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review

ESTROGEN AND ENDOMETRIAL CARCINOMA

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"The inseparable propriety of time, which is ever more and more to disclose truth" Francis Bacon (1561–1626). Advancement of Learning, bk, I.i.3 (ed. 1605)

INTRODUCTION

The role of estrogen in the pathogenesis of endometrial carcinoma has been considered almost from the time of its isolation by Allen and Doisy in 1923 (4), but its exact role is still not fully understood. A review of the conflicting evidence was systematically and admirably accomplished by Larson (102) in 1954, Andrews (7) in 1961 and Gusberg (68) in 1967. It is again felt to be necessary to review our present knowledge because of the steadily increasing amount of literature implicating estrogen in the development of endometrial cancer.

BACKGROUND

The clinical impression that estrogens must be a causative agent of endometrial carcinoma arose out of its occurrence in patients with hormone-secreting tumors which were reported many times in the medical literature. The first report in the American literature was in 1936 by Novak and Yui (124), although the original mention of the association was made by Schröeder (140) in 1922. Since then many series have been published with a marked difference in the occurrence of such carcinomas, ranging from 0.00 percent, (30, 44, 71) to 12.1–20.0 percent (33, 47, 69, 115, 151). A complete summary and analysis was compiled by Green (61), a student of this relationship and reporting originally in 1941 (60). He feels there is an association, but it is probably a rare event. Recently Gusberg and Kardon (69) noted a high correlation and recorded 115 patients with so-called feminizing ovarian tumors in which 21 percent were found to have corpus cancer and 43 percent cancer precursors. This was the highest incidence recorded, but the authors were still unable to draw any "firm conclusions about the carcinogenic activity of estrogen in human beings." Larson (102) concluded that the association "is not as high as some have previously claimed, but it certainly is greater than chance." Larson also noted a 1.3 percent incidence of endometrial carcinoma in premenopausal women, but a more significant 10.3 percent incidence in postmenopausal women with feminizing tumors of the ovary. No conclusions were drawn from this group difference, but a similarly increased incidence in the postmenopausal female with feminizing ovarian tumors was documented by Dockerty and Mussey (33)-27 percent, Ingram and Novak (87)-12 percent, and Hertig (83)-24 percent.

The opinions and assertions contained herein are those of the author and do not necessarily reflect the views of the Navy Department or the Department of Defense.

ENDOGENOUS ESTROGEN–GONADAL

It is well known that the endometrial carcinoma patients tend to be lower in parity and have menstrual irregularities, which may reflect anovulatory cycles and therefore continuous "unopposed estrogen stimulation." This unopposed estrogen occurs not only with feminizing tumors of the ovary, as mentioned above, but also with "polycystic ovary syndrome," as described in 1935 by Stein and Leventhal (156) and later by Jackson (88). The increase in pre-malignant and malignant endometrial change associated with this latter form of continuous endogenous estrogen production is well documented. Andrews and Andrews in 1960 (6) reviewed a total of 29 cases of Stein-Leventhal syndrome with endome-

trial carcinoma and "in 3 reports dealing with endometrial carcinoma in young women, Stein-Leventhal syndrome was present in 19, 21 and 25 percent of cases" (34, 150, 152). With the advent of ovulation initiated by wedge resection (97) or estrogen antagonist clomiphene citrate* (3, 67, 99) the pre-malignant lesions revert to normal, at least temporarily. This is consistent with the findings of Kistner (100) in that progestogens have caused regression of hyperplasia and carcinoma in-situ of the endometrium. All this could indicate that progesterone or its analogue is required to prevent carcinoma of the endometrium. More importantly, anovulation may carry with it an alteration in estrogen metabolism. Ultimately this could be the result of a derangement of gonadotropic activity (86, 98, 144) and thus be the key to an extremely complex chain of events. This will be further discussed below, but if true, all conditions which affect estrogen metabolism could be involved with an increased incidence of corpus carcinoma.

A monumental effort was recently put forth in the comprehensive work of Lucas (108) which covers the possible factors involved in the development of endometrial carcinoma. He so aptly pointed out the varied conditions which could result in deranged estrogen metabolism and implicated metabolic factors such as obesity, diabetes, cirrhosis, in addition to the effects of abnormal gonadotropin, growth hormone and enzyme production or utilization.

ENDOGENOUS ESTROGEN—EXTRAGONADAL

Kase (94) and MacDonald in 1967 (111, 112) and more recently Schindler (139) and Speroff (153) pointed to the extragonadal contribution to blood estrogen level. "While the adrenal gland does not secrete appreciable amounts of estrogen into the circulation, its normal function contributes to the total circulating levels of estrogen. This is accomplished by the extragonadal peripheral conversion of C-19 androgenic precursors of estrogens, such as androstenedione. In addition, recent evidence suggests that adipose tissue is capable of converting androstenedione to estrone (139), and this may be of significance in the well-known association between obesity and anovulation" (153). The conversion of Δ4 androstenedione to estrone was carried out by Schindler (139) *in vitro*, using human female fat tissue of patients with endometrial carcinoma. Estrone (E_1) and estradiol (E_2) are derived to a certain extent from circulating Δ4 androstenedione (A) in adrenalectomized, oophorectomized and normal menstruating women (112). Furthermore, almost all estrogen in postmenopausal women results from this same peripheral conversion (107, 112). Schindler observed that in patients with endometrial carcinoma an average conversion of 0.1 percent was found while in normal patients the average conversion was only 0.027 percent.

Hemsell, et al (77) studied the relationship of aging and the extent of conversion of plasma androstenedione to estrone. These studies were carried out on 23 women and 26 men to whom ^{3}H estrone and ^{14}C androstenedione were administered intravenously. It was found that with aging in both women and men there was a progressive increase in the efficiency with which androstenedione is converted to estrone. This conversion was in the order of 2 to 4 times that observed in the young adult. A similar increased conversion of C-19 plasma steroids to estrogens was noted by the same investigators and others in obese patients (77, 134).

Not only is it important that there is a greater efficiency of conversion, but also with an increased pool of precursor there would be in turn a greater amount of similar estrogen production. This was observed by Aiman, et al (2) in three groups of hirsute or virilized women (i.e., polycystic ovarian disease, hyperthecosis and lipoid cell tumors of the ovary). These subjects not only had androgen excess, but estrogen production was also high and arose principally from extraglandular utilization of plasma precursor.This increased precursor was found in patients with endometrial carcinoma, atypical adenomatous hyperplasia and postmenopausal bleeding by Edman, et al (39).

In postmenopausal women the estrogen production is principally estrone produced from aromatization of plasma androstenedione which in turn principally arises from the adrenal. It is unlikely that either adrenal or ovarian secretion of estrone or estradiol contributes significantly to the total estrogen in postmenopausal women (63).

The estrogen composition therefore gains in

* 1-(p(B-diethylaminoethoxyl)phenyl)-1-phenyl-2-anisylethanol, Merrell-National Laboratories, Cinn. Ohio.

importance as will be seen later with the experience of long term stilbestrol therapy where carcinoma was observed while not previously observed with steroidal estrogen treatment (27).

The corollary is that extraglandular estrone production can be greater in the female who is postmenopausal, older, obese, anovulatory, or who has increased androgenic precursor from either the ovary or adrenal. It must be clearly pointed out that the patient with corpus cancer does not generally have an increased total estrogen secretion (15, 75, 138). This impression of hyperestrogenism came from a higher number of cornified vaginal cells in corpus cancer patients (10, 21, 22), though Liu (106) observed that vaginal hypoestrogenism rather than hyperestrogenism is more common in postmenopausal patients with carcinoma. These varied vaginal cytology findings are consistent with the lack of correlation with the plasma estrogen levels and maturation index in postmenopausal females noted by Stone (160) and Charles (22).

A decrease in the urinary excretion of etiocholanolone and androstenedione in patients with endometrial hyperplasia and carcinoma was also reported (29, 138). An editor's comment (38) concludes that this may represent a "relative biological preponderance of estrogen among patients who develop corpus cancer" and additionally "the estrone-estradiol ratio in the serum has been found to be abnormal in postmenopausal women with corpus cancer" (135). The ratio was 1.20 in patients with cancer as compared with a ratio of 0.58 in patients without cancer. It has also been observed that postmenopausal women with endometrial carcinoma excrete less total estriol glucuronide than estrone glucuronide when compared to normal postmenopausal females (75). The conclusion is that the production of estriol precursor, other than estrone, was decreased in the corpus cancer patients. More recently Hausknecht and Gusberg (76) studied 21 patients with purified and labeled tracers (6, 7-^{3}H-estrone and 4-^{14}C androstenedione) and measured the ^{3}H/^{14}C ratios in estrone and estriol as well as the percentage of conversions of estrone from androstenedione in normal postmenopausal women. It was concluded that androstenedione was the major precursor of urinary estrogen in postmenopausal women and that there was a significantly greater conversion of androstenedione to estrone in the endometrial cancer women than found in healthy, postmenopausal women. There was also no difference in the ^{3}H/^{14}C ratio in estrone as compared to estriol.

During the reproductive years it is known that estradiol secreted by the ovaries is the major source of estrogen, while plasma Δ4 androstenedione is produced equally by the ovaries and adrenal and is converted peripherally to estrone. Postmenopausal women cease ovarian estrogen production and consequently the principal source of estrogen is extragonadal conversion of adrenal Δ4 androstenedione to estrone. Approximately 3 mg of Δ4 androstenedione is produced in 24 hours and peripheral conversion will create 40-120 μg of estrone per day.

An observation by Vermeulen (175), of unclear significance, indicates that the postmenopausal ovary is not fully inactive, but appears to be responsible for about 50 percent of the plasma testosterone and 30 percent of androstenedione levels. It was also observed that hCG stimulation with 5000 IU daily for 3 days hardly influences this steroid secretion.

A recently published series of Edman (39) indicated that normal postmenopausal women had a blood/urinary production rate of estrone (PRE_1) of 53/54 μg/day while endometrial carcinoma – PRE_1 122/122 μg/day, atypical adenomatous hyperplasia PRE_1 161/181 μg/day and postmenopausal bleeding patients had PRE_1 158/164 μg/day. Interestingly, uterine bleeding was observed in all postmenopausal patients in whom estrone production rates were greater than 100 μg/day.

The dilemma at hand is, does the estrone excess create a carcinogenic milieu in a susceptible patient or conversely does an at-risk patient have altered estrogen metabolism and if so for what reason?

ENDOGENOUS ESTROGEN – HYPOTHALAMIC CONTROL

Now shifting attention from the main character, estrogen, there must be an attempt to assess the reason for the increased peripheral androgen aromatization or increased androgen precursor production in patients at risk for carcinoma of the endometrium. As underscored by Dilman (31), there is an increased phenolic steroid excretion in menopausal patients with endometrial carcinoma, while classical estrogen secretion is normal and he feels that "these qualitative disturbances correspond to gonadotropin secretions."

Even though there is a decrease in total gonadotropin excretion as measured by bioassay, there is an increase in LH as measured by immunoassay. It therefore is felt that endometrial carcinoma is a disease associated with hypothalamic "hyperactivity." Dilman (32) subsequently demonstrated that the immunologic assay of LH was 7 times higher than the bioassay and after treatment with a progestogen (17α hydroxyprogesterone caproate) the LH returned to normal. These changes were not observed in cervical, ovarian or mammary cancer. This report discusses the importance of the dissociation of immunologic and biologic activity (as it is measured) of LH. It defined the modification of a hormone protein molecule which still retains not only its specific antigenicity, but also affinity for the target tissue or an ability of participating in hormonal self-regulation as an "*anahormone*." Similarly this dissociation occurs in trophoblastic disease where immunologic hCG may be several times higher than biologically active hCG. Both examples may indicate a qualitative disturbance in hormonogenesis and thereby an altered pathway of steroidogenesis.

Similarly LH secretions in patients with polycystic ovary disease (PCO) were generally found to be elevated in a third or more of patients (163, 182). Stahl, et al (154) felt the excess LH production when present was the result rather than the cause of excess adrenal and ovarian testosterone. This was also felt to be possible by Polansky (131). No patient demonstrated excess androgen of ovarian origin alone. Bardin, et al (9) demonstrated that this adrenal androgen-secreting mechanism seems not to be under ACTH control. DeVane (28) confirmed in 10 patients with PCO a significantly higher LH, but not FSH, while estrone (E_1) levels were also significantly high, but not estradiol (E_2). Consistent with this were elevated levels of testosterone (T), $\Delta 4$ androstenedione (A) and dehydroepiandrosterone sulfate (DHEA-S).

A most interesting effort by Abraham (1) found that, in general, steroid levels were lower in postmenopausal women. Since the adrenal cortex contributes more than 95 percent of DHEA-S in premenopausal women, the marked drop in DHEA-S level after menopause is the result of the cessation of ovarian influence on the steroidogenic activity of the adrenal cortex. It was found that estrogen therapy in 10 postmenopausal women significantly increased $\Delta 5$ pregnenalone ($\Delta 5$-P) dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEA-S) (all $\Delta 5$ steroids) and confirmed the postulate that estrogens stimulate the secretion of adrenal androgens. From this it can be pointed out that with the *lack* of ovarian estrogen there is a relative excess of other adrenal androgens, such as testosterone (T), dihydrotestosterone (DHT) and androstenedione (A), the major precursors to extraglandular estrone production.

EXOGENOUS ESTROGEN—IN ANIMALS

The only spontaneous occurrence of endometrial carcinoma in animals is in the rabbit and was reported in 1910 by Boycott (12), in 1911 by Leith (104) and Marie (116) and 2 years later by Stilling (158). Since these early reports there have been many others (17, 58, 59, 129, 130, 132, 136, 180). Greene and Saxton (58) (1938) reported 83 instances of adenoma or adenocarcinoma of the endometrium in their stock of rabbits. Burrows (17) in 1940 found among 25 unmated female rabbits of mixed breeds, which had lived for 900 days or longer, 15 animals (60%) who died with spontaneous uterine adenocarcinoma (normal life span for rabbits is 8 years). Whatever factors are involved, aging seems to play a role. A similar relationship in the spontaneous occurrence of adenomatous cystic hyperplasia of the endometrium was also observed in mice and reported by Malinin (114) in 1972. Here the incidence also increased with age, though no carcinomas were found.

The experimental induction of neoplastic change using estrogens has been attempted in many animal species. The first was reported by Zondek (186) (1936) in the rabbit, and in 1937 Nelson (122) described endometrial hyperplasia in the guinea pig, while a similar change was noted in aged mice (26). Endometrial carcinoma was induced in mice and rats under continuous estrogen, but it necessitated the use of methylcholanthrene (11, 95, 165). There is, however, a report of endometrial carcinoma in mice induced by the use of only estrogen when fed continuously for over a year (162). Munoz (120) found endometrial carcinoma in inbred and non-inbred mice from the National Cancer Institute between 1950–1967. All the mice were old and many had been treated previously with estrogen to promote the development of mammary tumors.

The often quoted work of Meissner, Sommers

and Sherman (119) in 1957 produced 6 endometrial cancers in rabbits given stilbestrol while none was noted in control or non-stilbestrol treated rabbits. The alloxan induced diabetes in some of these animals seemed to have no statistical significance in the incidence of cancer.

O'Shea (125) was able to produce proliferative lesions of serous membranes in ovariectomized female and entire male dogs using stilbestrol. Here only the genital serosa was affected, though no mention was made of endometrial changes.

Finally, Scott and Wharton (141) (1955) induced adenomatous hyperplasia in monkeys with diethylstilbestrol. Previously Hartman in 1941 used various estrogens in oil in 20 female Rhesus monkeys and felt that there were indications of the production of adrenal injury and noted one case of endometrial hyperplasia. No malignant endometrial changes have been induced in the subhuman primates to date with the use of estrogens. McClure (117) did, however, as noted above in the dog (125), produce metastatic mesotheliomas of the uterine serosa in squirrel monkeys by the use of prolonged stilbestrol treatment. This malignant uterine mesothelioma was felt not to be of endometrial origin. Even with the use of stilbestrol and carcinogenic hydrocarbons, Pfeiffer (128) was unable to produce corpus cancer in monkeys. Gusberg (68) feels the inability to produce estrogen induced endometrial cancer in the monkey is due to two factors: "(1) the clear species variation of endometrial response to hormonal stimulation, i.e., the lack of the appropriate genetic substrate in these animals, and (2) the relatively short duration of most experiments of this type in these relatively long lived animals." The latter must be underlined since it again appears that time and/or aging has notable importance.

EXOGENOUS ESTROGEN—IN HUMANS

Ten years after the isolation of estrogen by Allen, Kaufmann (96) reported the first use of estrogenic hormone to produce cyclic endometrial changes in ovariectomized women and 5 years later in 1938 Dodds (35) announced the discovery of stilbestrol. This same year it was used therapeutically in pregnant women (149). Since then reports of patients who have developed endometrial carcinoma from long term estrogen treatment have appeared in the literature.

A continued excess of estrogen leads to hyperemia, edema and hypertrophy of the uterus including the endometrium. The consequence here is hyperplasia which may be the forerunner of endometrial cancer (18). As early as 1940 hyperplasia of the endometrium was induced by the administration of estrogen (187) and hyperplasia has been associated with the later development of endometrial adenocarcinoma. This event is documented by Hertig (81, 82, 150) and Gusberg (64, 65, 66, 67). Both Geist (51) in 1939 and Allen (5) in 1940 voiced their fears of the possible carcinogenic effect of estrogenic substance on the breast and uterus, with Allen criticizing its indiscriminate use.

Prolonged estrogen therapy was strongly implicated with the first case report in 1946 by Freemont-Smith (49) in a patient who was administered intramuscular estrone for 5 years and stilbestrol for 19 years (crystalline estrogen added the last 9 years). Similar claims have been made by others (14, 64, 66, 90, 93, 126, 159, 173) and this possible carcinogenic effect of estrogen is said to be operative in women predisposed by hereditary factors (24, 176). Prior reports associating exogenous estrogen to malignant transformation of the endometrium have failed to demonstrate a higher incidence than in the untreated women (181). Likewise, the fears related to the development of breast carcinoma secondary to estrogen therapy have also failed documentation (16, 27), though Leis (103) feels that genetic factors are of cardinal importance and the loss of the host's immunologic defense mechanism may permit breast cancer, with estrogens a powerful promoter of carcinogenesis. McFadyen, et al (118) also found a significantly higher testosterone level in breast cancer patients than the matched controls.

Ovarian agenesis, described by Turner in 1938 (172), identifies a group of patients in whom prolonged stilbestrol therapy has frequently been used. Since that time 6 cases of carcinoma of the endometrium have been reported (19, 27, 36, 142, 179). All were on stilbestrol therapy and for four or more years. Cutler, et al (27) reported 24 patients with gonadal dysgenesis treated for five or more years with stilbestrol, in whom 2 and possibly 3 patients developed endometrial carcinoma. Three of the reported 6 cases had an unusual mixed or adenosquamous type and the average age was 30 years. Because of the early age of onset and the incidence stated in Cutler's report, it suggests a carcinogenic role of stilbes-

trol in these patients. There is, however, a case report of endometrial carcinoma in a 79-year-old patient with ovarian agenesis who at no time in her life had received exogenous hormones (57). (This tumor had a clear cell appearance.) The latter case may very well exemplify the need for (1) a susceptible subject and (2) aging. It is obvious that ovarian agenesis does not indicate an absence of extragonadal estrogen production as has been discussed earlier. The factor of time was also noted by Pacheco and Kempers (127) since two-thirds of all the endometrial neoplasms they encountered were in patients 11 or more years past the menopause.

Reid and Shirley (133) published a case of endometrial carcinoma after 17 years of stilbestrol therapy as replacement after pituitary necrosis (Sheehan's syndrome). Since the above patients were all treated with diethylstilbestrol (DES) there may be an added factor introduced as indicated by the development of vaginal and cervical clear cell adenocarcinoma in young patients with prenatal exposure to DES or other non-steroidal estrogens. (20, 52, 62, 73, 78, 79, 80, 167) A review (105) of the California Tumor Registry from 1950–1969 showed a relative increase in cancer of the vagina, corpus uteri, prostate, testis and bladder (in males) in the 10–19 year age group, but no such increase appeared for cancer of the vulva, ovary, cervix, breast, stomach, colon, rectum and bladder (in females). It was speculated that this may indicate a possible relation between stilbestrol and other sites of cancer besides the vagina.

Lyon and Frisch (109, 110) observed that long term sequential oral contraceptives have been implicated in the development of adenocarcinoma in young women with the usage ranging from 4–12 years. These carcinomas were well differentiated and, interestingly, one patient had an associated carcinoma of the breast while one patient had a twin sister who used sequential oral contraceptives for 9 years and was found to have atypical adenomatous hyperplasia. It was pointed out that the estrogen form in this preparation is ethinyl estradiol.

Though estrogens can produce endometrial changes, including atypical endometrial hyperplasia, these changes are reversed when the hormones are withdrawn (174). Therefore, it would still appear that exogenous estrogens continue to be suspected as a factor in the development of endometrial carcinoma, but incontrovertible proof seems lacking.

In December of 1975 two studies were published that had a significant clinical effect and brought about a reassessment of estrogen replacement therapy. Ziel and Finkle (184) on the premise that estrone might be associated with the development of endometrial cancer, investigated patients who were using conjugated estrogens. This use was recorded for 57 percent of 94 patients with endometrial carcinoma, but only 15 percent of controls. They felt the risk ratio increased with the duration of exposure. (5.6 for 1 to 4.9 years of exposure and 13.9 for seven or more years). This factor of duration of exposure is consistent with previously mentioned animal and human studies. It was felt by the authors that these data suggest an etiologic role in endometrial carcinoma.

At the same time Smith, et al (148) retrospectively compared 317 patients with adenocarcinoma with an equal number of controls having other gynecologic neoplasms. They found that 152 patients with endometrial cancer used estrogens (48%) while only 54 of the control patients had used estrogens (17%). They calculated the relative risk, "completely unadjusted," to 4.5 of cancer developing among women exposed to estrogen therapy as compared to those not exposed. This investigation did not address dosage, length of administration or type of estrogen. Noteworthy is the observation that patients with hypertension or obesity had a decreased risk of endometrial cancer association (though still greater than the controls) and that the related risk was highest for women classified as normal. This is not easily interpreted, but one wonders if exogenous estrogen might not stimulate adrenal androgen production as noted by Abraham (1). This stimulation produces an increase of $\Delta 5$ steroids whereas with the lack of ovarian estrogens there was an increase in androgenic precursors to extraglandular estrone production.

Mack, et al (113) reviewed all cases of endometrial cancer in an affluent retirement community and noted a risk ratio for any estrogen use to be 8.0 and found an increase of both invasive and non-invasive cancer with a dose-response effect demonstrated.

The association is further supported by Weiss (177) who referenced unpublished data indicating a 1 per 1000 per year risk of endometrial carcinoma in postmenopausal women who did not use estrogens, with a 4–8 per 1000 per year risk for estrogen users. In response to these retrospective studies the Food and Drug Adminis-

tration (45) stated early in 1976, that "prolonged use of estrogens by postmenopausal women apparently is associated with a marked increased risk of cancer of the endometrium." In view of this suggested greater risk and the known increased estrogen usage, an increased incidence in endometrial carcinoma should be observed. Cramer (25) found he was unable to document a significant increase in the absolute incidence of endometrial cancer in the United States from 1947 and 1970 in either whites or blacks, but subsequently there seemed to be an apparent 50 percent increase in the incidence of invasive endometrial cancer between 1969 and 1974 as reported from the California Tumor Registry by Austin (8). It was concluded that the increase is in fact real and "due to the relatively recent introduction of some carcinogen or carcinogens into the white affluent postmenopausal females." Weiss, et al (178) also reported a sharp rise in the United States in the 1970's. These data finally prompted the FDA in September 1976 (48) to require a change in labeling directed to the physician and patient. It stated that estrogens be used only for treating patients with moderate to severe vasomotor symptoms and administered in the lowest effective dose cyclically, and discontinued or reduced in dosage at regular intervals to assess whether it is still needed. It was concluded that "there is no evidence at the present that 'natural' estrogens are more or less hazardous than 'synthetic' estrogens at equiestrogenic doses." Still a more recent report has been published specifically pointing to estrone, noting conjugated estrogen use in 70 percent of endometrial carcinoma patients, while only used by 23 percent of matched control subjects. Parenthetically this report found an earlier onset by 5 years over those cancer patients not taking systemic estrogen (185).

Ryan (137) felt the available data have not established that administration of estrone sulfate is a form of estrogen which is uniquely associated with cancer and that it is still not known whether one type of synthetic or natural estrogen should be more or less suspect. This seems consistent with the observation of Siiteri, et al (147) who stated in 1974 that it is still not known if the proliferative response of estrogen target cells differs for estrone and estradiol. An additional reason for not suspecting any one form of oral estrogen could be that even orally administered micronized 17β-estradiol (E_2) causes up to a 2000 percent increase in serum concentration of estrone (E_1) as reported by Yen (183). It is felt that micronized E_2 peros is readily absorbed, but that during this process a significant portion of the hormone is converted to E_1 by the gastrointestinal tract.

Many caveats were published (54, 56, 121, 143) to modulate what seems to be an oversimplified thesis. Caution was suggested in separating reversible hyperplasia from true neoplasia (56) and that perimenopausal estrogen usage may be placing the matter too late, since the cancer tendency may be set as early as the age of 30 (143). Another contradictory report noted a series of 100 endometrial carcinoma patients where only 18 percent of the patients were on estrogen therapy (54).

For the student of scientific argument Gordan and Greenberg (55) published an exceedingly comprehensive clinical, statistical and epidemiologic evaluation. It was felt that the recent studies were not adequately well designed to warrant such a strong belief of causation and that retrospective studies of this kind can never prove cause; "it can show only an association between the two factors." "The acquisition of an unbiased control group is the prime requirement if valid conclusions are to be made" was a restatement from Dunn and Bradbury (37) and this series was felt to be the only well controlled study of estrogen and endometrial cancer. Here only 28.6 percent of those found to have endometrial cancer had received estrogen therapy while the bleeding controls in the study group had a 27.5 percent estrogen usage rate.

It seems there is an association of estrogen therapy and the development of endometrial carcinoma, but the role estrogen plays is unclear. There is real doubt that this role is carcinogenic, but it is more likely one added factor to an already spontaneous event.

RECEPTOR SITES

Target organs for estrogen have been shown to be the uterus, vagina, anterior pituitary, hypothalamus, breast and breast tumors (41, 53, 91, 155, 161). The target organ accumulation of hormone is thought to be due to a binding protein ("receptor" protein) in the cytoplasma of the receptor cell. The early studies were carried out using ^{3}H-hexestrol (41), but later Eisenfeld noted that other drugs can attach to the estradiol (E_2) binding sites and are diethylstilbestrol, clomiphene, MER-25,* and ethinyl estradiol,

while mestranol does not (42). Mestranol apparently requires metabolism in the body to ethinyl estradiol prior to its binding (92).

Estradiol enters the cell and attaches to the estradiol binding protein an 8S-"receptor" protein in the cytoplasm (R_c). The estrogen-binding protein complex crosses the nuclear membrane and attaches to an "acceptor" protein associated with chromatin. In the uterus there is noted to be first an increased RNA synthesis followed by increased protein synthesis. This modulated RNA synthesis is thought to contain portions with messenger RNA activity (72). Thus activation of transcription by the steroid-receptor-acceptor complex is the most likely hypothesis (89). The effect of estrogen on cytoplasmic protein seems indirect, with effects of the hormone on genetic transcription, resulting in a regulation of the rate and amount of genetic translation (72).

Estradiol seems to enhance the biosynthesis of its own receptors in the uterus. This role was proposed by Eisenfeld and Axelrod (40) and recently confirmed in the monkey by Elsner (43), demonstrating that "the cellular distribution, sedimentation characteristics and levels of specific estradiol receptors are influenced by the hormonal status of the primate."

Trams, et al (166) found that the concentrations of spare estrogen receptors were markedly higher during the proliferative phase as compared with the secretory phase of the menstrual cycle in humans and were inversely correlated with the concentration of free estrogen in the blood. They felt this finding could be explained by "saturated" receptor sites, since the decreased binding capacity correlated with the increase in endogenous estrogen production. This point is still unclear. Tseng and Gurpide (170) concluded that the lower level of E_2 in secretory endometrium indicated that the concentration of E_2 receptors in human endometrium declines significantly during the secretory phase of the menstrual cycle and did not imply saturation. Evidence indicates that progesterone may also act at the nuclear transcription level in the stimulation of protein synthesis (70), but more recently Nordqvist (123) demonstrated rapid and pronounced inhibitory effects on DNA and RNA synthesis in tissue suspensions of normal endometrium after the administration of progesterone. Tseng and Gurpide (171) observed a reduction of E_2 receptor level in patients pretreated with medroxyprogesterone acetate for 2–4 days in the follicular phase. This was also demonstrated in mice using progesterone in oil (84). Progesterone and other estrogen antagonists inhibit estrogen action by interfering with the replenishment of cytoplasmic receptor (R_c) (85) and probably account for the reduced E_2 receptors in the secretory phase.

Some isolated observations are that: (1) Estrone (E_1) is more abundent and more easily removed from the nuclei of human endometrial slices than E_2. (2) Progesterone (P) behaves as E_1 rather than E_2 in similar studies (168). (3) Contrary to animal studies "E_1 and E_2 are extensively interconverted in the human endometrium and both compounds must be considered when studying mechanism of action of the hormone in this tissue." (168) These interconversions of E_1 and E_2 take place throughout the menstrual cycle (169). (4) Neither progesterone nor estrone compete directly with estradiol (5). Estriol (E_3) is a potent inhibitor of estradiol binding to a specific end organ receptor protein, suggesting a more passive role of this material in metabolic processes (13, 40). It is possible that E_2 and E_3 bind to the same protein, but not necessarily to the same site. Some feel therefore that estriol may protect the endometrium from growth stimulation (75).

Estrone, reportedly as estrone-receptor complex, dissociates readily and it is implied that estrone (E_1) is not active (145), but because of large quantities of E_1 associated with the "particulate" fraction, by inference, with the nuclear site of action of the estrogen, might be taken as presumptive evidence that estrone is itself active (50). Siiteri and MacDonald (146) more recently stated that estrone is the hormone "that interacts on a predetermined genetic predilection for the development of endometrial anaplasia." With this predilection a normal quantity of postmenopausal estrone is a sufficient provocateur, whereas even with a lesser genetic risk the increased quantity of estrone produced in an individual with certain constitutional stigmata may bring about neoplasia.

One effect not previously mentioned is the mitogenic action of estradiol. Chen, et al (23) observed that E_2 increased thymidine incorporation into DNA and increased cell division in tissue culture of human endometrial and myometrial cells. These cell colonies showed a significantly higher efficacy of colony formation (in-

crease of about 60% and 90% for endometrial and myometrial cell colonies respectively). This mitogenic effect of E_2 persisted for several days. Estrone can effect the same early biochemical functions in target cells as estradiol (146, 147). This seems to hold true especially in the absence of E_2 though prolonged exposure to either E_2 or E_1 may ultimately lead to abnormal proliferation and neoplasia by the same mechanisms. The question of whether the proliferative response of target cells differs for estrone and estradiol is still unanswered. It is felt however that true uterine growth requires the direct and prolonged influence of the nuclear estrogen-receptor complex (85).

Evans, et al (46) observed that the concentration of estrogen receptors in postmenopausal women is similar to that seen in proliferative phase endometrium. The receptors in hyperplastic proliferative endometrium of presumed anovulatory cycles are significantly less than in normal proliferative endometrium. Cystic hyperplasia reveals a wide range of values while endometrial carcinoma correlated with the different stage of differentiation of the tumor, well differentiated having a higher concentration of receptors than poorly differentiated tumors (46). Carcinoma of the cervix exhibits very low levels of estrogen receptors while several tumors of the vagina and vulva virtually lack estrogen receptors (164). These same investigators found in 9 cases of endometrial carcinoma 4 tumors with very high receptor content, 3 tumors with intermediate levels and in 2 tumors receptors were essentially absent. The receptors again related directly to the maturity of the tumor.

Receptors for estrogen in the endometrium hold much information as to the genesis of corpus cancer, but again it must be stated that the effect of long term unopposed E_1 stimulation on nuclear activity needs further investigation.

SUMMARY

1. It has become evident that the estrogen secreting tumors of the ovary are associated with endometrial carcinoma, but this association is most easily observed in the postmenopausal patient where the incidence of carcinoma has been reported at 10.3 percent (102) to 24 percent (83).

2. The most consistent association of endometrial carcinoma is with polycystic ovarian disease, where 19 (34), 21 (152), and 25 percent (150) of young women with endometrial carcinoma had Stein-Leventhal syndrome (67).

3. A very significant discovery became known in 1967 when the peripheral aromatization of Δ4 androstenedione to estrone was reported by Kase (94) and MacDonald (111, 112). Since that time we have learned that endometrial carcinoma patients have an increased peripheral conversion (139) (0.1% compared to 0.027%), which is similar to that found in obese and aging patients, by Hemsell, et al (77). This can be 2 to 4 times greater than the young adult or the patient without cancer. Estrone produced peripherally in normal postmenopausal women can amount to 40–60 μg/day and rise as high as 120–180 μg/day in the endometrial neoplasia group (39). Similarly patients with polycystic ovary disease, hyperthecosis and lipoid cell tumors of the ovary demonstrate androgen excess with extraglandular conversion to estrone (2).

4. It has become apparent that the principal estrogen in the postmenopausal patient is estrone and that the estrone-estradiol ratio in the serum is higher in postmenopausal women with corpus cancer than similar patients without cancer (135). Clearly, we must find the effect of this estrone excess at the nuclear "acceptor" level; and does this imbalance create a hormonal environment conducive to the development of endometrial carcinoma when age (an extremely important factor) and an oncogenic agent are added?

5. With the lack of ovarian estrogen there is a relative excess of adrenal testosterone, dihydrotestosterone and Δ4 androstenedione, the available precursors of extraglandular estrone (1).

6. With the passage of time it appears that endometrial carcinoma is associated with hypothalamic "hyperactivity" (31) which exhibits immunologic-biologic dissociation of LH as previously observed in persistent trophoblastic disease when measuring hCG. The significance of this is still unknown. In a like fashion a significant number of the at risk polycystic ovary disease patients have an increased LH secretion.

7. Patient susceptibility is required as seen in animal experiments where prolonged administration of stilbestrol is used and still only rabbits and mice developed a malignant change.

8. Long term exogenous estrogen appears to have caused malignant changes in the endometrium, but it was universally given over a pro-

longed period (4 or more years). The recent retrospective studies demonstrate an association of oral estrogen therapy with endometrial cancer, but prospective studies investigating dose and duration of all estrogen preparations need to be undertaken.

9. Finally, it appears likely that if there is (1) *adrenal androgen production of androstenedione*, associated with a normal to increased (2) *peripheral conversion to estrone* a hormonal milieu is created, (possibly acting as a mitogen (23) at the chromatin level), which can lead to endometrial carcinoma in a (3) *susceptible patient* (24, 176) if this hormonal alteration persists for a (4) *period of time*. The role of elevated immunologic LH is problematical and needs further clarification as does the effect of long term exogenous estrogen replacement in patients with an intact uterus.

"And diff'ring judgements serve but to declare that truth lies somewhere, if we knew but where." William Cowper (1731–1800). Hope, $1_{.3}$

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