

Dl-norgestrel at a dose of 150 µg induced secretory histology in 5 of 5 women, but, at 500 µg, in only 6 of 8. This apparent paradoxical effect was also reported for doses of 10 mg of MPA in another study (Lane et al., 1986b). It is possible that the higher dose of progestogen down-regulates receptors for progestogen so that, in some women, no effect of progesterone can be seen.

One or more of the ultrastructural criteria for secretion were found at all dosage levels of norethindrone. With dl-norgestrel, the doses of 150 and 500 µg produced a similar incidence of ultrastructural evidence of secretion (Whitehead et al., 1981).

A second study reported from England also examined morphologic changes in women given 0.625 mg of CEE daily and then treated with norethindrone, 2.5 mg daily or 5 mg daily, or dl-norgestrel, 150 mg or 500 mg daily, for 10 days each month (Whitehead et al., 1982a). The 2.5-mg dose of norethindrone induced secretory histology in seven of eight patients examined, but the 5-mg dose induced secretory histology in only two of four patients examined. Biopsies from all patients sampled showed secretory histology after both doses of dl-norgestrel.

Eight of nine women receiving the lower dose of norethindrone showed at least one of the ultrastructural features of secretion and all five women receiving 5 mg of norethindrone daily showed at least one of the ultrastructural features of secretory endometrium. All women receiving either 2.5 or 5.0 mg of dl-norgestrel showed all three ultrastructural features of secretory endometrium (nucleolar channel systems, giant mitochondria, and basal glycogen).

Clinical Studies

Early retrospective and prospective clinical studies demonstrated the beneficial effects of sequential estrogen-progestogen therapy in reducing the incidence of endometrial hyperplasia and endometrial carcinoma. In a double-blind, 10-year prospective study, 2 of 84 women not receiving estrogen or progesterone developed endometrial carcinoma, whereas none of the 84 patients receiving estrogen and progesterone regimens developed carcinoma (Nachtigall et al., 1979). In another study, endometrial cancer was reported in

11 of 201 patients receiving cyclic estrogens, while none of 72 women receiving estrogens and progestogens developed endometrial carcinoma (Hammond et al., 1979). In a 9-year prospective study, endometrial carcinoma was found in 31 women during 27,243 patient years of observation (Gambrell, 1986). The incidence of endometrial carcinoma from 100,000 patient years of observation was 49.0 in estrogen-progestogen users, 390.6 in estrogen-only users, and 245.5 in women receiving no replacement therapy. The decreased incidence of endometrial carcinoma in women receiving a combination of estrogen and progestogen as compared to women receiving estrogen or no replacement therapy is significant, demonstrating the beneficial effects of the addition of progestogens.

Progestogens have also been shown to protect against the development of endometrial hyperplasia. Whitehead et al. demonstrated that the incidence of hyperplasia ranged from 16 to 32% in women treated with cyclic estrogens, whereas the addition of a progestogen for 7 days each month reduced the incidence to 3-4% (Gambrell, 1986). Studd et al. reported similar findings and, in addition, demonstrated the importance of the duration of progestogen therapy in reducing the incidence of endometrial hyperplasia (Studd et al., 1980). In this study, 66% of women receiving subcutaneous implants of 50 mg of estradiol for two months or more developed hyperplasia. Addition of norethindrone for 5 and 10 days reduced the incidence to 9 and 3%, respectively. Norethindrone for 13 days completely prevented endometrial hyperplasia. This result emphasizes the importance of the duration of progestosterone therapy in the prevention of endometrial disease.

Recent clinical studies have been concerned with incidence of vaginal bleeding and endometrial hyperplasia in women treated with estrogen alone and with combination estrogen-progestogen therapy. Regimens investigated include cyclic unopposed estrogen, continuous unopposed estrogens, sequential estrogen-progestogens and various regimens employing continuous estrogen with progestogen.

Cyclic Unopposed Estrogen

Twenty-four percent of women treated with unopposed estrogens (CEE [1.25 mg], piperazine estrone sulfate [3.0 mg], or estradiol valerate [2.0 mg], daily) experienced

breakthrough bleeding. Patients who develop endometrial hyperplasia may experience breakthrough bleeding, regular withdrawal bleeding, or amenorrhea. In 106 such patients, 25 experienced breakthrough bleeding and nine had endometrial hyperplasia. Twenty-six patients experienced regular withdrawal bleeding and nine had hyperplasia. Of far greater concern, 10 of 55 patients with amenorrhea also had endometrial hyperplasia.

In a review of several studies, Fraser reported that women treated with 1.25 mg CEE in cyclic fashion experienced a high incidence of withdrawal and breakthrough bleeding and endometrial hyperplasia. Withdrawal bleeding occurred in 48%, and 30% of women experienced timely withdrawal in at least one cycle. Breakthrough bleeding occurred at least once in 40% of women or in approximately 28% per cycle. Hyperplasia was seen in 15% of the endometrial biopsies, but the pattern of bleeding was not necessarily associated with the presence of hyperplasia.

Continuous Unopposed Estrogen

Continuous unopposed estrogen therapy is also associated with an unacceptably high incidence of endometrial hyperplasia. In a prospective study, women were treated with continuous or cyclic doses of 0.625 mg CEE daily. With cyclic therapy, the incidence of hyperplasia was 4.5% and with continuous therapy the incidence was 3.7%. The difference was not statistically significant. The incidence of irregular bleeding was unacceptably high in both groups (Schiff, 1982).

Sequential Estrogen-Progestogen

Several studies have demonstrated that sequential addition of a progestogen to ERT virtually eliminates the risk of endometrial hyperplasia and carcinoma, when the progestogen is given at a proper dose for more than 10 days each month, and decreases the incidence of irregular uterine bleeding (Nachtigall et al., 1979; Hammond et al., 1979; Gambrell, 1986). There is significant interpatient variation in the response to similar doses of estrogen and progestogens. In general, the dose of estrogen and progestogen and the type of

compound impact significantly on the regularity of uterine bleeding and endometrial hyperplasia.

For example, one study employing sequential MPA combined with 0.625 mg CEE daily resulted in withdrawal bleeding in 9.7% of women (Fraser, 1986). In contrast, regular bleeding occurred in 78% of women on a high-dose combination of estradiol (E_2 ; 4 mg) and estriol (E_3 ; 2 mg) with sequential norethindrone acetate. Only 64% of women receiving a smaller dose of estrogen (2 mg E_2 and 1 mg E_3) had regular vaginal bleeding; reducing the dose further to 1 mg E_2 and 0.5 mg E_3 resulted in a 40% incidence of regular bleeding.

The endometrial effects of progestogens are highly dependent on the type and dose of progestogen. In one study, 100 mg daily of micronized oral progesterone resulted in regular withdrawal bleeding in 43%, whereas 77% of women experienced regular bleeding when taking 300 mg of micronized oral progesterone daily (Lane et al., 1983). Hyperplastic features were noted in the endometrium of three of eleven patients receiving the 100-mg dose. None of 25 patients receiving 200 or 300 mg showed evidence of endometrial hyperplasia.

In another study, eight women, five postmenopausal and three perimenopausal, were treated with continuous transdermal estrogen therapy with estradiol skin patches (Whitehead et al., 1985). Norethindrone, 0.35 mg, was given daily for the first 12 days of each calendar month. Every patient experienced withdrawal bleeding at some time during the study. One patient experienced breakthrough bleeding during each of three months. There were wide variations in the number of days of bleeding experienced among individual patients and in the same patients at different times during the study. Endometrial biopsies revealed proliferative endometrium in six of the eight patients, nonsecretory endometrium in the seventh and atrophic endometrium in the eighth.

In one study, estrogen was administered continuously either by mouth, percutaneously, or by subcutaneous implantation of crystalline estradiol. Progestogens were added for 12 days each month. Day one of the "cycle" was defined as the first day of combined estrogen and progestogen therapy. During a three-month period of observation of 100 women with "normal" bleeding, the onset of bleeding varied by less than three days in 96. In one of the remaining four patients,

the onset of bleeding was between day 3 and day 8. The endometrium shown a mixed proliferative and secretory pattern. A second patient's onset of bleeding varied between day 7 and 14. Her pattern was secretory. The third patient's onset varied between day 9 and 12. Her pattern was mixed. The onset of bleeding in the fourth patient varied between day 8 and 13. Her pattern was secretory (Padwick et al., 1986b).

Of the 96 patients in whom the onset of bleeding varied by less than three days, proliferative endometrium was found in those who bled on or before day 10. A full secretory pattern was found in those who bled between days 11 and 18. Mixed patterns were found in 11 patients. In five, the dominant pattern was proliferative. Their onset of bleeding ranged between day 8 and day 10. In six, a secretory pattern was dominant. The onset of bleeding in these six patients ranged between day 12 and day 13. Thus, regular bleeding on or after day 11 was associated with secretory endometrium. This bleeding pattern could be induced by norethindrone at a dose of 0.35 to 1.05 mg daily, depending upon the patient's sensitivity to the hormone.

Continuous Estrogen-Progestogen

The available data suggest that continuous therapy with oral estrogens and progestins results in amenorrhea in a significant number of patients (Weinstein, 1987; Magos et al., 1985a; Magos et al., 1985b; Mattson et al., 1982). However, breakthrough bleeding is a problem with all continuous regimens. It may be possible to infer the endometrial pattern from the timing of the onset of bleeding, in patients on a regimen of continuous estrogen and sequential progestogen.

A study of women taking 0.625 mg daily of CEE and treated with varying regimens of MPA was designed as follows. All women received the CEE continuously by mouth from days 1 through 28. Twelve women were given 2.5 mg daily of MPA on days 1 through 28. Six of the twelve experienced breakthrough bleeding. Bleeding occurred in 24% of the total observed weeks of the study. A second group received 5.0 mg of MPA daily for days 1 through 28. Nine of the twelve experienced bleeding. Bleeding occurred in 25% of weeks observed. Group three received 5.0 mg of MPA daily during days 17 through 28. Bleeding occurred in ten of the twelve

patients in this group. Bleeding was noted in 23% of the observed weeks of the study. In spite of the prevalence of bleeding, the endometrium was atrophic in all patients in the first two groups. In the third group, nine patients had atrophic endometria, one had a mixed secretory and adenomatous pattern and one had evidence of adenomatous hyperplasia (Weinstein, 1987).

Continuous therapy with E_2 via subcutaneous implants has also been studied (Magos et al., 1985a). The patients were given subcutaneous implants of 50 mg of E_2 and 100 mg of testosterone. They were also treated with continuous daily norethindrone at a dose of 0.35, 1.05, 1.75 or 5.0 mg per day. All seven women who were started on the highest dose of norethindrone (5 mg) discontinued treatment within 12 months. Three months of amenorrhea was seen immediately in 5.4% to 55.6% of women, depending upon the initial dosage of the progestogen.

The progestogen was increased at three-month intervals in women who bled. Despite this incremental dosage, only 51% of patients were amenorrheic after six months and 63.2% after one year. Eight women remained amenorrheic for 12 to 27 months. There was a high dropout rate, mainly because of excessive, irregular vaginal bleeding. Without regard to the bleeding pattern, endometrial biopsies taken six months after treatment revealed endometrial atrophy.

Another study involved 28 women treated with continuous daily doses of 2 mg E_2 , 1 mg E_3 and 1 mg norethindrone acetate for one year. Breakthrough bleeding occurred frequently during the first 3 months. Bleeding occurred on 8% or fewer treatment days after the first 3 months. During the third month of treatment, endometrial biopsy showed no evidence of hyperplasia or malignancy (Mattson et al., 1982).

CONCLUSIONS

Estrogen offers significant beneficial effects to symptomatic menopausal women: prevention of vasomotor symptoms, genitourinary atrophy, and bone loss; and improvement in lipid profiles which may be protective against cardiovascular disease. The primary adverse effect of estrogen is the increased risk of endometrial hyperplasia and carcinoma. The

addition of a progestogen has been advocated to avoid this problem.

Many progestogenic compounds are available for clinical use. The effect of each on the endometrium depends on the dose and the route of administration. Although several bioassays of progestogenic potency are available, data from these assays do not accurately reflect a progestogen's ability to protect women from endometrial disease.

The daily doses of commonly used progestogens needed to protect against endometrial abnormalities are: norethindrone, 0.7 mg; dl-norgestrel 150 µg; oral progesterone, 300 mg; and medroxyprogesterone acetate; 10 mg. The progestogens should be prescribed for 12 days each month.

There are few, long-term clinical studies of the prevention of endometrial disease by administration of progestogens to women on estrogen-replacement therapy. The studies available demonstrate that progestogens are protective, but further work is needed to identify the optimal compound, dose and regimen to minimize the adverse effects of progestogens on serum lipid profiles.

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ENDOMETRIAL RESPONSE TO ESTROGEN-ANDROGEN STIMULATION

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INTRODUCTION

Estrogen has been the major hormone used for menopausal hormone replacement therapy since the 1950's. Its use decreased in the late 1970's, in response to reports of increased rates of endometrial cancer after chronic administration of relatively large doses of Premarin (Smith et al, 1975; Ziel and Finkle 1975; Weiss et al, 1979). The subsequent addition of progestagen to lower-dose hormone-replacement regimens, which reversed the results of over-stimulation of the endometrium by estrogen, and the demonstrated beneficial effects of estrogens on bone and lipid metabolism led to the reinstatement of estrogen-replacement therapy as a desirable and medically sound treatment (Lindsay et al, 1976; Nordin et al, 1980; Nachtigal and Nachtigal 1979; Gambrell, 1982).

Estrogen-androgen hormone replacement therapy (EA/HRT) was first employed in the early 1950's. Greenblatt et al., (1950) compared therapy with an androgen alone and with an androgen-estrogen combination, and an estrogen and a placebo in the treatment of the symptoms of menopause. The preparations used were administered orally and the authors' conclusion was that the best results of treatment were obtained with the androgen-estrogen combination. It was also felt believed that the estrogen and androgen each had a specific stimulatory action independent of the other. Grody et al., (1953) also reported results of estrogen-androgen substitution therapy in the menopausal female. They felt that administration of testosterone effectively inhibited estrogenic

stimulation. Testosterone, after inducing an initial progesterone-like effect on an estrogen-primed endometrium, subsequently produced sustained hypoplasia and atrophy. In actual fact, however, the endometrial changes illustrated and described in their paper are those that result from either estrogenic stimulation or regeneration of the endometrium after chronic bleeding which was presumably induced by the estrogen-androgen therapy.

In the U.S., the use of EA/HRT on a routine basis has been very limited, mainly because of the absence of well-controlled studies on the clinical and biochemical consequences of the exogenous administration of androgen to women. In Canada, Australia and Europe, however, there has been an increased interest in EA/HRT, and, as a result, information on the effects of estrogen-androgen on various psychologic and metabolic functions is now available (Sherwin and Gelfand, 1985a; Sherwin and Gelfand, 1985b; Sherwin and Gelfand, 1987a; Sherwin and Gelfand 1987b; Bancroft et al, 1984; Berger et al, 1984; Brincat et al, 1984). In Canada, for example, one of the authors of this chapter (MMG) has been using EA/HRT since 1980, and the effects of EA/HRT on patients who had previously undergone total abdominal hysterectomy and bilateral salpingo-oophorectomy have been evaluated. In this prospective, double-blind, randomly assigned study, we found that the energy level, well-being, and appetite were significantly increased in patients who received either combined estrogen-androgen therapy or androgen alone, as compared with patients who received estrogen alone or a placebo ($P<0.01$) (Sherwin and Gelfand, 1985). It was also noted that women who had received exogenous estrogen-androgen therapy over a long period of time reported higher rates of sexual desire ($P<0.01$), sexual arousal ($P<0.01$) and number of fantasies ($P<0.01$) than those who were given estrogen alone or were untreated (Sherwin and Gelfand, 1987b). These results suggest that the exogenous use of estrogen-androgen is a highly attractive modality for treating women for menopausal symptoms. Indeed, estrogen-androgen therapy improved the "quality of life" of menopausal women, particularly with respect to sexuality, energy, and well-being.

Scientific data on the effects of estrogen-androgen preparations on the endometrium are not readily available. However, it is very important that this issue be carefully examined since the woman with an intact uterus can also

benefit from estrogen-androgen hormone-replacement therapy. During the past few years we have been involved in the evaluation of endometrial responses to EA/HRT and some of our preliminary data are presented below.

ENDOMETRIAL RESPONSE

Definition of Endometrial Hyperplasia and Neoplasia

One of the end points of the effects of administration of exogenous sex-steroid hormones on the endometrium is the development of hyperplasia or, rarely, of cancer. It is appropriate, therefore, to review and discuss the definitions of hyperplasia and neoplasia as they relate to clinical implications and management. Traditionally, endometrial hyperplasia (EH) has been considered to represent a continuum of morphologic changes in which the most severe form, referred to as atypical adenomatous hyperplasia by some, or carcinoma *in situ* by others, if untreated, carried a significant risk of carcinoma (Gusberg et al., 1974). Since the less severe form of EH was believed to precede the more severe form of EH, all forms of hyperplasia were considered precursors of invasive adenocarcinoma of the endometrium. In recent years, however, the significance of the cytologic alterations that accompany EH has led to a reinterpretation of the traditional data, and the concept of a continuum has been challenged (Fox and Buckley, 1982; Ferenczy and Gelfand, 1986). It appears today that cytologic atypia is the only important morphological feature that distinguishes between endometrial lesions with and without invasive carcinomatous potential (Fox and Buckley, 1982; Ferenczy and Gelfand, 1986; Colgan et al., 1983; Kurman et al., 1985; Ferenczy and Gelfand, 1988). As a result, EH without cytologic atypia is not considered a precursor lesion to carcinoma, whereas in the case of EH with atypia, the risk of carcinoma ranges between 11% and 35%, with a mean 30% at 7-10 years. We refer to the latter lesion as endometrial intraepithelial neoplasia (EIN), a term that unifies previously used, poorly understood and confusing terms, such as atypical adenomatous hyperplasia, severe hyperplasia, atypical complex hyperplasia, etc.

The morphologic similarity between proliferative endometrium and hyperplasia (Ferenczy and Gelfand, 1986), the relatively high incidence of EH in women with hyperestro-

genism (Gelfand and Ferenczy, *in preparation*) and secretory conversion of EH by exogenous progestagens (Ferenczy and Gelfand, 1988) are evidence of a cause-and-effect relationship between estrogenic stimulation and the development of EH. The relatively frequent association of EH and EIN and/or carcinoma in the same endometrium, particularly in younger, premenopausal women with hyperestrogenic stigmata (obesity, anovulation), and in those women receiving replacement therapy with estrogen alone, suggested to some investigators that the latter conditions were also estrogen-related (Bokhman, 1983). In these women, and in those with hyperplasia alone, estrogenic stimulation in the absence of progestagen is believed to have an exclusively growth-promoting effect on gland cells, some of which are presumably "cancer initiated", whereas others are not (Ferenczy and Gelfand, 1986). Estrogenic stimulation of the "cancer initiated" cells may lead to the development of neoplasia, and stimulation of the "non-initiated" cells to hyperplasia. Conversely, numerous studies carried out and published during the past decade have shown the "anti-hyperplastic-neoplastic" effect of exogenous progestagens (Whitehead, 1978; Gambrell, 1979; Ferenczy and Gelfand, 1982). Secretory differentiation of estrogen-primed proliferative endometrium is believed to be the major mechanism involved in the prevention of the development of hyperplasia-neoplasia of the endometrium. Progestagens may, however, produce side effects, both in terms of symptoms and in terms of metabolism. They may produce abdominal bloating, migraine headaches, and premenstrual tension, which in our experience may occur in as many as 30% of women treated (Gelfand and Ferenczy, *in preparation*). Metabolically, progestagens may decrease levels of high-density lipoproteins (HDL) in favour of the putatively atherogenic, low-density lipoproteins (LDL).

CLINICAL STUDIES

In 1984 we undertook a prospective study which was aimed at evaluating the incidence of EH at one year in 176 post-menopausal women with disease-free endometrium who were treated with estrogen alone or with an estrogen-androgen preparation (*unpublished data*). All patients who entered the study had a proliferative, secretory, or atrophic endometrium, as proven by prior biopsy. Hormone-replacement therapy consisted of either Premarin (0.625 mg, orally) given during the first 21 days of a 28-day cycle, or the estrogen-androgen

Table 1. COMPOSITION OF THE PREPARATION OF ESTROGEN-ANDROGEN* (CLIMACTERON)

| | |
|--|----------|
| TESTOSTERONE ENANTHATE | |
| BENZILIC ACID HYDRAZONE (EQUIVALENT TO 69 MG TESTOSTERONE) | 150.0 mg |
| ESTRADIOL DIENANTHATE | 7.5 mg |
| ESTRADIOL BENZOATE | 1.0 mg |

* per ml

preparation given by intramuscular injections once a month (Table 1). Endometrial evaluation was repeated one year after entry into the study by means of a four-stroke biopsy technique (Ferenczy et al., 1979). The incidence of EH in both treatment groups was similarly high and statistically not significantly different. No cancers were observed at one year. In another group of 29 patients, who were part of another investigational project initiated in 1986, and who received 1.25 mg of oral Premarin cyclically on 25 out of 30 days and who underwent biopsy at the end of one year, the incidence of hyperplasia (without atypia) was 57% (Gelfand and Ferenczy, in preparation). No cancers were found in this group of women either. Table 2 illustrates the comparative incidence of hyperplasia in the two study groups just described. The results clearly show that estrogen-androgen therapy is associated with an increased incidence of hyperplasia after one year of therapy. Although the incidence of hyperplasia was intermediate between that associated with an oral preparation of 0.625 mg Premarin and an oral preparation of 1.25 mg Premarin, the differences were not significant. We can conclude therefore that, from a morphologic point of view, the estrogen-androgen preparations which are given intramuscularly act on the endometrium in the same way as does estrogen alone. It appears, furthermore, that androgens fail to induce morphologic alterations similar to those seen after treatment with endogenous progesterone or its exogenous synthetic counterparts (Ferenczy and Gelfand, 1982).

The above findings lead us to consider adding medroxyprogesterone acetate (Provera) to our regimen of EA/HRT for

Table 2. INCIDENCE OF ENDOMETRIAL HYPERPLASIA (EH) AT 1 YR AND TYPE OF HORMONE-REPLACEMENT THERAPY (HRT)

| HORMONE-REPLACEMENT THERAPY | ENDOMETRIAL HYPERPLASIA NO. | % |
|-----------------------------|--------------------------------|----|
| Premarin 0.625 mg | 23/76 | 29 |
| Estrogen-Androgen** | 42/100 | 42 |
| Premarin 1.25 mg | 13/23 | 57 |

*NS: No significant difference

**CLIMACTERON, 1 cc I.M.

women with an intact uterus. In doing so, we hoped to eliminate the hyperestrogenic effect of EA/HRT on the endometrium. To test this hypothesis, we studied two groups of patients, one of which received 5 mg of Provera orally and the other 10 mg of Provera orally on days 12 to 25 of their E-A cycle (unpublished data). The first cycle day was defined as the day of monthly injection of the estrogen-androgen preparation. Endometrial biopsies were performed prior to and at the end of six months of therapy.

The results shown in Table 3 clearly indicate the greater protective effect of 10-mg Provera as compared to the 5-mg regimen with respect of prevention of the development of EH after 6 months of therapy. Indeed, with the 10-mg regimen all endometria examined were either proliferative, secretory or atrophic, whereas the 5-mg Provera regimen was associated with EH in 20% of cases. Breakthrough bleeding has been minimal. Some patients had withdrawal bleeding after the last day of administration of progestagen, whereas many failed to bleed at all. The only contentious factor in this hormone-replacement therapy involves the patient's tolerance of the progestagen. There has been difficulty in obtaining compliance in up to 30% of the women treated with E-A and Provera because of side effects related to the progestagen. The effects on the endometrium of oral progestagens given in combination with subcutaneous estradiol-testosterone implants in post-menopausal women have been evaluated (Cardozo et al., 1984; Magos et al., 1984).

Table 3. INCIDENCE OF ENDOMETRIAL HYPERPLASIA AT SIX MONTHS AND TYPE OF ESTROGEN-ANDROGEN* AND PROVERA THERAPY

| PROVERA | ENDOMETRIAL HYPERPLASIA | |
|--------------------|-------------------------|----|
| | No. of Cases | % |
| 5 mg (days 12-25) | 5/20 | 25 |
| p<0.01 | | |
| 10 mg (days 12-25) | 0/26 | 0 |

* CLIMACTERON 1 cc I.M.

Cardozo et al., (1984) used Norethisterone, taken orally for 10 to 13 days of each cycle, and were able to reverse cases of EH (cystic glandular hyperplasia) that developed 6 months after the initiation of estradiol-testosterone therapy. All cases of hyperplasia were successfully reverted to normal. The authors concluded that the presence of a uterus is not a contraindication for the use of E-A implants since endometrial pathology and its associated irregular bleeding can be corrected by the addition of cyclically administered oral progestagens. Magos et al. (1984) used subcutaneous implants of estradiol and testosterone similar to those used by Cardozo et al., (1984), but with the addition of the continuous administration of oral progestagen. At the end of six months, all of the endometrial biopsies from their post-menopausal patients revealed atrophic endometrium.

EXPERIMENTAL STUDIES

The presence of estrogen receptors (ER) and progesterone receptors (PgR) is a prerequisite for the expression of estrogen and progesterone, respectively (Lerner et al., 1986). Physiologically, normal endometrial growth is dependent on estradiol (E2) and progesterone inhibits E2-mediated proliferation of endometrial cells. However, it has been shown experimentally that high doses of androgens increase uterine weight in the rat (Lerner et al., 1986; Gonzalez-Didi et al., 1972). Such an effect is similar to that produced by

estrogens. The type of receptor associated with the effects of androgens remains in question. Steroid receptors are, by definition, specific for their respective hormones and can only bind hormones of the same class (Jensen et al., 1967; Baulieu, 1975). Androgens usually interact with androgen-specific receptors. However, androgen receptors are present at low levels in the rodent uterus (Gianopoulos, 1973). Nonetheless, when hormones are present at relatively high levels, there is sometimes a "spillover of specificity" (Katzenellenbogen, 1980), and experiments in the rat suggest that low doses of androgens produce only "an androgen effect, while high doses elicit an estrogen-like effect, presumably via estrogen receptors" (Garcia and Rochefort, 1977; Tochefort et al, 1972; Schmidt et al, 1976). Similar experimental studies have yet to be performed on women. More specifically, we need to ascertain, in the human, whether androgens, particularly at pharmacological doses, act via the androgen-specific or estrogen-specific receptors. If androgens do, in fact, act via the latter class of receptors, is this interaction agonistic or antagonistic? As a preliminary effort, we have initiated studies to determine the level and distribution of circulating sex-steroids and estrogen receptors in five women who developed EH while receiving intramuscular EA/HRT. All of them had levels of circulating estradiol within normal limits and increased levels of androgen during therapy. The estrogen receptors were localized in fresh-frozen sections using the ER-ICA kit (Abbott Laboratories) by an immunoperoxidase technique. The results showed that estrogen receptors are present at high levels in both the epithelium and the stroma of the endometrial hyperplasia induced by EA/HRT. The levels and distribution of the receptors appeared identical with those found in hyperplastic endometria induced by either exogenous or endogenous estrogens alone (Bergeron et al., 1988). Although the results are too preliminary to allow us to draw definite conclusions, they seem to indicate that 1) androgens do not have a progesterone-like effect, at least with respect to the turnover of estrogen receptors, and 2) androgens may act via estrogen receptors to induce estrogen-like effects in human endometrium. The high incidence of hyperplasia in women on EA/HRT and the need for relatively high doses of Provera to correct these lesions, despite normal levels of plasma estradiol in these women, support this hypothesis.