and its management. *In* Pituitary-Ovarian Endocrinology. Edited by RI Dortman and M Neves e Castro. San Francisco, Holden Day, Inc., 1963.

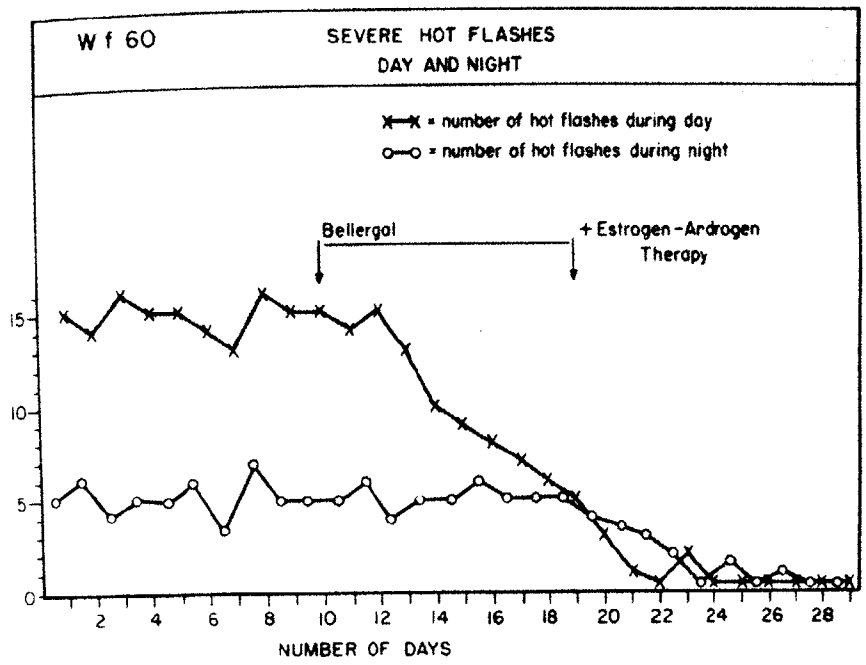

FIG. 2. Bellergal, as autonomic depressant drug, decreased daytime hot flushes, whereas nighttime hot flushes persisted until gonadal steroids were added.

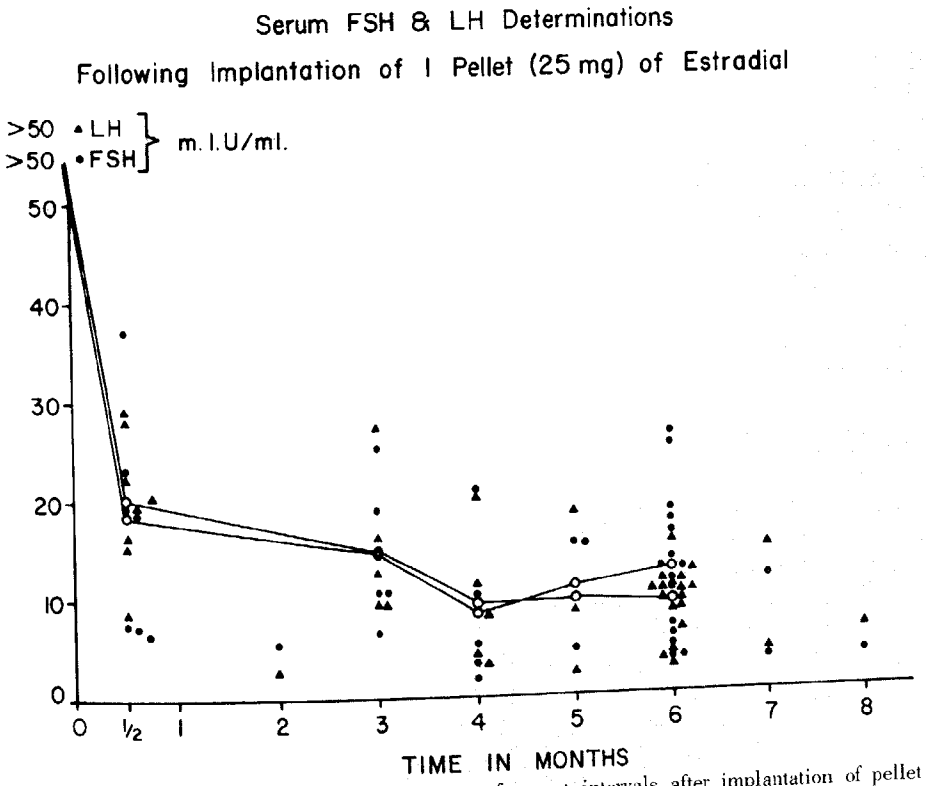

FIG. 3. Serum FSH and LH levels taken at frequent intervals after implantation of pellet of estradiol.

TABLE III

HORMONE PROFILE OF SEVERAL TYPICAL PATIENTS FROM OUR FILES TO SHOW EFFECT OF ESTRADIOL PELLETS (ALL HAD ELEVATED SERUM FSH AND LOW ESTRADIOL PRIOR TO THERAPY)

Patient	Age	FSH	LH	PRL	Δ^4A	T	E_1	E_2
J. S.	58	6.34	8.26	12.76	0.17	0.14	155.1	104.7
K. F.	60	3.69	4.52	12.14	0.69	0.44	199.7	219.6
C. S.	55	3.05	2.57	15.54	0.58	0.18	100	121

FSH = follicle stimulating hormone mIU/ml; LH = luteinizing hormone mIU/ml; PRL = prolactin ng(ml); Δ^4A = Δ^4androstenedione ng(ml); T = testosterone ng(ml); E_1 = estrone pg(ml); E_2 = estradiol pg(ml).

15% to 20% of women will undergo a symptom-free menopause.[28]

Vaginal cytology has been the standard modality used to assess the hormonal status of menopausal women. Cytologic evaluation has limitations.[5,23] Individual sensitivity to various levels of estrogens causes differences in vaginal maturation.[21] Hormone profiles—elevated serum FSH and LH and low estradiol—are far more accurate methods of assessing the menopause state. Table III illustrates hormone profiles obtained in a select group of postmenopausal women on estradiol pellet therapy.

Few will deny that sex steroids are of value in relieving menopausal symptoms. Oral and injectable modalities have long earned their place in therapy. For a small percentage, perhaps as high as 10% to 15% of estrogen-deficient women, oral medication is not completely satisfactory for a variety of reasons: unreliability in taking the drug, poor absorption and untoward effects such as nausea, headache or incomplete relief. Intramuscular therapy, at two- to four-week intervals, may be inconvenient. For such patients, one of us (R.B.G.) has utilized pure, crystaline pellets of estradiol-17-β, with or without testosterone (T), for the past 35 years.[9,16,20] Ex-

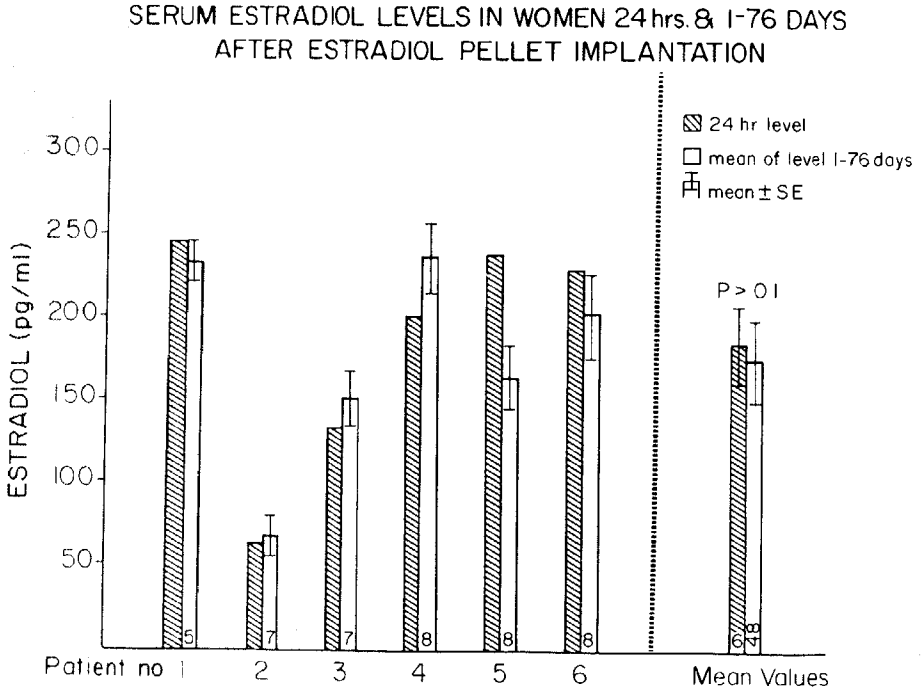

FIG. 4. Note that serum estradiol levels are elevated immediately and remain essentially stable throughout the period of observation after implantation of two pellets of E_2. From Nagamani, et al, unpublished data.

TABLE IV

LONG-TERM ESTRADIOL THERAPY (25 MG PELLETS) IN DECREASING DOSAGE (4, 3, 2, 1)

NOTE PERSISTENT AND RELATIVELY CONSTANT ELEVATION OF ESTRADIOL WITH PROGRESSIVELY INCREASING LEVELS OF ESTRONE, SUGGESTING *IN VIVO* CONVERSION $E_2 \rightarrow E_1$

		Blood steroids during and six months after estradiol implants					
Implant		No. of patients	No. of	Estrone pg/ml	Estradiol pg/ml	Total	Progesterone
100 mg	During	10	125	70 ± 3	178 ± 6	248	
	6 months after	35	35	57 ± 7	182 ± 11	239	194 ± 37
75 mg	During	7	29	107 ± 3	189 ± 7	296	
	6 months after	25	25	69 ± 10	207 ± 17	276	172 ± 19
50 mg	During	3	28	116 ± 8	229 ± 13	345	
	6 months after	20	20	113 ± 12	197 ± 13	310	97 ± 21
50 mg	During	3	28	116 ± 8	229 ± 13	345	
	6 months after	20	20	113 ± 12	197 ± 13	310	97 ± 21
25 mg	During	2	21	167 ± 12	199 ± 12	366	

cellent patient acceptance and remarkable relief of symptoms have been the rule. Bishop[3] first described the use of estrogen pellets in treatment. Pellets have since been used by numerous other investigators.[4,7,22,33]

HOW AND WHERE PELLETS ARE IMPLANTED

The skin is cleansed with Betadine and 95% ethyl alcohol. A half cc of 2% xylocaine is injected intradermally, creating a wheal. A Kearn's implanter is inserted through the wheal into the subcutaneous fat approximately 4 to 5 cm above and parallel to Poupart's ligament.

PELLET THERAPY*

A variety of regimens is employed: from one to four E_2 pellets (25 mg) may be implanted at six-month intervals. The dosage may be increased or decreased according to response. In those with an intact uterus, a progestogen (Provera 10 mg or Norlutate 5 mg p.o. per day for five to seven days each month) must be given to induce withdrawal bleeding and avoid abnormal bleeding episodes as well as atypical endo-

*Estradiol pellets are available from Schering Corporation, Bloomfield, New Jersey (Progynon pellets). The implants and estradiol pellets are available from Barter Pharmacals, Rye, New York or Barter International, Box 1242, Palm Desert, California 92260.

TABLE V

PREMARIN (MOSTLY ESTRONE SULFATE), 50 MG I.V., RESULTED IN MARKEDLY ELEVATED LEVELS OF ESTRADIOL WITHIN 15 MINUTES, DEMONSTATING RAPID *IN VIVO* CONVERSION OF $E_1 \rightarrow E_2$

		Premature menopause—BG Mc 25 years					
		FSH	LH	Prol.	Δ^4A	Test	Estradiol
Control		102.4	74.4	3.6	0.39	0.53	13.1
I.V. premarin 50 mg	15 m	97.3	74.4	3.2	0.31	0.38	1046.4
	60 m	97.3	56.4	3.0	0.39	0.34	963.9
	120 m	95.5	56.3	9.3	0.59	0.57	881.4

<0.1% Conversion $E_1 \rightarrow E_2$.

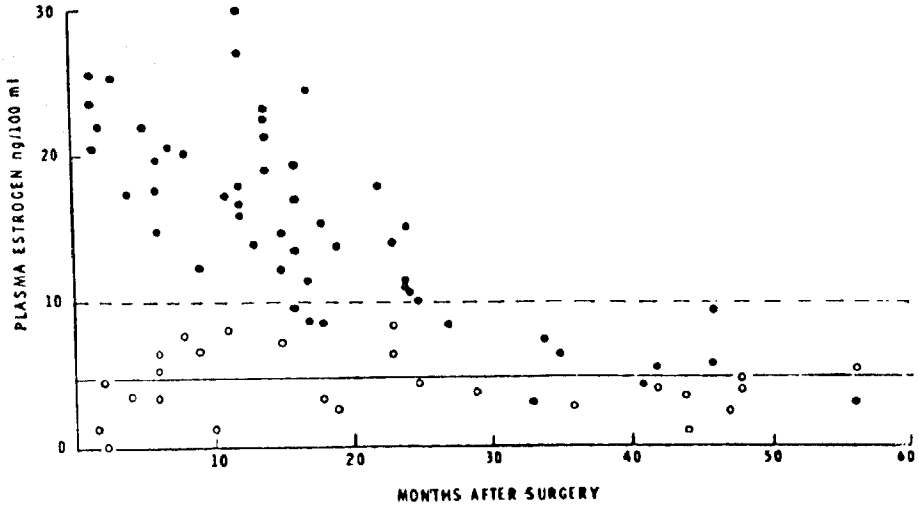

FIG. 5. Plasma estradiol levels after oophorectomy in patients who had received an estradiol implant (●) and those who did not (○). The broken line is two standard deviations above the mean (continuous line) of oophorectomized patients without implant. From Hunter DJS: Oophorectomy and the surgical menopause. *In* The Menopause. Edited by RJ Beard. Lancaster, England, MTP, 1976.

metrial hyperplasia. One or two pellets of T (75 mg) may be added, according to symptoms. Increased anabolic needs, loss of libido, migrainoid headaches and fatigue are indications for an androgen supplement. Physicians who fear the virilizing effect of testosterone should consider the fact that the dosage on pellets is far less than when the drug is administered orally or by injectables. For instance, one 75-mg pellet over six months will deliver less than 0.4 mg of T per day.

The amount and rate of absorption will vary depending on the implantation site and the number of pellets implanted (surface area).[16,20] The serum estradiol levels will depend on the number of pellets implanted. Premenopausal levels were attained with-

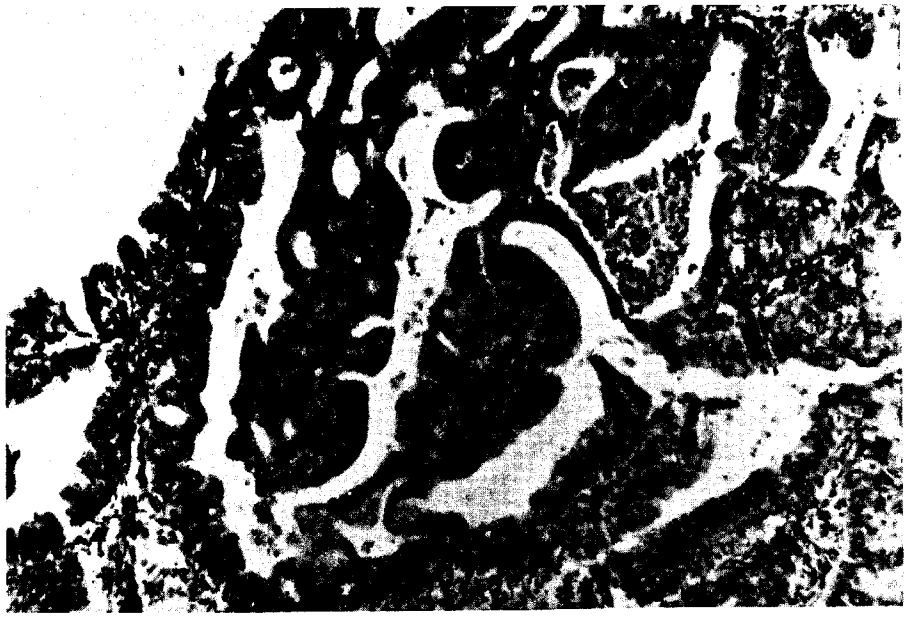

FIG. 6. Menopausal patient with histopathologic diagnosis of endometrial carcinoma on endometrial biopsy.

FIG. 7. Same patient as in Figure 6. No change after course of oral progestogen.

in 24 hours[29] (Figure 4). When four pellets of estradiol were implanted and decreased by one every six months, the estradiol levels were maintained, and estrone values progressively increased[13] (Table IV). Intravenous administration of a 50-mg bolus of conjugated estrogens USP (Premarin) resulted in a 70+-fold rise in serum E_2. Conversion from (E_1) to (E_2) was estimated at less than 1% (Table V). These studies provide strong evidence of E_2 conversion to E_1, and vice versa.

Hunter[21] utilized a 100-mg pellet of estradiol implanted under the rectus sheath at the time of surgery for total hysterectomy and bilateral oophorectomy.

FIG. 8. Atypical adenomatous hyperplasia, diagnosed by some pathologists as carcinoma *in situ*.

FIG. 9. Same patient as in Figure 8. Note change to secretory endometrium after 200 mg of Norelutate divided over five days.

Plasma E_2 remained in the premenopausal range for 18 months and proved effective in preventing menopausal symptoms (Figure 5).

HORMONES AND ENDOMETRIAL CANCER

Again, exogenous estrogens have been incriminated as possibly carcinogenic.[26,34,35,37] In over 35 years of estrogen use by one of us (R.B.G.), the incidence of endometrial cancer appears to have been much lower than what would be expected, perhaps because we have administered cyclic courses of oral progestogen practically to all patients on estrogen therapy. Whenever spotting or irregular uterine bleeding occurs, an endometrial biopsy is obtained. If hyperplasia or mild atypical changes are present, the monthly doses of oral progestogen are doubled. When severe atypia is encountered, 200 mg of a potent oral progestogen, in divided doses, is administered over a period of 5 to 10 days. Repeat biopsy is then obtained. If the endometrium fails to be transformed into a normal secretory one, then hysterectomy is performed (Figure 6 and 7). We have had numerous cases of atypical adenomatous hyperplasia, carcinoma *in situ* and well-differentiated adenocarcinoma that were completely transformed by an adequate course of progestogens[37] (Figure 8 and 9).

AVOIDANCE OF UNTOWARD EFFECTS

Estrogen therapy probably should not be used in patients with a history of phlebitis or thromboembolic episodes, undiagnosed vaginal bleeding, history of breast (unless therapeutic) or endometrial carcinoma and, possibly, hypertension. Hypertension and liver disease rarely are sequelae of natural estradiol, estrone or estriol administration but may follow synthetic estrogens and estrogen-like substances. Weight gain can be controlled by diet; mild edema may be managed by limitation of salt and, if necessary, by a mild diuretic. Breakthrough bleeding or menorrhagia occasionally occurs in those patients for whom the progestogen dosage is inadequate or after the patient's failure to take the progestogen as directed. If this happens, bleeding may be arrested readily (after obtaining an endometrial biopsy) by the administration of two 5-mg tablets of norethindrone acetate (Norlutate) or two 10-mg tablets of medroxyprogesterone acetate (Provera) every two to four hours until bleeding stops, then one b.i.d. for 10 days; an orderly withdrawal period usually takes place two to three days after completion of a course of progestogen therapy.

Other untoward reactions are the production of an occasional hematoma. Persistent oozing or bleeding from the site of implantation may be arrested by

continuous pressure. A foreign body reaction, with suppuration and expulsion of the pellet, may be an unexpected but occasional complication.

Untoward effects are uncommon with androgen therapy if patients are selected carefully. Should acne, hypertrichosis or voice changes occur, androgen therapy is discontinued. However, there are some women who prefer to continue despite mild signs of virilization.

Mazoplasia occasionally occurs and may be lessened by decreasing the estrogen or increasing the androgen dosage. Estrogens may stimulate a small locus of neoplasia to grow, thus bringing a silent malignant nodule to earlier attention by the physician and prompting an immediate diagnostic mammogram and biopsy.

Conclusion

Crystalline pellets of estradiol-17β offer excellent relief of symptoms for those postmenopausal women who fare poorly on oral estrogens or intramuscular injectables. Although somewhat more expensive than other modes of therapy, pellet use is convenient, highly effective and associated with few side effects.

Because of the increasing numbers of women living longer and thus entering the postmenopausal years, there will be a relative increase in endometrial carcinoma. This has not been the case in our experience. Judicious patient selection and utilization of a potent oral progestogen for five to seven days per month for withdrawal bleeding will minimize the occurrence of endometrial carcinoma, except in the few who are cancer prone. By obtaining endometrial biopsy whenever abnormal bleeding occurs, one may uncover early endometrial cancer, the result of which is early and definitive management and an excellent prognosis. The addition of testosterone should be considered when frigidity is a complaint and when estrogens alone fail to add well-being and a zest for living.

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