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A PHYSIOLOGICAL ROLE FOR ESTROGEN AND PROGESTERONE IN BREAST CANCER

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SUMMARY

Breast cancer is often hormone responsive, since growth or regression of tumors can often be modulated by appropriate endocrine manipulations. Estrogen and progesterone are major hormones involved in regulation of breast cancer tumor growth. Considerable insight into the mechanism of action of these hormones on tumor growth stimulation has been provided by demonstration of specific receptors for each. The inference that each hormone acts independently through its receptor to control tumor growth is belied by current studies which show that certain hormones are capable of regulating the receptor sites, metabolism, or nuclear translocation of others. This may begin to explain the complex hormonal interactions and requirements of normal and neoplastic breast tissues. Considerable progress has thus been made in understanding the basis for success of various ablative therapies.

The pharmacologic actions of estrogens and progestins in causing breast tumor regression is much less well understood. The role of hormone receptor sites has not been established in the mechanism of tumor regression caused by these pharmacological therapies. Nevertheless, when estrogen receptors are absent in a tumor, we can with accuracy predict that endocrine therapies will fail, whereas when ER is present the likelihood of a successful response to pharmacological or ablative therapy is high.

Receptor sites seem to be a common denominator and useful marker for hormone dependence or hormone responsiveness, irrespective of their actual role in the tumor regression process. Further investigations into the receptor functions should lead to new approaches in the endocrine management of patients with breast cancer.

ESTROGEN

Estrogen acts directly on the normal mammary gland to promote growth and differentiation [1]. However, estrogen also stimulates the release of pituitary prolactin, which likewise acts upon the mammary cell [2]. Since estrogen cannot support mammary tumor growth in the absence of a pituitary [3], whereas prolactin reportedly supports both normal mammary gland and mammary tumor growth in the absence of ovaries and adrenals [4, 5], estrogen is considered by many to play only a secondary role in tumor growth and regression [6]. Prolactin stimulation of tumor growth in the absence of ovarian steroids is of brief duration, however. If DMBA-tumor-bearing rats are ovariectomized and simultaneous lesions are placed in the median eminence to increase prolactin release, the tumors grow at an accelerated pace for only 10–12 days and then regress, even though prolactin levels remain elevated [7, 8]. Furthermore, the transplantation survival of the MTW9 rat mammary tumor appears to depend on ovarian hormones [9], and growth of MTW9 tumors is impaired in rats immunized with estradiol-BSA conjugates [10]. One might summarize the role of physiologic estrogen levels as follows: estrogens are probably essential but not sufficient for growth of certain mammary tumors.

On the other hand, estrogens in pharmacologic doses cause regression of mammary tumors [11]. This paradoxical effect of estrogen may involve interference with the prolactin stimulation of growth, since the effect can be overcome by increasing endogenous [12] or exogenous [13] prolactin.

There is considerable current information on portions of the intracellular estrogen response mechanism in both rat mammary tumor systems and human breast cancer. We will now examine aspects of this mechanism and its role in endocrine control over mammary cancer cells.

Localization of estrogens in responsive tumors

In 1959, two laboratories reported that radioactively labeled estrogen injected *in vivo* into experimental animals was localized in those organs which either respond to estrogen or excrete it [14, 15]. Soon after, breast cancer patients scheduled for adrenalectomy to remove the source of circulating estrogens were given tritiated hexestrol just prior to surgery. It was discovered that the tumor metastases of the patients responding to the adrenalectomy concentrated a larger fraction of [^{3}H]-hexestrol than those of patients who failed to respond [16] as if only responsive tumors behaved as estrogen target tissues. Other investigators studying the uptake of radioactive estrogens into human mammary tissue [17–20] found a correlation between the uptake of estrogen by malignant breast tissue and the response to endocrine therapy, but this correlation was not sufficiently strong to be useful for predicting response in an individual patient.

Similar results were obtained in experimental mammary carcinomas, and hormone-dependent tumors *in*

vitro also took up more estrogen than autonomous tumors [21–28]. This *in vitro* uptake could be completely inhibited by synthetic estrogen analogues while the relatively low uptake in other tissues such as muscle could not be inhibited, indicating specificity of the uptake into tumors. From these results, Jensen proposed that the *in vitro* technique might be extended to human tumor tissue samples to predict the respose to adrenalectomy. By this time, estrogen receptor had been discovered in target tissues including tumors [29–33] and appeared to be responsible for the specific uptake of estrogen by these tissues. Direct studies of the presence and role of receptor in mammary tumors followed, and raised the possibility of using the presence of the receptor to predict hormone dependence.

Measurement of estrogen receptor

There are now several procedures for measurement of ER in cytosols of target tissues. The receptor can be quantitated by demonstration of specific 8S and 4S binding of [^{3}H]-estradiol on sucrose density gradients (SDG). The dextran-coated-charcoal (DCC) assay is equally quantitative and less expensive. Non-receptor bound [^{3}H]-estradiol is removed from specific estradiol-bound receptor by charcoal. The binding data obtained from incubating cytosol with increasing concentrations of hormone can be plotted by the method of Scatchard to determine both the number and affinity of estrogen binding sites.

Assays based on protamine precipitation of receptor have recently been developed to measure both free and hormone bound receptor from cytoplasmic [36] and nuclear [37] extracts. The receptor is precipitated with protamine, then the solid phase protamine–receptor complex is incubated with radioactive estradiol. Incubation at 30° or 37° permits exchange of any previously bound nonradioactive ligand, while at 4° only unoccupied receptor is radiolabeled. The combination of these assays has the unique advantage of using only one basic technique to assess both free and bound estrogen receptor sites in tumor cytosol and nuclei. This procedure could prove particularly useful where premenopausal cancer patients might have high levels of plasma estrogens that would transfer cytoplasmic ER to nuclear sites making them inaccessible to assay by SDG or DCC. Since the presence of free cytoplasmic ER in tumors now has prognostic value in helping to predict the proper type of treatment for breast cancer patients (see below), those premenopausal women who have ER masked by endogenous estrogens might not be given treatment that would be of greatest benefit.

Rat mammary tumors as a model system

Because of many similarities to human breast cancer, DMBA-induced rat mammary tumors have been extensively studied to provide insight into the mechanism of hormonal influence in tumor growth. These tumors have complex hormonal requirements for growth [38, 6] and have ER values which range widely [38–40]. Absent or low levels of tumor ER are associated with a failure to regress after ovariectomy, whereas the majority of ER positive tumors regress following endocrine ablative procedures. The finding of ER positive DMBA tumors which do not respond is similar to the situation in human breast cancer and demands further study. It has been suggested [41] that the receptor might be defective in nonresponding tumors but nuclear translocation of ER is normal in rat DMBA tumors [42]. In addition, chromatin from autonomous rat mammary tumors is capable of binding ER under cell free conditions [43, 44]. It is fair to summarize that in DMBA rat mammary tumors, ER may be essential to hormonally regulated growth and regression but the mere presence of ER in a tumor does not guarantee that the tumor will behave in a hormone dependent fashion.

Estrogen receptor in human breast tumors

The properties of the estrogen receptor found in hormone-dependent rat tumors have now been demonstrated in human mammary tumors as well [45]. In ER positive tumors, Scatchard plots of the binding data from either DCC or protamine assays usually reveal a single class of receptor sites with a very high affinity binding component (K_d 10^{-10} M) [46, 47]. The receptor sediments primarily at 8S in low salt sucrose gradients and 4S in high salt gradients [45].

ER values in primary tumors range from 0 to almost 1000 fmol/mg of cytosol protein [48]. The wide range of values may be due to a combination of factors. *First*, since tumors commonly exhibit cellular heterogeneity, the ER content might vary directly with the proportion of those cells that contain cytoplasmic ER. Early reports indicated no obvious correlation between the histology of a tumor and its ability to bind E [34]. More recently, a strong association between ER and invasive lobular carcinoma has been described, while a low frequency of ER is seen in tumors with a prominent local lymphocyte reaction [49]. *Second*, one might suppose that contamination of a tumor specimen by normal mammary cells containing ER would give variable assay results. But this is not the case since ER cannot be readily detected in non-lactating human breast cells [50–52]. This last point has been confirmed in animal studies in which E uptake or actual ER levels are very low in virgin mammary glands but then markedly increase during lactation [53–56]. Finally, the amount of endogenous E secreted by the patient must be considered since endogenous E would occupy ER sites and make them unavailable for assay using conventional techniques. This may at least partially explain why the highest values for tumor ER are seen in postmenopausal patients. Exchange techniques for mea-

suring ER occupied by endogenous E are now available [57–59, 36, 37].

Jensen's original suggestion that the presence of ER in a human breast tumor might indicate that the tumor is hormone dependent and will regress with appropriate endocrine manipulation [27] has now been evaluated. A number of laboratories using a variety of techniques have assayed ER in breast tumor specimens and data on clinical response to endocrine therapy are now available in many of these cases. On July 18–19, 1974, an international workshop was held in Bethesda, Maryland, to correlate these data [34]. Details of both ER assay procedures and clinical evaluation criteria were examined, and 436 treatment trials in 380 patients were ultimately accepted. The general pattern of results was the same for all investigators, and the collective data are summarized below.

Surgical ablation (castration, adrenalectomy, hypophysectomy). Thirty-three per cent of 211 treatment trials yielded objective tumor regression. Of the 94 trials in patients with negative tumor ER values, only 8 (8%) were successful, whereas 59 (55%) of the 107 trials in patients with positive tumor ER values succeeded. Patients with borderline tumor ER values had a 30% response rate.

Additive therapy (pharmacological doses of estrogens, androgens, and glucocorticoids). Thirty-four per cent of 170 trials yielded objective tumor regressions. Of the 82 trials in patients with negative tumor ER values, 7 (8%) were successful, whereas 51 (60%) of the 85 trials in patients with positive tumor ER values succeeded.

Miscellaneous therapy. Twenty-seven per cent of 55 trials yielded responses to a variety of endocrine therapies including antiestrogens, aminoglutethimide, etc. Of 32 trials in patients with negative tumor ER values, 5 (16%) were successful, whereas 10 (43%) of 23 trials in patients with positive ER values succeeded.

There remains little doubt that estrogen receptor values can be helpful in predicting the results of endocrine therapy for metastatic breast cancer. It is clear that if a patient has a negative tumor ER value the chances of tumor regression in response to endocrine therapy are minimal. A large number of patients can thus be spared unrewarding major endocrine ablative therapy if ER assays are performed routinely. When the tumor ER value is positive, the response to endocrine therapy is 55–60%. This single piece of evidence when coupled with available clinical prognostic factors such as menopausal status, disease-free interval, site of dominant lesion, and especially response to previous hormonal therapies should permit the practicing oncologist to select or reject endocrine therapy with considerable confidence.

Why did 45 per cent of the patients with positive tumor ER values not respond to endocrine therapy? Several possible reasons can be proposed. *First*, the role of other hormone receptors must be considered, since ER is only one part of the complex hormonal control system which influences mammary cell growth and function. The mechanism(s) by which these other hormones affect breast tumor growth must be equally important since receptors for prolactin, progestins and androgens have also been identified in breast tumors. Perhaps simultaneous analysis of these receptor proteins in addition to ER will be helpful in eliminating the 45% of those patients who have positive tumor ER values but do not respond to any type of hormonal manipulation. *Second*, tumors might contain a heterogenous population of hormone-dependent and autonomous cell types and therefore express a mixed response to hormone therapy. Such conditions could explain why some ER positive tumors show only partial or short term remission before progressing to a completely autonomous condition. *Third*, tumors might contain defective cytoplasmic receptor proteins which prevent the induction of the incompletely known sequence of biochemical events ultimately leading to tumor regression upon hormone therapy. Defective receptor proteins have in fact been demonstrated in several experimental systems [41, 42] but no correlations to human tumor regressions have yet been made. *Fourth*, it has been suggested that specific nuclear acceptor sites for receptor are required for hormone action [60], and it is possible that absent or defective sites would lead to insensitivity to ER. The evidence for such sites remains controversial [61–64].

Antiestrogens

The discovery that certain estrogen analogues could antagonize estrogen stimulation of target tissues was promptly applied to the problem of breast cancer. Growth of DMBA tumors could be inhibited by clomiphene [65] or nafoxidine [66] or tamoxifen [68], though there exists one report of tumor growth-promoting activity of these agents [69]. Tumor induction was also prevented by nafoxidine [70]. The ability of tamoxifen to cause regression of a DMBA tumor was highly correlated with the presence of estrogen receptor in a biopsy of that tumor [71].

The positive results of these experiments led to clinical trials of antiestrogens for therapy of breast cancer patients. Tamoxifen was used successfully [72–74] as was nafoxidine [75–77] and clomiphene [78]. The remission rates were reported to be around 30%, the same as those achieved by other endocrine therapies. And as with other endocrine therapies, success was correlated with the presence of estrogen receptor in the patient's tumor [34], though the correlation did not appear to be quite as good as with other endocrine therapies.

The mechanism of action of antiestrogens has been studied principally in the rat uterus. They have been found not only to bind to the estrogen receptor [79, 80] but to translocate this receptor into the nucleus [81] and even to initiate early estrogenic re-

sponses [82]. A complete response does not develop, however, and the cells remain for a time refractory to the action of active estrogens. Because some antiestrogens retain receptor in the nucleus for many days in contrast to several hours for active estrogens [81], this retention was at first thought to be an essential feature of their effect. More recent work has shown that some do not share this property, though apparently all fail to replenish receptor in the cytoplasm [83], which may explain insensitivity to later estrogen action. Nothing is yet known of the differences between receptor-estrogen and receptor-antiestrogen complexes in the nucleus which might account for the differences in their activity.

Even less is known of antiestrogen action in human breast cancer, beyond the fact that antiestrogens bind to tumor estrogen receptor [84, 85] and decrease DNA synthesis in a human breast cancer cell line [86]. It has been suggested that a principal effect may be the reduction of estrogen-stimulated prolactin levels [68, 87, 88], but this effect does not seem to be sufficient to account for the response in rat DMBA tumors [66]. It is also possible that antiestrogens inhibit ovarian synthesis of estradiol. These questions are under active investigation.

PROGESTERONE

Clinical effects in breast cancer

Because of the cyclic changes in blood estrogen and progesterone levels which occur in females and these hormones' interrelationships in regulating target tissue development and growth, it was inevitable that progesterone would be studied for its effect on breast cancer.

That progesterone plays a role in stimulating tumor growth is suggested by the pioneering studies of Huggins *et al.* [89–91]. They showed that pregnancy promoted the growth of DMBA-induced rat mammary tumors. Administration of progesterone to intact rats accelerated the appearance of tumors, increased the number of tumors, and augmented the growth rate of established tumors.

Parturition and weaning are followed by regression of a large number of pregnancy-stimulated tumors [89, 92, 93]. The principal tumor growth-promoting factors of pregnancy and lactation are probably placental lactogen [94] and prolactin [95, 96]. Ovariectomy, however, blocks the stimulatory effects of endogenous or exogenous prolactin on tumor growth, and injection of progesterone removes this block [95]. Either prolactin stimulation of tumors under these circumstances is dependent upon progesterone, or alternatively the high levels of circulating progesterone stimulated by prolactin in the lactating rat [97] are responsible for the tumor growth. This does not mean that progesterone alone is responsible for maintaining rat mammary tumor growth, since in these experiments the animals had both high prolactin levels and intact adrenal glands. On the other hand they do suggest that progesterone plays an important physiological role in stimulating tumor growth.

In contrast to the stimulatory effects of progesterone described above, progesterone can induce rat mammary tumor regression or prevent tumor appearance, at least when combined with moderate to large doses of estrogen [89, 98]. In humans, too, the percentage of breast tumor regressions in response to a progesterone–estrogen combination is generally higher than with progesterone alone [99]. Postmenopausal patients with endogenous estrogen levels (presumably of adrenal origin) sufficient to cornify the vaginal mucosa have a 29% tumor remission rate with progesterone therapy, whereas patients with an atrophic vaginal smear experience only 6% remission rate with progesterone alone [100]. These data would support a requirement for estrogen in progesterone-mediated tumor regression and may be due to estrogen stimulation of progesterone receptor synthesis (see below). In fact, since moderate to large doses of estrogens alone can cause mammary tumor regression in rats [11–13] and humans [101], it is necessary to ask whether addition of the progestational agent accomplishes more than the estrogen alone. The answer would seem to be yes, at least in some cases, because patients whose tumors have failed to regress following treatment with high dose estrogen alone have responded to a combination of estrogen–progesterone [102–104].

The mechanism by which progesterone promotes tumor regression is not clear. Large doses of synthetic progestins can cause significant lowering of serum LH and cortisol levels, suggesting that alteration of pituitary function may be involved [105], but at least four previously hypophysectomized patients are reported to have had breast tumor regression following combinations of estrogen–progesterone [106, 107]. This is in contrast to the lack of tumor response to estrogens alone in hypophysectomized patients [108–110].

In sum, the specific mechanisms involved in progesterone-mediated breast tumor growth and regression are poorly understood. However, the hormone's binding to specific receptor proteins, and its effect on the actions of other steroid hormones have been extensively studied in several target tissues.

Progesterone interrelationship with other steroid hormones

Progesterone may control breast tumor growth or regression in several ways. The simplest mechanism involves a direct effect of the hormone on the tumor. However, progesterone can also modify the actions of the other steroid hormones which influence the mammary gland, and this may form the basis for interhormonal control mechanisms.

Estrogens. The ability of progesterone to antagonize and/or modify the action of estrogen is well documented [111, 112]. Tamoxifen and nafoxidine, two widely used antiestrogens, exhibit progesterone-

like effects [113–115]. Hsueh *et al.* [115] have shown that after depletion of cytoplasmic ER by high dose estrogen treatment, progesterone blocks the overshoot of ER seen during replenishment. They propose that this reduction of ER is correlated with reduced sensitivity of the uterus to estrogen. There is no evidence, however, that progesterone affects replenishment of ER after physiological estrogen treatments or alters basal ER levels. In sum, estrogen and progesterone may exert feedback control on each other in the target tissue. Estradiol pretreatment enhances tissue sensitivity to progesterone through increased progesterone receptor (PgR) levels. Progesterone in turn may modify cytoplasmic ER and redirect the cell's ability to respond to estradiol.

Androgens. The androgenic properties of progestins are well known, and fetal virilization can result from their use in man [116]. Progestins can masculinize the reproductive tract of rat fetuses [117] and can mimic androgen effects in several organs [118–121]. Recently Bullock *et al.* [120] and Mowszowicz *et al.* [118] have demonstrated that progestins can either be synandrogenic (by potentiating androgen effects) or antiandrogenic (by inhibiting these effects) depending on the steroid structure, dose and tissue. If androgens have similar modifying effects on progesterone actions it may be one reason why they are effective in treatment of hormone dependent breast cancer. Although the mechanism of androgen-induced regression of breast tumors is not known, androgens cause regressions of fetal mammary buds [122] and may have similar effects on dedifferentiated malignant cells. It is possible that progestin-induced tumor regression is a reflection of the progestins' androgenic properties.

Glucocorticoids. By far the most familiar model for the interaction of two differing steroids is that proposed by Rousseau *et al.* [123] to explain the inhibitory effects of progestins and the stimulatory effects of glucocorticoids on tyrosine aminotransferase production in rat hepatoma tissue culture (HTC) cells. Competition by progestins for glucocorticoid binding has also been demonstrated in mammary carcinomas [124, 125] and lactating mammary glands [126, 127]. Since glucocorticoids are involved in mammary gland maturation it is possible that progestins may affect mammary tumors by modifying glucocorticoid action.

We have recently shown that MCF-7, a stable cell line derived from a human mammary carcinoma, contains receptors for progestins, androgens glucocorticoids, and estrogens. These cells may prove useful for studying interrelationships between the binding and biological actions of these four steroids and their role in tumor endocrine response [128].

Progesterone receptors in human breast cancer

As discussed previously, around 40% of human breast cancers fail to respond to endocrine therapy in spite of the presence of estrogen receptor. However, since binding to receptors is only an early step in hormone action, it is possible that in ER+ tumors where endocrine manipulations fail, the lesion is at a later step. An ideal marker of an endocrine responsive tumor would, therefore, be a measurable product of hormone action rather than the initial binding step.

Because in estrogen target tissues the synthesis of PgR depends on the action of estrogen [129], we investigated the possibility that PgR might be such a marker. If so, it would be expected that PgR would be rare in tumors which lack ER. The presence of PgR in tumors containing ER would indicate that the tumor is capable of synthesizing at least one end product under estrogen regulation, and that the tumor remains endocrine responsive. Conversely, the prospect of a successful response to therapy would be low in tumors with ER but no PgR. We are now testing this hypothesis.

We have used 8S binding of the synthetic progestin ^{3}H-R5020 [130] to identify PgR in human breast cancer tissue [131, 132]. We have now determined PgR and ER in 520 human mammary tumors. Of 138 ER negative tumors only 12 (9%) had PgR while 289 of 392 (73%) ER positive tumors had PgR. Confirmation of the hypothesis requires direct correlation of the presence of PgR with objectively defined clinical remission. Our preliminary data is encouraging. We find that in cases where ER is positive and PgR negative successful response rate is very low, analogous to the response rates seen with ER negative tumors. In contrast, if both receptors are present, remissions are seen in a larger percentage of patients than would be predicted on the basis of ER alone. However, it should be emphasized that this is very preliminary data, representing only the simplest cases in which receptor measurements were performed on a single biopsy and response to a single trial of endocrine therapy is involved.

Most questions remain unsolved. How does one interpret contradictory responses to one or more therapeutic trials? What is the effect of previous therapy on receptor levels in multiple biopsies or metastases? How do menopausal status or menstrual cycle affect PgR levels in biopsies? Is measurement of only cytoplasmic receptors an adequate representation of the total receptor content of the cell? And, in considering cytoplasmic receptors, what constitutes a positive assay for PgR? How are we to interpret the tumors which have no 8S binding but considerable suppressible 4S? Finally, we have shown that human breast tumor cells can contain receptors for at least four steroid hormones. How are we to incorporate androgen and glucocorticoid receptor data in estimating the response potential of a tumor? Hopefully, current investigations will soon provide answers to these questions.

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DISCUSSION

Jungblut. What actually is the advantage of the nuclear exchange assays over a direct assay of the steroid by radioimmunoassay?

McGuire. Nuclear exchange assays measure receptor that has been translocated to the nucleus by steroids. Radioimmunoassay would measure any steroid present in the nuclei whether it was bound to receptor on not. This assumes, of course, that the affinity of the antibody for the steroid was at least equal or greater than the affinity of the steroid for the receptor. So then the two techniques might actually be measuring two different things.

King. In relation to your comment about the necessity of killing 99% of the cells, it is worth noting that in actively growing tumours approximately 80% of new cells are dying

anyway so the 99% figure you mentioned for tumour shrinkage is not too horrendous.

Have you come across any tumours that would have been classified as negative on the basis of a simple cytoplasmic assay but which would have been positive if a nuclear assay had been performed?

McGuire. Yes, I think there is some data on that question. Recent evidence from Denmark would suggest that this situation occurs about 10% of the time. Perhaps Dr. Saez has some information on that question.

Saez. What happens usually when one measures in the same patient plasma estradiol and receptors in the tumour, in any case where we found nuclear receptors we found receptors in the cytosol and circulating estrogens in plasma.

Pasqualini. I would like to make one comment to confirm the data of the presence of estrogen receptors in the nucleus of two cases of primary breast cancers. It is observed that 62–75% of the total cell receptors are localized in the nucleus and particularly in the fraction extracted by the 1M NaCl solution. Concerning the tumours in which only estradiol receptors are present in the nucleus but not in the cytosol, *in Table* 1 one case of human endometrial carcinoma is indicated in which receptors in the cytosol was not detectable but in the nucleus a total of 86 fmol/g tissue was found.

Table 1. Specific [^{3}H]-estradiol binding in the cytosol and nuclear extracts in a human endometrial carcinoma (60 years old)

	Specific binding (fmol/g Tissue)
Cytosol	0
Nuc. ext.	
0.1 M Tris	26
0.3 M NaCl	16
1 M NaCl	44

Siiteri. I am quite surprised at your distribution of progesterone receptor-positive patients. It would appear that you had more positives following the menopause at a time when presumably most of these patients would have a rather low estrogen environment. I wonder whether you have any information on actual hormone measurements? In view of the work of many in the room who have shown that progesterone appears to regulate estrogen receptor concentrations, do you think that there is a place for progesterone treatment in breast cancer?

McGuire. In answer to your first question, I don't believe our data show that progesterone receptor values are higher in postmenopausal patients. This is in contrast to estrogen receptor where everyone finds a higher estrogen receptor value in the postmenopausal group. Your second question regarding progesterone therapy has some support from actual clinical studies where tumour regressions have been seen following progesterone therapy. In addition, there is now some evidence that progesterone administration can prevent at least part of the replenishment of estrogen receptor that occurs after estrogen receptor depletion in the cytoplasm. There are certain other considerations, however, that suggest that the mechanism of progesterone induced tumor regression may be quite different. This topic deserves further study.

Mainwaring. Certain androgens have progestational activity. Does cytoproterone acetate compete for both progesterone and the androgen receptor in your tumour specimens?

McGuire. Yes.