STEROIDOGENESIS IN MENOPAUSE AND ENDOMETRIAL PATHOLOGY

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SUMMARY

After considering the postmenopausal variations in the hypothalamic-hypophyseal-ovarian feed-back system, the Authors review the medical literature about ovarian and adrenal contribution to postmenopausal steroidogenesis.

Comparisons are made between postmenopausal sex-hormone levels in controls and in endometrial cancer affected patients; estradiol is gien the main attention: its higher level in cancer patients seems closely related to their higher mean weight; indeed, no estradiol level difference is found between patients and controls correctly matched as to the body weight.

The possible role of estradiol in the pathogenesis of endometrial cancer is then discussed basing on data obtained from women affected with diseases generally considered to be estrogen dependent.

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The absence of evolutive follicles and the marked diminution of primordial follicles are the main morpho-functional characteristics of postmenopausal ovary [1]; 17-beta-estradiol and inhibin, the most important factors in gonadotrophin secretion feed-back system, are consequently lost [2]. The daily secretion of endogenous LhRh highly increases, and so do Fsh plasma levels which are constantly higher than their ovulatory peak; Lh plasma levels, on the contrary, don't overcome the ovulatory values [3], as they are modulated, though at a lesser degree, by estrogens originating from extraglandular production: this feed-back mechanism doesn't require inhibin action, which is essential in Fsh control. The feed-back system, in fact, seems to persist unaltered, as estrogens receptors probably survive beyond the drop of their own inducers [4]; their persistence also in peripheral tissues [4] accounts for the possibility of target tissue response to estrogen hormones wherever produced, even after long periods of estrogen deprivation.

The lack of progesterone, the natural modulator of estrogen activity, makes postmenopausal hormonal situation a matter of great clinical interest; many studies have been carried out to quantify and qualify the synthesis and origin of sex-steroids and their variations in hormone-dependent diseases. Postmenopausal estrogens seem mostly derive from the peripheral conversion of androgen precursors, mainly androstenedione [5]: inhibition [6, 7, 8] and stimulation [6, 7, 9, 10] dynamic tests proved a prevailing adrenal origin for them, but also the ovary seems to produce androgen precursors; the hormonal levels in blood drawn from the ovarian vein [11, 12] and from patients who were ooforectomized [3, 7, 13] and then hCG stimulated [7], seem to confirm the ovarian origin of 50% of circulating testosterone and 30% of circulating dehydroepiandrosterone. Whatever is their origin, hormonal plasma levels are much lower

than in the ovulatory cycle; on the other hand, their levels in the first four postmenopausal years seem significantly higher ([3, 5]) than in the following years. A negative correlation is reported between postmenopausal age and E1 ([14]), E2 ([14]), DHEA ([3]), DHT ([3]) plasma levels, but other Authors deny it ([5, 15]); there is, on the contrary, a general agreement on testosterone plasma level stability, probably due to a slower catabolism of the hormone ([3]).

When the discussion is limited to estrogens, mean postmenopausal estrone plasma levels are significantly higher than estradiol ones: for this reason E1 has long been considered the typical hormone of the postmenopause, and as such been studied in relation to the genesis of endometrial cancer. The lack of demonstration of nuclear specific estrone receptors in the endometrium ([15]) and the significant correlation ([5, 15]) between E1 and E2 plasma levels, made the searchers direct their attention to estradiol, whose biological activity is undoubtedly higher and whose nuclear receptors have been demonstrated also in the endometrial cancer cell. Since then, many data emerged in literature, which correlate estrogen (E1 and E2) levels to endometrial cancer and its risk factors; the conversion rate of Δ4 to E1, inversely related to Δ4 plasma levels ([8, 13, 16]), is not seen to increase in endometrial cancer if the patients and controls are matched for their body weight ([16]); the rate Δ4/E1, which is considered a satisfactory indicator of the conversion rate, is significantly correlated with the body weight and with the percentage of ideal weight ([5, 15]). A significant correlation with the two latter parameters is also evidenced for E1 and E2 ([15]).

An increase in E1 and E2 ([19]) and a diminution in Fsh plasma levels were found in endometrial cancer affected pa-

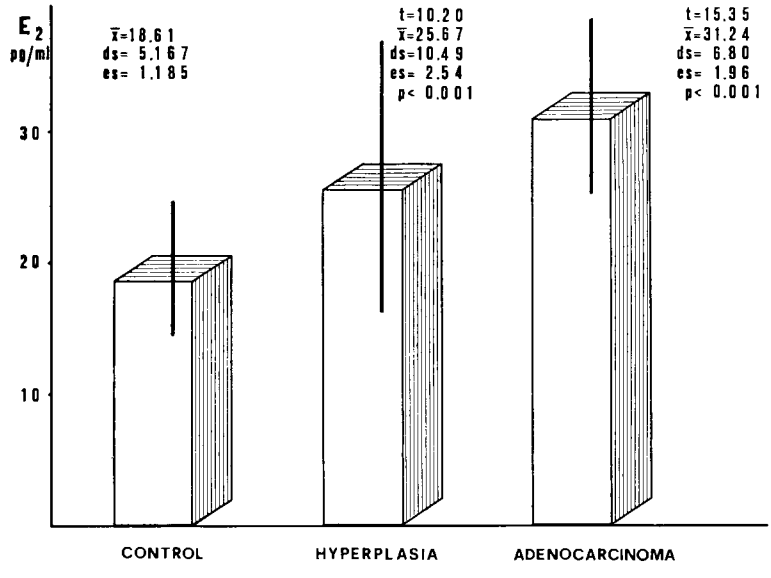

Fig. 1. — E2 plasma levels in patients affected with endometrial cancer (right) and endometrial hyperplasia (centre), compared to controls (left).

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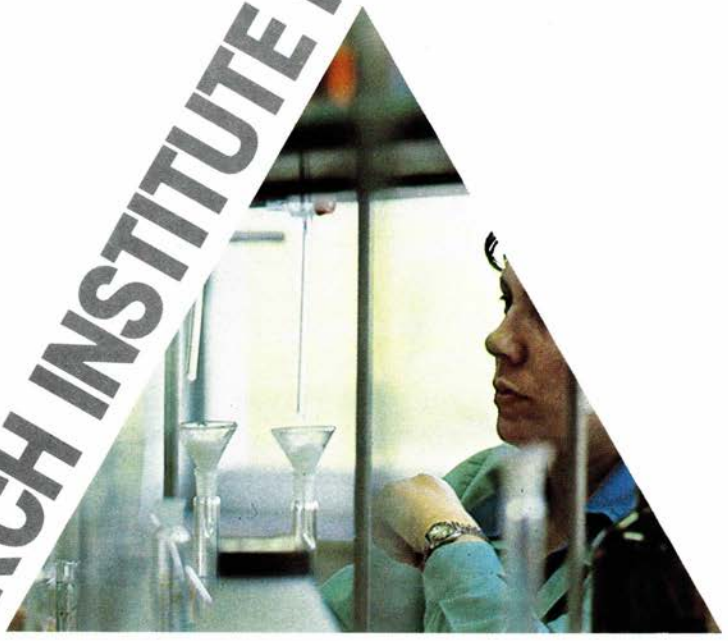

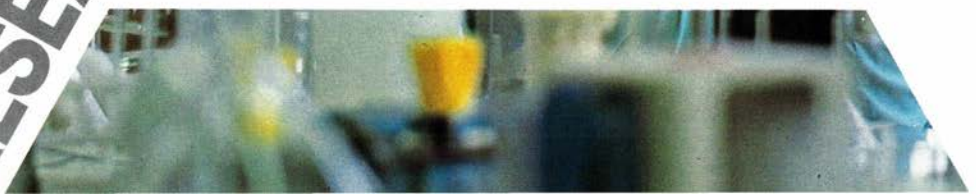

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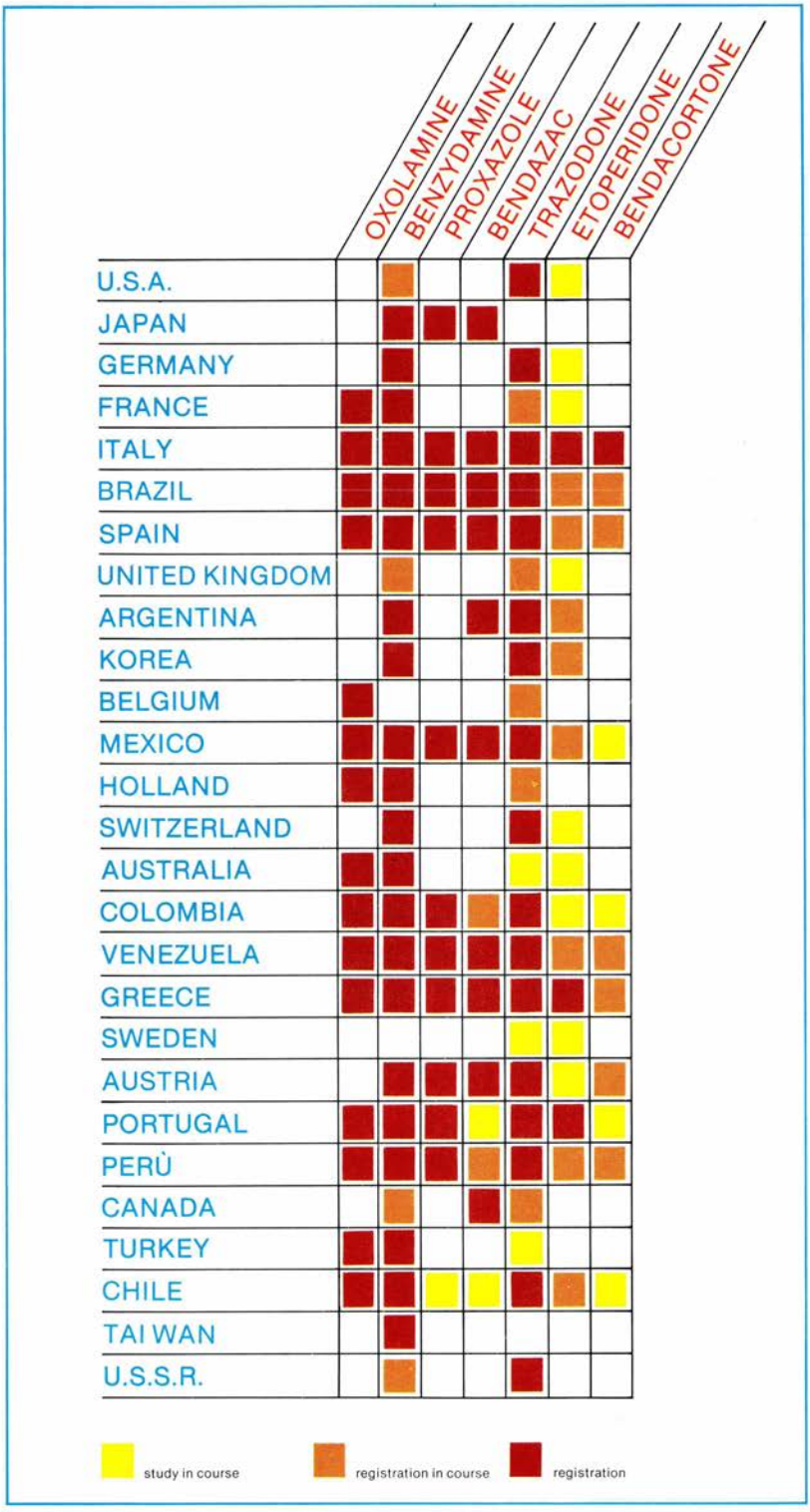

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tients, but their weights were higher than the controls' ([17]); our group obtained similar results and presented the data ([18]) in a study extended to endometrial hyperplasia, which is generally considered an estrogen dependent precancerous lesion (fig. 1).

In a study conducted on thirty-five postmenopausal women affected with endometrial cancer compared to controls matched for age and body weight, Judd and Coworkers ([15]) show that dehidroepiandrosterone, androstenedione, testosterone, estrone and estradiol values are quite similar in the two groups, and state that every variation in estrogen plasma levels should be attributed to the factor obesity. If this were confirmed, the role of estrogens in endometrial cancer pathogenesis would be less important: they could simply act as cofactors on an already sensitized ground; an endocrine study of this neoplasia could, at last, be useless if we don't identify first its true risk factors, the most important of which seems to be obesity.

After these considerations and in view of a correct identification of subjects at risk, made even more urgent by the increasing demand for hormonal therapy in menopause, we are going to report the results of a study we carried out on two groups of postmenopausal patients: twenty were free from any endometrial disease (group A), and twenty were affected with endometrial cancer (group B); we measured in them the mean plasma levels of E2, significantly correlated to E1 ([5, 15]), and testosterone, significantly correlated to androstenedione ([5]).

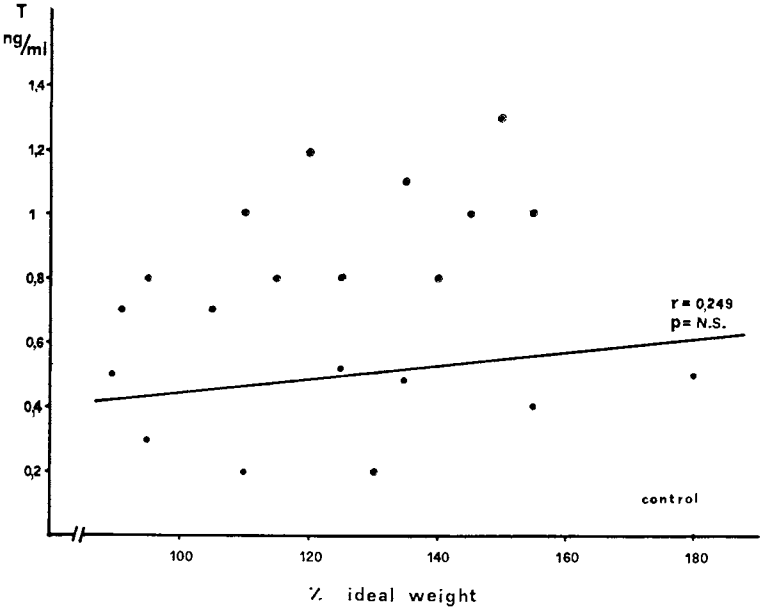

Fig. 2. — Correlation between testosterone plasma levels and percentage of ideal weight in the controls.

The Radio-immuno Assay was performed by the use of Serono-Biodata Kits, without a previous chromatographic separation. Blood samples were drawn from the cubital vein between 8AM and 10AM of three consecutive days; the expressed

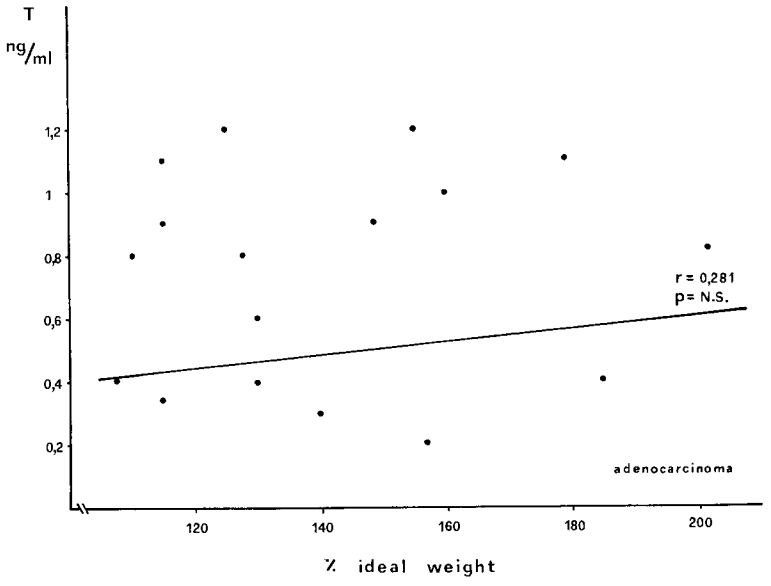

Fig. 3. — Correlation between testosterone plasma levels and percentage of ideal weight in the cancer patients.

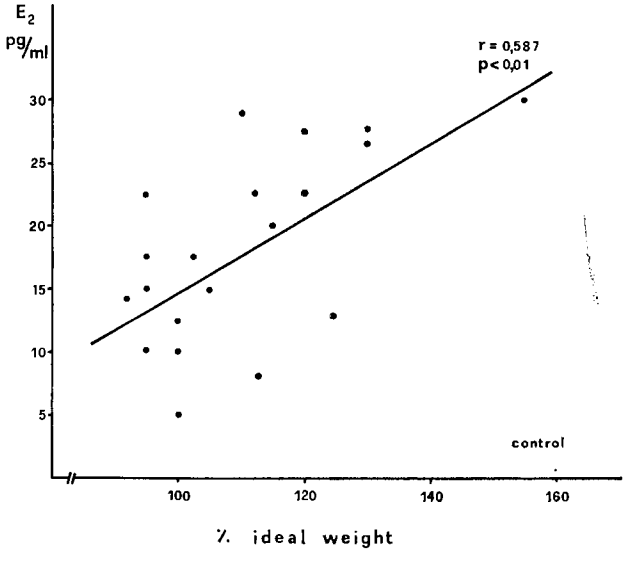

Fig. 4. — Correlation between estradiol plasma levels and percentage of ideal weight in the controls.

values, obtained from averaging the data from the three assays, were: for the group A: E2 = 18.61 ± 5.16 (SD) pg/ml; T = 0.66 ± 0.21 (SD) ng/ml; for the group B: E2 = 30.46 ± 6.45 (SD) pg/ml; T = 0.65 ± 0.26 (SD) ng/ml. The mean age was 57.05 ± 1.75 (SE) y.rs in the controls; 59.23 ± 1.86 (SE) y.rs in cancer patients. The difference between plasma levels in the group B; the correlation coefficient for estradiol is expressed by r = 0.587 ($p < 0.01$) in the group A, and by r = 0.596 ($p < 0.01$) in the group B (figs. 2, 3, 4, 5).

We can conclude that, in menopause, estradiol levels are correlated with the percentage of ideal weight both in the affected and in the disease free patients, while no correlation is seen for testoste-

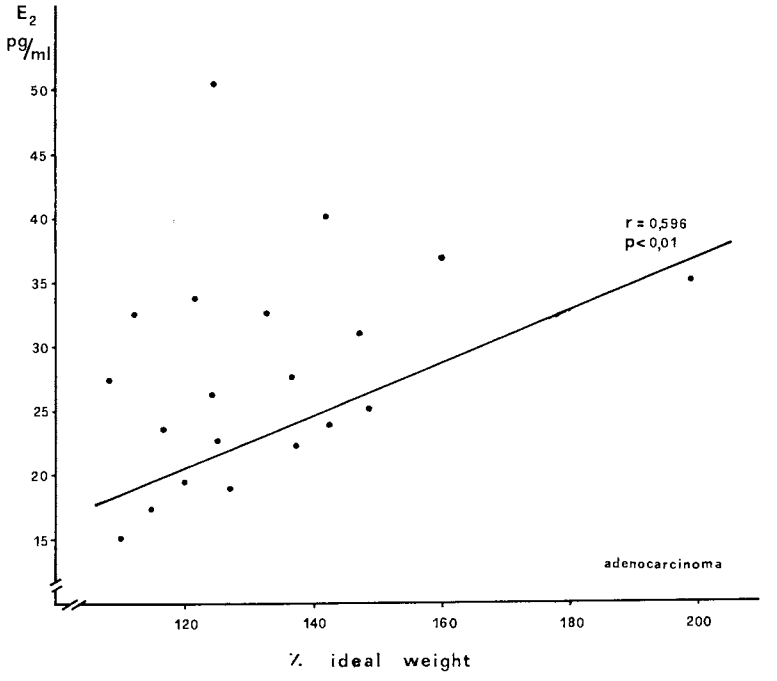

Fig. 5. — Correlation between estradiol plasma levels and percentage of ideal weight in the cancer patients.

the two groups is statistically significant as to estradiol ($p < 0.001$), while it is not as to testosterone. Correlating the mean levels of the two hormones with the percentage of ideal weight, calculated in each patient, in relation to height and age as is suggested in Geigy Tables ([20]), the correlation coefficient for testosterone is expressed by r = 0.249 (p = NS) in the group A, and by r = 0.281 (p = NS) in rone. The higher estradiol plasma levels in the affected patients should be ascribed to the fact that the range of values representing the percentage of ideal weight is higher in them than in the controls (group A = 94-155%; group B = 108-202%).

Our data, at last, though limited to the study of two only hormones, confirm the opinion expressed by Judd ([15]) and encourage to identify endometrial cancer

predisposing ground and more correctly evaluate the risk factors. Just to this purpose, in a work we considered extremely interesting, Geller ([4]) found a postclimateric preferential Lh release after LhRh stimulation test in women affected with policystic ovary, endometriosis and breast cancer, estrogen dependent considered diseases. The dynamic test in Geller's study is frequently associated with microdeformations of the sella turcica that might correspond to Lh-secreting pituitary focal hyperplasias, and with higher levels of E_2 receptors in target tissues.

In a study on twenty patients affected with endometrial cancer ([21]) we found similar results after LhRh stimulation test; Lh response area integral was greater than Fsh response area integral; Fsh release prevailed in the controls as one aspect in normal postmenopausal subjects. This particular kind of response seems to be due to an higher concentration, in the pituitary gland, of estrogen induced LhRh receptors, which appears correlated to the intensity and duration of estrogen impregnation itself ([4]). The latter would equally account for the induction of target tissue estradiol receptors, which, produced in amounts proportional to the intensity and duration of the stimulus, would made at risk a woman whose endocrine situation is otherwise normal.

Further studies are certainly opportune, but we think we can conclude that an effective prevention of endometrial cancer can already be done by treating every hyperestrinic state, whenever developing, which should be detected through a correct methodologic approach including the identification of the main risk factors as one of the most important diagnostic steps.

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