Effect of Estrogen and Progestin Treatments on Endometria from Postmenopausal Women

R. J. B. King, M. I. Whitehead, S. Campbell, and J. Minardi

ABSTRACT

Despite the implication that estrogen treatment of postmenopausal women produces hyperplasia and neoplasia of the endometrium, no systematic studies have been reported on the biochemistry of endometria from such women. We have measured nuclear and cytoplasmic estradiol receptor and cytoplasmic progesterone receptor in curettage samples of endometria from women receiving different estrogen preparations. Cyclical treatment with estrogen alone has been compared with sequential therapy with three weeks of estrogen plus one week of estrogen plus norethisterone. No difference in any of the receptor levels was found in samples obtained during Week 3 of any of the four-week treatment cycles examined. For two to three weeks of a treatment cycle, the receptor levels were similar to those seen in premenopausal, proliferative-phase endometria. This suggests that the postmenopausal endometrial cells are subjected to a very potent estrogenic stimulus for a considerable period. Ingestion of norethisterone for one week decreased both the amount of nuclear estradiol receptor and the percentage of total cellular estradiol receptor that was in the nuclear fraction. Estradiol dehydrogenase was also induced by the norethisterone, and the presence of this enzyme might result in the lowered nuclear estradiol receptor levels seen during the progesterogenic phase of the treatment schedule.

Nuclear estradiol receptor content was lower during Week 3 than during Week 2 of estrogen treatment. Furthermore, progesterone receptor was negatively correlated with nuclear estradiol receptor in postmenopausal endometria obtained during Week 3 in contrast to the positive correlation seen in premenopausal samples. It is possible that a three-week treatment with estrogen results in a refractory condition. Comparison of receptor levels in normal, cystic hyperplastic, and atypical hyperplastic endometria that had been returned to normal histology suggested that cells in atypical hyperplastic endometria may be more estrogen sensitive than in other types of endometria.

INTRODUCTION

Estrogen therapy for menopausal symptoms may carry potential hazards because of the increased risk of endometrial cancer. Most of the data on this topic have been derived from retrospective studies (5, 9, 21) and, to date, the results of only one prospective trial have been published. Whitehead et al. (27) have shown an increased risk of developing both cystic and atypical hyperplasia of the endometrium in women taking estrogen in a cyclical manner, a risk that is diminished when a sequential estrogen plus-progestin schedule is adopted. The implication of that study is that, given the association of hyperplasia with carcinoma (1, 10), unopposed, cyclical estrogen treatment will result in some cases of endometrial carcinoma and that the inclusion of a progestin will protect the endometrium against the development of neoplasia. Supportive data for this concept are available (8).

Despite the availability of large numbers of women receiving estrogen therapy, no systematic study has been reported on biochemical changes in the endometrium of women on such therapy. The present report describes experiments designed to answer several important questions about the biochemistry of the estrogen-stimulated, postmenopausal endometrium. In particular, we wished to know how much estrogen was entering the endometrial cells and the biological effectiveness of that estrogen in women receiving different forms of treatment. Such data are not available and would provide information as to the estrogenic stimulus impinging on the endometrial cell nucleus. Furthermore, intracellular changes in estrogen sensitivity occurring in the transition from a normal to a hyperplastic condition might be detected. We further wished to delineate the function of progestational agents in protecting the endometrium. The patients in the Whitehead trial (27, 28) provided the samples of endometria; REN3 levels were measured at different stages of treatment and RP was assayed as an index of the biological effectiveness of the estrogen. Estradiol dehydrogenase was measured in some samples.

MATERIALS AND METHODS

Postmenopausal patients were women attending the menopause clinic at the Chelsea Hospital for Women, London. Routine curettage was performed as a screening procedure at approximately 6-month intervals. A Vabra suction curettage apparatus was used (12). Premenopausal endometria were obtained from women undergoing surgery or curettage for various menstrual disorders. Wherever possible, a blood sample was also obtained. After removal of part of the endometrial sample for histology, the remain-
der was frozen on solid carbon dioxide and transported to the laboratory where it was stored in liquid nitrogen until assayed. The majority of samples were kept on solid carbon dioxide for less than 12 hr and in liquid nitrogen for less than 2 weeks. Receptors are stable under these storage conditions.

All postmenopausal patients were receiving hormone therapy p.o., the salient features of which are given in Table 1. Each treatment cycle covered a 4-week period. Except for the Menophase patients, estrogen was taken p.o. each day for the first 3 weeks of the cycle. Patients on cyclical therapy took nothing during the fourth week. Sequential patients took daily estrogen plus progestin (norethisterone) p.o. during the fourth week. Patients had received 1 to 48 months of treatment at the time of curettage. Further details can be found in the paper of Whitehead et al. (27). Women on Menophase received mestranol in daily graded doses of 1.0 to 2.5 mg for 1 5 days followed by graded doses of mestranol (20 to 30 mg) plus norethisterone (0.75 to 1.5 mg) for 13 days.

The weight of tissue was, with rare exceptions, less than 100 mg, wet weight, and an order of priorities was established for the assays such that RP was always measured; REN and REC were estimated whenever possible. The total estradiol receptor value was obtained as the sum of REN + REC. Endometria were homogenized by 10 hand-operated strokes of a Teflon pestle in a glass homogenizer. The homogenizing medium was 10 mM sodium phosphate buffer, pH 7.4, containing 10% v/v glycerol and 1 mM thioglycerol (13). The volume of homogenizing medium was dependent on tissue weight as follows: 30 mg, 1.3 ml buffer; 30 to 50 mg, 1.5 ml buffer; 50 to 100 mg, 2 ml buffer; 100 to 200 mg, 2.5 ml buffer. The minimum usable weight of tissue was 10 mg. These proportions gave a final protein concentration in the high-speed supernatant of 0.5 to 5 mg/ml. The homogenate was centrifuged at 800 x g for 10 min, and the supernatant was recentrifuged at 35,000 rpm in the 50 Ti rotor of a Beckman ultracentrifuge (Beckman Instruments Ltd., Glenrothes, United Kingdom). The fat-free supernatant was used for soluble receptor determination. The 800 x g pellet was efficiently suspended in 1.5 ml cold homogenizing medium and recentrifuged at 103 x g for 10 min. This procedure was repeated a further 2 times. The final pellet was white and gelatinous with a protein:DNA ratio of 6. Microscopically, it appeared as chromatin rather than intact nuclei. The pellet was suspended in homogenizing medium (1 to 2 ml) to give a DNA concentration of 100 to 200 µg/ml, and 0.2-ml aliquots were transferred to an equal volume of cold protamine solution (1 mg/ml water). After 5 min, the protamine-nuclear complex was sedimented at 103 x g for 10 min. The supernatant was discarded, and estrogen receptor was measured in the pellet. The method was adopted from that described by Zava et al. (29) and Nicholson et al. (23). It has been described in detail elsewhere (18), but in essence it involves incubation for 2 hr at 30º in the presence of 5 nm [3H]estradiol ([2,4,6,7-3H]estradiol, 100 Ci/mmol; Radiochemical Centre, Amersham, Buckinghamshire, United Kingdom) followed by washing and extraction of [3H]estradiol from the pellet. Maximal exchange occurred under these conditions when tested with Week 3 endometria. Nonspecific binding was assessed from triplicate incubations that also contained 10-4 M diethylstilbestrol. DNA was estimated in the final pellet by the method of Burton (2). Proteolytic destruction of receptor preparations obtained from frozen tissue can invalidate exchange assays but does not appear to be a major problem with our endometrial samples. This was tested in 2 ways. Nuclear pellets prepared as described above were extracted with 0.6 M KCl, and aliquots of the extract were added to protamine-precipitated rat uterine cytosol [3H]estradiol-receptor complex; specifically bound [3H]estradiol remaining in the pellet after incubation at 30º for 2 hr was measured. Comparison of the results obtained after incubation with and without the nuclear extract gave an indication of receptor destruction. In 3 cases, the KCl extract brought about no destruction while a fourth sample was capable of destroying only 0.12 pmol RE per 2 hr per mg nuclear DNA. Ideally, this type of experiment should have tested the destructive effect of the nuclear pellet but, because of technical difficulties in obtaining a valid interaction between 2 insoluble reactants, this method was not considered possible. The second method of testing for receptor destruction involved carrying out the exchange reaction beyond the 2-hr point at which equilibrium is reached. In 4 samples tested in this way, 2 showed no decline in REN and 2 showed losses of less than 15%. We should stress, however, that in our experience this exchange method will not work with nuclear preparations from frozen myometrium or human breast tumors.

RP was assayed with a single 10 nM concentration of [1,2,6,7-3H]progesterone (100 Ci/mmol; Radiochemical Centre, Amersham, Buckinghamshire, United Kingdom) in the presence of 10-4 M cortisol. Nonspecific binding was assessed in duplicate tubes containing 10-4 M norethister-
Endometrial Receptor Levels. There were no statistically significant differences in any of the receptor levels of endometria obtained during Week 3 of the different treatment regimens (Table 2). Data are too sparse to make individual comparisons for other weeks of treatment. However, because no differences were observed during Week 3, we have combined the results of all the cyclical treatments in order to facilitate comparison with sequential values (Chart 1). The only statistically significant difference between the REN and RP values of the sequential and cyclical

Table 2  
Receptor content of endometria from postmenopausal women during Week 3 of different estrogen treatment cycles  

<table>
<thead>
<tr>
<th>Treatment</th>
<th>REN</th>
<th>REC</th>
<th>RET^b</th>
<th>RP</th>
<th>RP:REN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequential</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Premarin</td>
<td>1.41 ± 0.18 (6)</td>
<td>4.01 ± 0.93 (6)</td>
<td>5.42 ± 1.02 (6)</td>
<td>18.09 ± 4.79 (6)</td>
<td>17.4 ± 7.4 (6)</td>
</tr>
<tr>
<td>High Premarin</td>
<td>1.23 ± 0.13 (7)</td>
<td>3.44 ± 0.79 (7)</td>
<td>4.66 ± 0.93 (6)</td>
<td>20.93 ± 3.83 (12)</td>
<td>16.4 ± 4.2 (7)</td>
</tr>
<tr>
<td>Harmogen</td>
<td>0.90 (1)</td>
<td>2.27 (1)</td>
<td>3.17 (1)</td>
<td>10.54 ± 2.79 (3)</td>
<td>16.7 (1)</td>
</tr>
<tr>
<td>High Progynova</td>
<td>1.25 (1)</td>
<td>11.55 ± 4.61 (3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mestranol</td>
<td>0.93 ± 0.20 (3)</td>
<td>4.02 ± 2.28 (2)</td>
<td>4.88 ± 2.01 (2)</td>
<td>14.34 ± 3.37 (4)</td>
<td>16.8 ± 4.7 (3)</td>
</tr>
<tr>
<td>Cyclic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Premarin</td>
<td>0.92 ± 0.17 (5)</td>
<td>1.93 ± 0.03 (3)</td>
<td>2.67 ± 0.26 (3)</td>
<td>16.77 ± 2.28 (5)</td>
<td>24.8 ± 9.5 (5)</td>
</tr>
<tr>
<td>High Premarin</td>
<td>1.01 ± 0.35 (3)</td>
<td>4.98 ± 2.10 (2)</td>
<td>5.90 ± 2.68 (2)</td>
<td>15.84 ± 1.71 (3)</td>
<td>25.5 ± 14.5 (3)</td>
</tr>
<tr>
<td>Harmogen</td>
<td>0.90 (1)</td>
<td>2.87 ± 1.58 (2)</td>
<td>3.83 ± 1.21 (2)</td>
<td>10.54 ± 2.79 (3)</td>
<td>36.4 ± 28.1 (2)</td>
</tr>
<tr>
<td>High Progynova</td>
<td>1.26 ± 0.24 (3)</td>
<td>2.84 ± 0.43 (3)</td>
<td>4.10 ± 0.57 (3)</td>
<td>24.63 ± 4.49 (3)</td>
<td>20.3 ± 2.9 (3)</td>
</tr>
</tbody>
</table>

a For definitions, see Table 1.  
b RET, total estradiol receptor.  
c Mean ± S.E.  
d Numbers in parentheses, number of observations.  

Results

Plasma estrone and estradiol levels were quantitated immunologically after their chromatographic separation (6). The antibodies used for these estimations had the following cross-reactivities. Antiestradiol-equilin, 0.07%; equilenin, 0.59%. Antiestrone-equilin, 20%; equilenin, 12%.

one. The method has been detailed elsewhere (15). REC was assayed in the protamine-precipitated pellet by the method of Chamness et al. (3). Incubations were at 30° for 2 hr.

Estradiol dehydrogenase was measured as previously described (16). Duplicate aliquots (25 μl) of the 800 × g supernatant were added to 0.25 ml of homogenizing buffer plus 50 μl of NAD⁺ (3.3 mg/ml) plus 50 μl of 0.3 mM [2,4,6,7-^3H]estradiol (100 mCi/mmol). After a 30-min incubation at 37°, 25 μg each of estradiol and estrone were added, together with 2.5 ml ether:chloroform (3:1). The aqueous phase was reextracted with a further 2.5 ml ether:chloroform. The combined organic phase was taken to dryness under nitrogen and redissolved in 50 μl ethanol; then a 25-μl aliquot was applied to a silica gel thin-layer plate. The plate was developed with toluene:ethyl acetate (40:80), and the estrone region was eluted with ethanol and counted.

Protein was measured by the method of Lowry et al. (20).
endometria was in the RP values obtained during Week 4; the cyclical endometria had a higher RP content than did the sequential samples \((p < 0.02)\). The biological significance of this observation is unclear because the sequential patients were taking norethisterone at the time of curettage. This could result in artifactually low RP values because of either receptor transfer to the nucleus or blocking of soluble [\(\text{H}\)]progesterone binding sites by norethisterone. Progesterone will exchange with specifically bound [\(\text{H}\)]progesterone under the assay conditions, but because of the greater affinity of norethisterone for RP \((17)\) it is not certain that complete exchange would occur between norethisterone and [\(\text{H}\)]progesterone. There was an interesting difference in mean RP content of Week 1 endometria from the sequential and cyclical patients. The lower values in the sequential endometria might indicate that the depressive effect of norethisterone is prolonged for some days after the progesterin had been stopped.

In looking at the changes in receptor levels during the sequential treatment schedule, it is clear that norethisterone ingestion reduced the REN content (Week 3 versus Week 4, \(p < 0.01\)), but interestingly there was also a drop between Weeks 2 and 3 \((p < 0.02)\). Because the treatment regimen was identical in Weeks 2 and 3, the latter result suggests that an inhibitory effect may exist after prolonged estrogen treatment and raises the question of whether the fall in REN from Weeks 3 to 4 is truly an effect of norethisterone or simply an extension of the change from Week 2 to 3. The former explanation is at least partially applicable because, while there was no change in proportion of endometrial RE in the nucleus from Weeks 2 to 3, there was a fall in Week 4 (Chart 2).

The low RP values seen in Week 1 of sequential therapy would indicate that norethisterone does depress the number of [\(\text{H}\)]progesterone binding sites rather than only artifactually losing them to the assay procedure (see above).

The data are more sparse for the cyclical patients, but the REN pattern was similar to the sequential one. Interestingly, REN was detected in 3 of the 4 samples obtained during the estrogen-free week (Week 4). The proportion of endometrial RE present in the nucleus fell from Weeks 3 to 4 \((p < 0.05)\).

The majority of patients were receiving sequential, high-dose Premarin plus norethisterone. Their receptor pattern through the treatment schedule (Chart 3) was essentially similar to that seen with the combined sequential results (Chart 1). Thus, Week 4 REN values were lower than those at Week 3 \((p < 0.02)\), while the mean value at Week 3 was lower than that at Week 2. The latter result approached statistical significance \((0.1 > p < 0.05)\).

REC was measured infrequently, but no difference with time or type of treatment was observed.

In premenopausal patients receiving no exogenous hormones, proliferative-phase endometria contained higher REN, total RE, and RP levels than did secretory-phase samples \((p < 0.001, < 0.002,\) and \(< 0.05,\) respectively). Comparison of the REN and RP values obtained with pre- and postmenopausal endometria (Chart 3) indicates that the estrogenic stimulus to the postmenopausal endometria is high for 2 to 3 weeks of the treatment schedule.

**Relationship of Receptor Levels to Plasma Estriadiol and Estrone.** In the results to be presented in this section, sequential and cyclical treatments with Premarin, Harmogen, or Progynova have been combined. This was considered to be permissible on the basis of the results presented in Table 2 and Charts 1 and 2. The Menopause patients were omitted inasmuch as mestranol might give rise to estrogenic compounds in the plasma other than estradiol and estrone.

Where any correlations between receptor levels and plasma estrogens were found, they were always with plasma estradiol concentrations; no significant correlates were observed with estrone levels. There was a positive correlation between RP but not REN (Chart 4) levels at Week 3 and plasma estradiol. Too few plasma estimations were performed on premenopausal patients to indicate whether results thus obtained differed from those accruing from postmenopausal women.

When RP was plotted against REN, a significant positive correlation was obtained with premenopausal (either proliferative alone or proliferative plus secretory) endometria (Chart 5A). Conversely, postmenopausal samples obtained during Week 3 exhibited a negative correlation (Chart 5B).

**Duration of Treatment.** Neither REN nor RP content of Week 3 postmenopausal endometria changed with the
length of treatment that the women had received (Chart 6).

Abnormal Endometria. Results obtained with cystic and atypical hyperplastic endometria were compared with those of normal histology (Chart 7). Although the number of hyperplastic samples was small, an interesting trend was observed. No statistically significant differences were noted with REN, RP, or RP:REN ratio between premenopausal (proliferative), normal (no evidence of previous or subsequent hyperplasia), or cystic hyperplastic, postmenopausal samples. However, the 3 atypical hyperplasias exhibited normal levels of REN but high RP content (normal, postmenopause versus atypical hyperplasia, postmenopause \( p < 0.05 \)). Atypical hyperplasias that had reverted to normal histology under the influence of progestational treatment also had a more normal receptor pattern. It should be stressed that these reverted normal samples were obtained during Week 3 of a sequential regimen and therefore that

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**Chart 3.** The effect of sequential Premarin (1.25 mg) and norethisterone (5 mg) on REN (●) and RP \( \times 10^{-10} \) (○) content of endometria from postmenopausal women. Comparison with proliferative (P) or secretory (S) endometria from premenopausal women. For definitions, see legend of Chart 1. Each point represents a minimum of 4 and a maximum of 12 patients.

**Chart 4.** Relationship of RP (A) and REN (B) content of endometrium to plasma estradiol levels in postmenopausal women receiving estrogen therapy. All samples were obtained during Week 3 of treatment, and endometria were of normal histology. Correlation coefficients for linear regression: A, \( r = 0.746, p < 0.001 \); B, \( r = 0.064, p > 0.1 \).

**Chart 5.** Relationship of RP to REN in endometria from premenopausal, proliferative (●), or secretory (△) histology (A) or postmenopausal women on estrogen therapy during Week 3 of treatment (normal histology) (B). Correlation coefficients for linear regression: A, proliferative plus secretory histology, \( r = 0.634, p < 0.01 \); proliferative histology only, \( r = 0.666, p = 0.05 \); B, \( r = 0.631, p < 0.01 \).
Estrogen Effects on Postmenopausal Endometria

Chart 6. Long-term effect of estrogen treatment on RP (A) and REN (B) content of postmenopausal endometria. All samples were of normal histology and were obtained during Week 3 of each treatment cycle. Correlation coefficients for linear regression: A, r = 0.247, p > 0.1; B, r = 0.187, p > 0.1.

Chart 7. Comparison of [A] RP × 10⁻¹¹ ([F]) and REN (I) content of premenopausal proliferative and postmenopausal endometria with normal (N), cystic hyperplastic (CH), or atypical hyperplastic (AH) histology. “N” samples had normal histology but were obtained from patients who had previously presented with atypical hyperplastic histology. B, ratio of RP to REN in same samples. All postmenopausal samples were obtained during Week 3 of a treatment cycle. The number of patients in the premenopausal and the postmenopausal normal, cystic hyperplastic, atypical hyperplastic, and normal with previous atypical hyperplastic histology groups was 9, 16, 4, 3, and 4, respectively. Mean ± S.E.; * normal postmenopause versus atypical hyperplasia, p < 0.08.

DISCUSSION

It is clear from the present data that the postmenopausal endometrium is capable of extensive stimulation such that, for 2 to 3 weeks of the treatment schedules, receptor levels are similar to those seen in premenopausal, proliferative-phase samples. No significant differences between any of the forms of treatment were noted in samples obtained during Week 3 of the treatment cycle. The similarity in receptor levels with sequential and cyclical regimens is in marked contrast to the histological data, indicating a higher incidence of hyperplasia (28) and neoplasia (8) as a result of cyclical therapy. The same point can be made about the discordance of biochemical and histological results obtained with low- and high-dose estrogen regimens. This would indicate that, with the treatment regimens studied
here, suppression of cell activity as determined by receptor assays does not give a complete indication of the mechanism whereby progestins exert their protective effect. The efficiency of endometrial shedding is greater in sequential than in cyclical patients (7, 29), and bleeding may be an effective way of removing abnormal cells. Alternatively, duration of stimulation may be important, but insufficient data were available to make comparisons at other time points either within any 4-week treatment cycle or over multicycle periods. All that can be said is that, with the sequential regimen, there was no change in the Week 3 REN or RP content of endometria from women who had been on treatment for up to 48 months.

The similarity of REN and RP values obtained with the estrone- and estradiol-type preparations is also noteworthy. The REN assay does not give information as to what estrogen is in the nucleus, but the RP levels would indicate that a similar response was being elicited. This point is further discussed below.

Some indications of the way in which progestins might influence the endometrium were obtained in our experiments with sequential patients. Norethisterone decreased both the amount of REN and the percentage of total cellular estrogen receptor that was in the nucleus. Although no conclusions can be drawn about the low RP values seen in Week 4 of sequential treatment, the low RP values noted in Week 1 would suggest that the low REN values also reflect a lowered estrogenic potency in the presence of norethisterone. At least part of the explanation as to why norethisterone should decrease the amount and proportion of estrogen receptor in the nucleus lies in the induction of estradiol dehydrogenase. This enzyme works primarily in the direction of estrone production (26), thus decreasing the effective affinity of intracellular estrogen for the receptor and lowering its biological effectiveness. This view is supported by direct analysis of estradiol and estrone content of endometrial nuclei. Regardless of whether patients are receiving Premarin, Harmogen, or Progynova, the estradiol:estrone ratio is 5 to 6; but during the week of norethisterone ingestion, the ratio falls to 2 to 3. If the induction of estradiol dehydrogenase is an important factor in mediating the effect of progestins, then it follows that only estrogens which can be substrates for the enzyme should be administered; estriol or the synthetic estrogens would not fall into this category. In rodents, progesterone can affect estrogen action by decreasing the synthesis of estrogen receptor (4). We could not detect such an effect in our postmenopausal patients but, given the wide variation in our total estrogen receptor values, such an effect could have been missed.

Tseng et al. (25, 26) concluded that estradiol was the principal intracellular estrogen in endometrium; therefore, it is not surprising that RP levels should correlate with plasma estradiol rather than with estrone levels. Surprisingly, REN levels of postmenopausal women on Week 3 of treatment did not correlate with plasma estradiol. This led to the finding that RP showed a positive correlation with REN in premenopausal endometria but a negative correlation in Week 3 postmenopausal specimens. The basis of the postmenopausal result is not known.

The REN content is low during norethisterone ingestion, rises to a peak on Week 2, and then falls by Week 3 with a further decline during the 4th week. The drop from Week 2 to Week 3 occurs without any change in type or amount of

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Chart 8. Estradiol dehydrogenase activity of premenopausal, proliferative (P), and secretory (S) and postmenopausal endometria from women on sequential estrogen plus progestin treatment. For definitions, see legend of Chart 1.
steroid being taken. This raises the possibility that chronic estrogen treatment leads to refractoriness of the estrogen receptor machinery. The mechanism for such a change is not known, but the proportion of cellular RE found in the nucleus does not alter from Weeks 2 to 3; therefore the change would seem to affect the whole cellular receptor machinery. We cannot say if the decline in REN is translated into loss of response. The continual rise in RP content from Weeks 1 to 3 cannot be used as evidence against inhibition of RP synthesis. There are several evidences that a partially refractory state does occur after prolonged estrogen treatment (11, 14, 18, 19, 22, 24).

It has long been hypothesized that changes in endometrial sensitivity to estrogen occur somewhere along the neoplastic pathway, but direct evidence for such a phenomenon is lacking. A change in sensitivity might be detected by changes in receptors. Our data suggest that sensitivity changes may occur by the time that atypical but not cystic hyperplasia is present. Furthermore, the receptor abnormality can be corrected by progestin therapy. The mechanisms are numerous whereby such a change in sensitivity might be mediated. Given the indications of refractoriness in endometria of normal histology after 2 to 3 weeks of estrogen, it is tempting to speculate that the increased acquisition of a stimuliatory process.

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