Eur J Cancer Clin Oncol, Vol. 22, No. 8, pp. 953–961, 1986.
Printed in Great Britain.

0277-5379/86$3.00+0.00
Pergamon Journals Ltd.

The Relationship between Oestradiol Metabolism and Adrenal Steroids in the Endometrium of Postmenopausal Women with and without Endometrial Cancer

R. C. BONNEY, M. J. SCANLON, D. L. JONES, M. J. REED, M. C. ANDERSON* and V. H. T. JAMES

*Department of Chemical Pathology, St. Mary's Hospital Medical School, London W2 and *Department of Histopathology, Samaritan Hospital for Women, London NW1, U.K.*

Abstract—*The aim of the present study was to investigate the hypothesis that adrenal androgens are contributory to the development of endometrial cancer either by the oestrogenic action of 5-androstene-3β, 17β-diol (androstenediol) or through the inhibition of oestradiol metabolism. Concentrations of androstenediol, dehydroepiandrosterone (DHA), DHA sulphate (DHAS), oestrone and oestradiol were measured in plasma and endometrium from postmenopausal women with and without endometrial cancer. There was no difference between normal postmenopausal women and endometrial cancer patients with respect to either tissue or plasma adrenal androgens although there was a tendency for plasma DHAS levels to be increased in cancer patients (normal women: 640 ± 156 ng/ml; cancer patients: 808 ± 159 ng/ml). There was a positive correlation between endometrial tissue concentrations of androstenediol and DHA in both normal women ($P < 0.05$) and cancer patients ($P < 0.01$) but for DHAS the relationship was only significant for non-malignant tissue (androstenediol : DHAS, $P < 0.05$; DHA: DHAS, $P < 0.02$). A significant positive correlation was found between all three plasma adrenal androgens for both groups.*

In cancer patients there was a trend towards an inverse correlation between endometrial tissue concentrations of DHAS and the enzyme 17β-hydroxysteroid dehydrogenase (17OHSD) although the relationship was not significant ($r = 0.49$).

In endometrium, oestradiol was present in significantly higher concentrations than oestrone whereas in plasma the reverse was the case. There was also a tendency for plasma oestradiol levels to be elevated in the cancer subjects.

These data do not support a substantial role for adrenal androgens in endometrial cancer but suggest that a relationship may exist between DHAS and 17OHSD and that an imbalance between sulphatase and sulphotransferase activities may be involved.

INTRODUCTION

SEVERAL conditions known to be associated with an increased risk for the development of endometrial cancer are also associated with elevated plasma concentrations of dehydroepiandrosterone sulphate (DHAS). It has been shown for instance that DHAS production is increased in obese women [1]. Also, plasma concentrations of DHAS are raised in patients with hypertension [2], in women with the polycystic ovary syndrome [3] and following oestrogen administration [4]. Furthermore, plasma DHAS concentrations have been reported by Carlstrom *et al.* [5] to be elevated in women with endometrial cancer. The evidence therefore suggests that the disease may be associated with some aspect of adrenal cortical hyperfunction. Since the incidence of endometrial cancer rises markedly following the menopause any endocrine abnormality could be age related.

The unopposed action of oestradiol on the endometrium is the accepted trigger to the development of endometrial hyperplasia and subsequently endometrial cancer. *In vivo* studies in this laboratory [6] have demonstrated a negative correlation between plasma concentrations of DHAS and oestradiol metabolism in postmenopausal women with endometrial cancer, endometrial hyperplasia and cirrhosis. As a result of this finding it was proposed that increased plasma concentrations (and consequently increased tissue concentrations) of DHAS

Accepted 3 January 1986.
Correspondence to Dr. R. C. Bonney.

or a metabolite e.g. 5-androstene-3β,17β-diol (androstenediol) or dehydroepiandrosterone (DHA) could be responsible for the inhibition of oestradiol metabolism in the endometrium and thus increase the exposure of the tissue to oestradiol. Support for this hypothesis comes from *in vitro* studies in which it was shown that in endometrium all three adrenal androgens were effective inhibitors of the enzyme 17β-hydroxysteroid dehydrogenase (17OHSD) [7]. In this tissue the kinetics of the reaction favour the oxidation of oestradiol to oestrone [8] and therefore inhibition of the enzyme will lead to increased tissue concentrations of oestradiol.

The adrenal androgens could also be instrumental in the development of endometrial cancer through the oestrogenic action of androstenediol. This steroid has been shown to bind with relatively high affinity to the oestrogen receptor in rat [9,10] and human [11] uterine tissues and is present in human endometrium in significant amounts [12]. However, concentrations in malignant endometrium have yet to be reported.

In order to pursue these hypotheses we have measured concentrations of androstenediol, DHA, DHAS, oestrone and oestradiol in endometrium and plasma from postmenopausal endometrial cancer patients and normal postmenopausal women. We have subsequently related concentrations of these adrenal androgens to the activity of 17OHSD in the endometrium of cancer patients.

MATERIALS AND METHODS

Subjects and clinical material

Endometrial tissue was obtained from postmenopausal women (aged 49–81 yr) admitted for hysterectomy following diagnosis of endometrial cancer and from postmenopausal women (aged 49–68 yr) who were under investigation for non-malignant gynaecological disorders (postmenopausal bleeding 60%, vaginal hysterectomy repair and prolapse 40%). There was no significant difference between the mean age of the two groups (62.4 ± 9.6 (S.D.) and 56.6 ± 6.8 years respectively). Obesity (i.e. 15% in excess of ideal body wt) was evident in 38% of the cancer patients and 20% of the control group.

Samples of endometrium were transported on ice, snap frozen in an ethanol/dry ice mixture within 30 min of collection and stored at −20°C until required for assay. No difference was observed between tissues frozen in theatre and those transported as described above.

Blood samples were withdrawn into heparinized tubes at the time of operation and plasma was stored as for endometrium.

Steroids

[1,2-^{3}H(N)]-Androst-5-ene-3β, 17β-diol (sp. act. 45 Ci/mmol) and (7-^{3}H(N)]-DHAS (sp. act. 24 Ci/mmol) were obtained from New England Nuclear, Dreieich, F.R.G., while [7-^{3}H]-DHA (sp. act. 14 Ci/mmol), [2,4,6,7-^{3}H]-oestradiol (sp. act. 85 Ci/mmol), [2,4,6,7-^{3}H]-oestrone (sp. act. 89 Ci/mmol) and [4-^{14}C]-oestrone (sp. act. 55.8 mCi/mmol) were purchased from Amersham International plc, Bucks, U.K. Labelled DHA and DHAS were purified before use by thin-layer chromatography (TLC) on silica gel thin-layer plates (E. Merck, Darmstadt, F.R.G.) using the systems chloroform : acetone (90 : 10 by vol.) for [^{3}H] DHA and chloroform : methanol : ammonia (80 : 19.8 : 0.2, by vol.) for [^{3}H] DHAS. The purity of [^{3}H] androstenediol was checked by paper chromatography using iso-octane : tert-butanol : methanol : water (10 : 2 : 7 : 1, by vol.) and that of labelled oestrogens by TLC using dichloromethane : ethyl acetate (80 : 20 by vol.).

Unlabelled steroids with the exception of DHA were purchased from Sigma (London), Poole, Dorset. DHA was obtained from Steraloids Ltd., Croydon, Surrey.

Extraction of androgens from endometrium

The tissue was washed, weighed and homogenized (Polytron homogenizer) in distilled water at a concentration of 80–120 mg tissue/ml. Duplicate aliquots of homogenate (1.0 ml) were equilibrated for 30 min at room temperature with 2000 c.p.m. each of [1,2-^{3}H(N)]-androstenediol and [7-^{3}H] DHA and then extracted for 15 min, using a Multi Vortex shaker, with 5 ml diethyl ether. Organic and aqueous layers were separated by freezing, the aqueous layer was retained for DHAS assay and the ether extracts then chromatographed by TLC using the system dichloromethane : dioxane (94 : 6 by vol.). Areas corresponding to androstenediol and DHA were located by a radiochromatogram scanner (Panax) cut out and eluted overnight in 6 ml diethyl ether and the ether eluates then evaporated to dryness. The androstenediol residues were reconstituted in 0.4 ml assay buffer (0.1 M phosphate buffered saline, pH 7.0 containing 0.1% sodium azide and 0.1% gelatin) and the DHA residues were reconstituted in 1.0 ml ethanol.

Radioimmunoassays

Androgens. Endometrial tissue and plasma concentrations of androstenediol were measured as described in detail elsewhere [12]. Cross-reactivity with other androgens was negligible with the exception of 5-androstane-3β,17β-diol (7.0%), 16α-hydroxy DHA (3.5%) and 4-androstene-3β,17β-

diol (4.4%). Between assay variation was assessed by the assay of aliquots of two plasma pools in successive assays and the coefficients of variation obtained for high and low pools (in 10 assays) were 8.4% (mean 1.22 ± 0.10 (S.D.) ng/ml) and 12.2% (mean 0.57 ± 0.07 ng/ml) respectively. The within assay variation was determined by repeated assay of a tissue homogenate pool (1.16 ± 0.087 ng/g, $n = 8$) and a plasma pool (0.52 ± 0.03 ng/ml, $n = 10$) in a single assay and gave coefficients of variation of 7.4% and 5.9% respectively.

Plasma and tissue concentrations of DHA and DHAS were measured using an antiserum raised in this laboratory against DHA-7-0-carboxymethyloxime-bovine serum albumin. DHAS was assayed after enzyme hydrolysis at pH 4.7 using a sulphatase from *Helix pomatia* (Sigma 9626). These assays have also been fully validated for both endometrium and plasma in this laboratory. Cross reactions of the antiserum with other androgens were negligible with the exception of 16 α-hydroxy DHA (3.4%). Intra-assay coefficients of variation for plasma measurements were 7.4% for DHA ($n = 83$, mean concentration 4.82 ng/ml) and 9.7% for DHAS ($n = 66$, mean concentration of 2.26 μg/ml). For tissue, the intra-assay coefficients of variation were 10.7% for DHA ($n = 32$, mean concentration 69.1 ng/g tissue) and 7.1% for DHAS (n .004 27, mean concentration 118.4 ng/g). Inter-assay coefficients of variation for a plasma pool ($n = 46$) were 8.3% for DHA (mean concentration 5.02 ng/ml) and 9.3% for DHAS (mean concentration 2.11 μg/ml).

Oestrogens. Tissue and plasma concentrations of oestrone and oestradiol were measured according to methods described for plasma [13] and breast tissue [14]. Where possible, duplicate (0.5 ml) aliquots of homogenate were assayed. Thin layer chromatography was included in the assay procedure for oestradiol but not for oestrone. When endometrial samples ($n = 5$) were analysed for oestrone before and after TLC the coefficient of correlation between the two methods was 0.999 ($y = 0.96x + 25.21$). The intra-assay coefficients of variation for tissue oestrone (0.52 ± 0.03 (S.D.) ng/g tissue, $n = 10$) and oestradiol (1.02 ± 0.07 ng/g, $n = 10$) were 7.4% and 5.9% respectively and for plasma oestrone and oestradiol were 10.0% ($n = 12$, concentration range 30–100 pg/ml) and 13.0% ($n = 12$, concentration range 30–120 pg/ml) respectively. The inter-assay coefficients of variation for plasma pools (oestrone: mean concentration 51.5 ± 3.1 pg/ml; oestradiol: mean concentration 43.9 ± 4.0 pg/ml) were 8.0% for oestrone and 13.0% for oestradiol ($n = 10$). When a range of volumes of tissue homogenate was assayed (0.2–0.7 ml) a linear relationship was obtained for both oestrone ($y = 97.4x + 1.19$, $r = 0.967$) and oestradiol ($y = 44.81x + 4.45$, $r = 0.983$). There was also a good correlation between the amount of cold oesrone or oestradiol added to tissue homogenate and the amount recovered ($r = 0.998$ and 0.989 respectively). When 7, 15, 30 or 60 pg unlabelled oestrone were added to 0.5 ml homogenate the amounts recovered in each case were 6.3, 13, 26 and 58 pg ($n = 2$). Similarly for oestradiol the amounts recovered were 9, 13.3, 26 and 67 pg ($n = 2$).

Enzyme activity

The activity of 17OHSD was measured in endometrium by a double isotope method described previously [7].

Expression of results and statistical analysis

Results were expressed as ng/g tissue wet wt and ng or pg/ml plasma. Statistical significance was determined by Student's t-test and correlation coefficients were calculated by standard regression analysis.

RESULTS

Concentrations of androstenediol, DHA and DHAS in endometrium from postmenopausal women with and without endometrial cancer are compared in Fig. 1 and Table 1. It is evident that there was no difference between the two groups of subjects with respect to all three adrenal androgens. Tissue concentrations of DHAS were much more variable than those of the free steroids but again no difference was found.

Concentrations of androstenediol and DHA in plasma from normal women and cancer patients were also in close agreement (Fig. 2 and Table 1). There was a trend towards a discernible difference between the two groups with respect to DHAS concentrations. However, the mean values of 640 ± 156 ng/ml for normal subjects ($n = 10$) and 808 ± 159 ng/ml for cancer subjects ($n = 11$) were not significantly different ($t = 0.77$, d.f. 19). If 1 ml plasma is assumed to be equivalent to 1 g tissue, then tissue concentrations of both androstenediol and DHA were greater than those found for plasma whereas the reverse was true for DHAS (Table 1). No marked differences were noted between the ratios obtained for cancer and non cancer subjects.

The relationship between endometrial tissue concentrations of adrenal androgens in the normal postmenopausal group is presented in Fig. 3. A significant positive correlation was found for all three androgens. The correlation coefficients for concentrations of androstenediol : DHA, androstenediol : DHAS and DHA : DHAS were 0.71 ($P < 0.05$), 0.85 ($P < 0.05$) and 0.92 ($P < 0.02$)

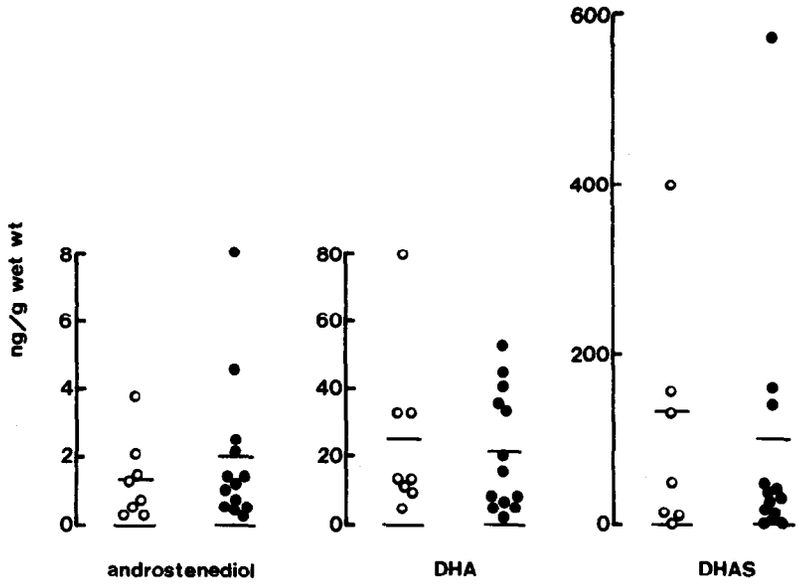

Fig. 1. Concentrations of 5-androstene-3β,17β-diol (androstenediol), dehydroepiandrosterone (DHA) and DHA sulphate (DHAS) in endometrium from normal postmenopausal women (○) and cancer patients (●). Each observation is a mean value of duplicate determinations made on individual subjects. The mean concentration of each androgen (ng/g wet wt tissue) is represented by a horizontal bar. There were no significant differences between the two groups of subjects.

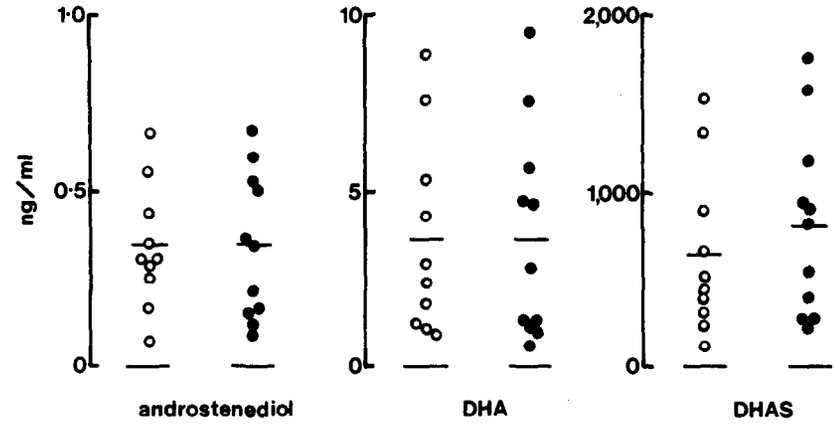

Fig. 2. Concentrations of 5-androstene-3β,17β-diol (androstenediol), dehydroepiandrosterone (DHA) and DHA sulphate (DHAS) in plasma from normal postmenopausal women (○) and cancer patients (●). Each observation is a mean value of duplicate determinations made on individual subjects. The mean concentration of each androgen (ng/ml plasma) is represented by a horizontal bar. There were no significant differences between the two groups of subjects.

Table 1. Concentrations of adrenal androgens in endometrium and plasma from postmenopausal women with and without endometrial cancer expressed as mean values ± S.D.

		Androstenediol	DHA	DHAS
Tissue (ng/g)	Normal (8)*	1.34 ± 0.44	24.9 ± 9.2	126.2 ± 66.3†
	Cancer (13)	1.93 ± 0.63‡	21.6 ± 5.1	99.4 ± 52.0
Plasma (ng/ml)	Normal (10)	0.34 ± 0.06	3.66 ± 0.94	640 ± 156
	Cancer (11)	0.34 ± 0.07	3.66 ± 0.94	808 ± 159
Tissue: plasma ratio	Normal	3..94	6.80	0.20
	Cancer	5.68	5.90	0.12

*Number of observations per group in parentheses.
†$n = 7$.
‡Exclusion of one exceptionally high value gave a mean concentration of 1.42 ± 0.37 ng/ml and a tissue : plasma ratio of 4.18.

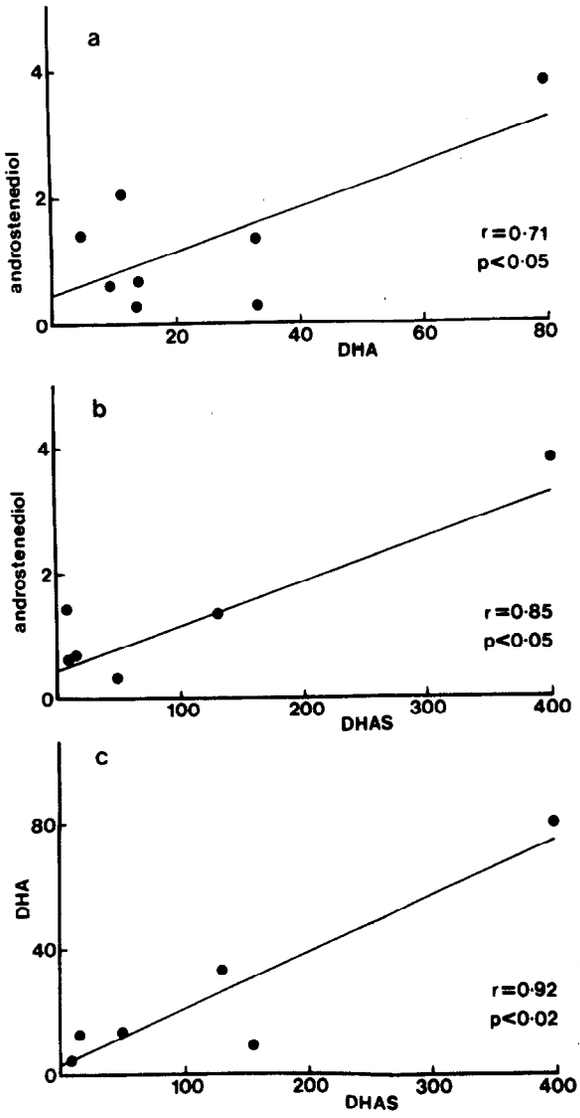

Fig. 3. The relationship between concentrations of (a) 5-*androstene*-3β,17β-*diol* (*androstenediol*) *and dehydroepiandrosterone* (*DHA*) (b) *androstenediol and DHA sulphate* (*DHAS*) (c) *DHA and DHAS* (ng/g *wet wt tissue*) *in endometrium from normal postmenopausal women. Significant correlations were found between all three androgens:- androstenediol : DHA*, r = 0.71, P < 0.05; *androstenediol : DHAS*, r = 0.85, P < 0.05; *DHA : DHAS*, r = 0.92, P < 0.02.

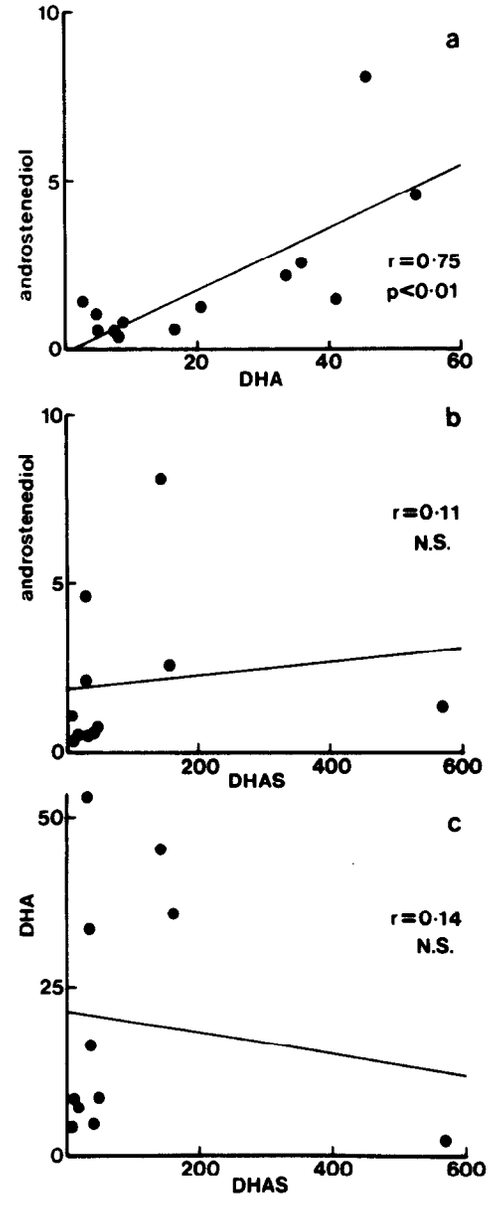

Fig. 4. *The relationship between concentrations of* (a) 5-*androstene*-3β,17β-*diol* (*androstenediol*) *and dehydroepiandrosterone* (*DHA*) (b) *androstenediol and DHA sulphate* (*DHAS*) (c) *DHA and DHAS* (ng/g *wet wt tissue*) *in endometrium from cancer patients. A significant correlation was found for androstenediol : DHA* (r = 0.75, *P* < 0.01) *but there was no significant relationship between either androstenediol and DHAS* (r = 0.11) *or DHA and DHAS* (r = 0.14).

respectively. However, a different relationship emerged for the cancer patients (Fig. 4). While there was a significant positive correlation between androstenediol and DHA concentrations ($r = 0.75$, $P < 0.01$) there was no relationship between concentrations of either androstenediol and DHAS or DHA and DHAS ($r = 0.11$ and 0.14 respectively).

The relationship between plasma levels of the three adrenal androgens is summarized in Table 2. As shown, there was a significant positive correlation between all three androgens in both the cancer group and the normal group, although the relationship between DHA and DHAS for the normal women in this study was only significant at $P < 0.1$ ($t = 1.97$).

The relationship between tissue concentrations of DHAS and 17OHSD activity is depicted graphically in Fig. 5 which demonstrates the trend towards an inverse correlation between the two parameters i.e. high concentrations of DHAS associated with low 17OHSD activity and vice versa. Regression analysis of these data gave a negative correlation coefficient of 0.49 ($n = 11$) which was not significant. There was no correlation between tissue concentrations of free adrenal androgens and 17OHSD activity (androstenediol: $r = 0.03$; DHA: $r = 0.2$, $n = 12$).

Table 2. Correlation between adrenal androgen concentrations in plasma from normal postmenopausal women and endometrial cancer patients

	r	*P*	*Regression line*
Normal postmenopausal women ($n = 10$)			
Androstenediol: DHA	0.82	< 0.01	$y = 50.8x + 156.8$
Androstenediol: DHAS	0.79	< 0.01	$y = 0.3x + 153.9$
DHA : DHAS	0.57	< 0.1	$y = 0.003x + 1.49$
Cancer patients ($n = 11$)			
Androstenediol: DHA	0.84	< 0.01	$y = 58.5x + 129$
Androstenediol: DHAS	0.84	< 0.01	$y = 0.37x + 27.2$
DHA : DHAS	0.64	< 0.05	$y = 0.004x + 0.54$

Androstenediol, 5-androstene-3β,17β-diol; DHA, Dehydroepiandrosterone; DHAS, DHA sulphate.

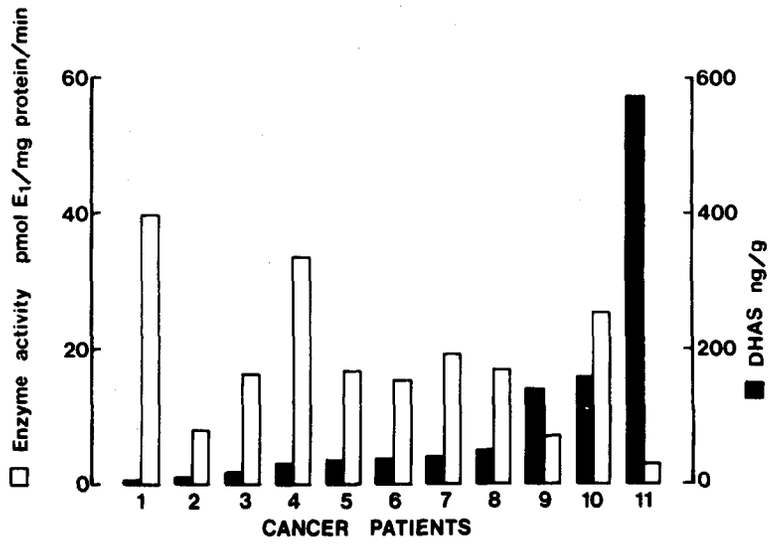

Fig. 5. The relationship between 17β-hydroxysteroid dehydrogenase (17βHSD) activity and dehydroepiandrosterone sulphate (DHAS) concentrations (ng/g wet wt tissue) in endometrium from cancer patients. The activity of 17βHSD is expressed as pmol *oestrone* (E_1)/mg protein/min.

Concentrations of oestradiol and oestrone were only measured in endometrium from cancer patients since insufficient tissue was available for similar measurements in the normal subjects. The data for the cancer patients are shown in Fig. 6 and Table 3. Tissue concentrations of oestrone were significantly lower ($t = 2.9$, d.f. 18, $P < 0.01$) than those found for oestradiol.

Plasma concentrations of oestrogens for both groups of subjects are shown in Fig. 7 and Table 3. It can be seen that there was no difference between the oestrone levels for the two groups.

With respect to the data for oestradiol, the mean values measured were lower than those for oestrone but there was a tendency for the levels to be higher in cancer patients. However, this difference was not significant ($t = 1.37$, d.f. 19). Calculation of the plasma oestradiol : oestrone ratio revealed a more noticeable difference between the two groups, the ratio for the cancer group (0.83 ± 0.07, S.D.) being significantly higher ($t = 2.73$, d.f. 19, $P < 0.02$) than for the normal group (0.6 ± 0.27). When the oestradiol : oestrone ratio was calculated for endometrial tissue (pg/g) from cancer patients a ratio of 1.87 was obtained which was more than double the plasma value quoted above. The mean tissue- : plasma ratio for oestradiol for cancer patients was calculated to be 11.6 which was more than 2-fold higher than for oestrone (5.3).

DISCUSSION

It has been proposed that adrenal androgens may be responsible for increased oestrogenic activ-

Table 3. Concentrations of oestrogens in endometrium and plasma from postmenopausal women with and without endometrial cancer. The values are expressed as mean ± S.D.

		Oestradiol	Oestrone
Tissue (ng/g)	Cancer	0.43 ± 0.06 [a](10)	0.23 ± 0.03 [b](10)
Plasma (pg/ml)	Normal	26.7 ± 0.39 [c](10)	46.1 ± 3.0 [d](10)
	Cancer	37.0 ± 1.1 [e](10)	43.5 ± 5.2 [f](11)

a > b, $P < 0.01$, e/f > c/d, $P < 0.02$.

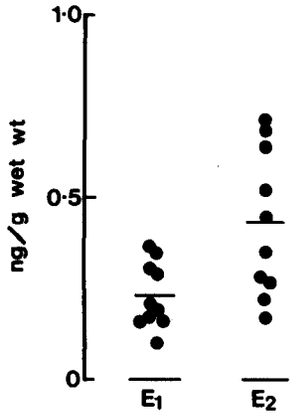

Fig. 6. Concentrations of oestrone (E_1) and oestradiol (E_2) in endometrium from cancer patients. Each observation is a mean of duplicate determinations made on individual subjects. The mean concentration of each oestrogen (ng/g *wet wt tissue*) *is represented by a horizontal bar.*

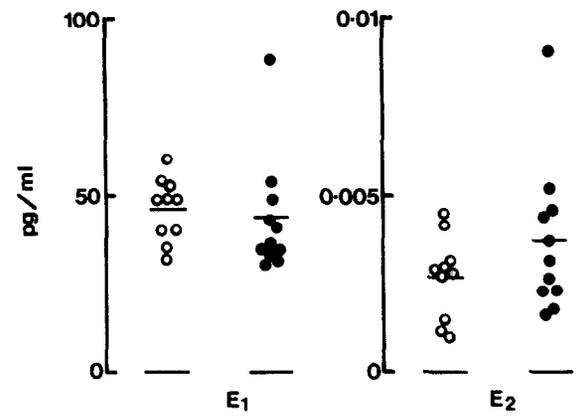

Fig. 7. Concentrations of oestrone (E_1) and oestradiol (E_2) in plasma from normal postmenopausal women (○) *and cancer patients* (●). *Each observation is a mean of duplicate determinations made on individual subjects. The mean concentrations* (pg/ml *plasma*) *are represented by a horizontal bar.*

ity in the endometrium of cancer patients either directly by binding to the oestrogen receptor or indirectly through inhibition of oestradiol metabolism. Should this be the case one might expect concentrations of adrenal androgens to be higher in the endometrium of cancer patients than in healthy women of the same age. In this study the concentrations of adrenal androgens in the endometrium of postmenopausal cancer patients were essentially identical to those found for normal postmenopausal women, implying that adrenal androgens play no part in the development of endometrial cancer. However, possible differences in the cellularity of malignant and non-malignant tissue should be taken into account and expression of the data on the basis of DNA content as opposed to wet weight may be more representative of the concentration per cell. It should also be borne in mind that diagnosis of the cancer may succeed the initiation of the disease by many years and that it is at the time of the menopause when significant hormonal changes are known to occur. There is certainly a decline in endometrial tissue concentrations of androstenediol and DHA at the onset of the menopause [15] and the decrease in plasma levels of adrenal androgens with age is well established [16,17]. In accordance with this age-associated decline in adrenal androgens, endometrial tissue concentrations measured in this study were slightly lower than those reported for proliferative phase endometrium from younger women [15].

Plasma concentrations of adrenal androgens reported here were within the range expected for postmenopausal women [17] and there was no difference between concentrations of androstenediol and DHA for normal women and cancer patients. There was a trend towards increased plasma levels of DHAS in the cancer group but the mean concentrations of 640 ± 156 (S.E.M.) for normal subjects and 808 ± 159 ng/ml for cancer patients were not significantly different. Carlstrom *et al.* [5] did show a significant difference between plasma DHAS concentrations for cancer patients [1020 ± 76 (S.E.M.) ng/ml] and healthy women (507 ± 46 ng/ml) but it is not clear whether blood was taken under the same conditions for each group of women. We have, ourselves, observed a 2-fold elevation in DHAS concentrations in plasma collected at the time of operation compared to that obtained 24 hr before operation. It is therefore important that blood is collected under the same conditions.

A low tissue : plasma ratio for DHAS suggests

either a low uptake by the tissue or metabolism within the tissue whereas a high ratio for androstenediol and DHA implies that the tissue is able to concentrate the free steroids, possibly through involvement of a binding protein.

There was a positive relationship between concentrations of all three androgens in endometrium from normal postmenopausal women but only between androstenediol and DHA for patients with endometrial cancer. The data suggest that in cancer patients there could be a breakdown in the relationship between DHAS and the unconjugated steroids. This point is of interest since we have found a similar pattern of relationships between these steroids for normal breast tissue and tumour tissue [18]. The reason for the discrepancy between healthy and malignant tissue is unclear, but in the breast cancer study we considered the possibility of an impairment in the balance between sulphatase and sulphotransferase activity in tumour tissue.

There was a positive correlation between plasma concentrations of all three androgens for both normal women and cancer patients although the relationship between plasma levels of DHA and DHAS just failed to attain the 5% level of significance. These findings compare with those of the breast cancer study [18] and imply that there is no apparent impairment in adrenal androgen relationships in the plasma of cancer patients.

The evidence of a trend towards an inverse relationship between endometrial tissue concentrations of DHAS and 17OHSD activity in cancer patients does lend some support to the proposed hypothesis. The implication is that 17OHSD activity tends to be lower in cancer patients with high concentrations of tissue DHAS but whether these findings are of physiological importance cannot be ascertained from the present data.

In the cancer patients in this study we measured significantly more oestradiol than oestrone in the endometrium whereas in the plasma higher concentrations of oestrone were present. It is well-established that in postmenopausal women circulating concentrations of oestrone are higher than those of oestradiol [19] and it has also been shown that oestradiol is present in endometrium in significantly greater amounts than oestrone. Vermeulen-Meiners *et al.* [20] reported mean values of 270 pg/g oestrone and 417 pg/g oestradiol in endometrium from normal postmenopausal women. Our data are in close agreement with their findings (oestrone : 230 pg/g, oestradiol : 430 pg/g) which suggests that there is little difference between normal postmenopausal women and cancer patients with respect to tissue oestrogens.

As might be anticipated from the data quoted above, the tissue : plasma ratio was higher for oestradiol (11.6) than for oestrone (5.3). Vermeulen-Meiners *et al.* [20] also found a higher tissue : plasma ratio for oestradiol than oestrone in their study of postmenopausal women (50 and 9.1 respectively) as did Wiegerinck *et al.* [21] (30 and 7 respectively). Thus accumulation of oestradiol in endometrium is a consistent finding whether the tissue be normal atrophic endometrium or malignant tissue.

Although the mean plasma levels of oestradiol were lower than those of oestrone there was a tendency for oestradiol levels (but not oestrone) to be higher in cancer patients (26.7 and 37 pg/ml respectively). Similar findings were reported by Benjamin and Deutsch in 1976 [22] for their study of endometrial cancer patients. Furthermore, the cancer group in this study had a significantly higher plasma oestradiol : oestrone ratio than the normal group, but whether this observation is of significance remains to be established.

The present investigation has not provided conclusive evidence to support the hypothesis relating adrenal androgens and endometrial cancer. It is acknowledged that there are limitations to this study. In the first instance, cancer and control groups were not weight matched. We have attempted to overcome this by ensuring that approximately equal numbers of obese patients were included in each group. Secondly, due to the difficulty of obtaining endometrium from normal postmenopausal women, one control group included patients who were not free from gynaecological abnormalities. Despite this, however, there was no evidence of malignancy in this group. These findings represent a preliminary study and further investigations will be necessary to confirm or refute the significance of the relationship between DHAS and 17OHSD.

Acknowledgements — This work was supported by a grant from the Cancer Research Campaign. We gratefully acknowledge the assistance of the surgical staff of the Samaritan Hospital for Women, London, in supplying the samples of endometrium and blood used in this investigation.

REFERENCES

1. Feher T, Halmy L. Dehydroepiandrosterone and dehydroepiandrosterone sulphate dynamics in obesity. *Can J Biochem* 1975, **53**, 215–222.
2. Sekihara H, Ohsawa N, Kosaka K. Serum dehydroepiandrosterone sulphate and dehydro-

epiandrosterone levels in essential hypertension. *J Clin Endocrinol Metab* 1975, **40**, 156–157.
3. Yen SSC, Chaney C, Judd HL. Functional aberrations of the hypothalamic pituitary system in the polycystic ovary syndrome: a consideration of the pathogenesis. In: James VHT, Serio M, Giusti G, eds. *The Endocrine Function of the Human Ovary*. London, Academic Press, 1976, 373–385.
4. Abraham GE, Maroulis GB. Effect of exogenous estrogen on serum pregnenolone, cortisol and androgens in postmenopausal women. *Obstet Gynecol* 1975, **45**, 271–274.
5. Carlstrom K, Damber M-G, Furuhjelm M, Joelsson I, Lunell N-O, Schoultz B. Serum levels of total dehydroepiandrosterone and total estrone in postmenopausal women with special regard to carcinoma of the uterine corpus. *Acta Obstet Gynecol Scand* 1979, **58**, 179–181.
6. Reed MJ, Noel CT, Johns EA, Jones DL, James VHT. Oestradiol production and factors that influence the interconversion of oestrone and oestradiol in postmenopausal women with endometrial hyperplasia, endometrial cancer or cirrhosis. In: Fioretti P, Martini L, Melis GB, Yen SSC, eds. *The Menopause: Clinical, Endocrinological and Pathophysiological Aspects*. New York, Academic Press, 1982, 325–330.
7. Bonney RC, Reed MJ, James VHT. Inhibition of 17β-hydroxysteroid dehydrogenase activity in human endometrium by adrenal androgens. *J Steroid Biochem* 1983, **18**, 59–64.
8. Tseng L, Mazella J, Tseng L. Kinetic studies of human endometrial hydroxysteroid dehydrogenase. *J Steroid Biochem* 1981, **14**, 437–442.
9. van Doorn LG, Berenschot-Roozsendaal J, Poortman J, Thijssen JHH. Binding characteristics of 5-androstene-3β,17β-diol and estradiol -17β to the cytoplasmic estrogen receptor of the immature rat uterus. *J Steroid Biochem* 1985, **16**, 661–671.
10. Seymour Munn K, Adams J. Estrogenic effects of 5-androstene-3β,17β-diol at physiological concentrations and its possible implication in the etiology of breast cancer. *Endocrinology* 1983, **112**, 486–491.
11. Kreitmann B, Bayard F. Androgen interaction with the oestrogen receptor in human tissues. *J Steroid Biochem* 1979, **11**, 1589–1595.
12. Bonney RC, Scanlon MJ, Reed MJ, James VHT. Endometrial tissue and plasma concentrations of 5-androstene-3β,17β-diol during the menstrual cycle in normal premenopausal and perimenopausal women. *J Steroid Biochem* 1983, **19**, 1627–1634.
13. Braunsberg H, Reed MJ, Short F, Dias VO, Baxendale PM. Changes in plasma concentrations of oestrogens and progesterone in women during anaesthesia and gynaecological operations. *J Steroid Biochem* 1981, **14**, 749–755.
14. Bonney RC, Reed MJ, Davidson K, Beranek PA, James VHT. The relationship between 17β-hydroxysteroid dehydrogenase activity and oestrogen concentrations in human breast tumours and in normal breast tissue. *Clin Endocrinol* 1983, **19**, 727–739.
15. Bonney RC, Scanlon MJ, Jones DL, Reed MJ, James VHT. Adrenal androgen concentrations in endometrium and plasma during the menstrual cycle. *J Endocrinol* 1984, **101**, 181–188.
16. Vermeulen A. Adrenal androgens and aging. In: Genazzani AR, Thijssen JHH, Siiteri PK, eds. *Adrenal Androgens*. New York, Raven Press, 1980, 207–217.
17. Bonney RC, Scanlon MJ, Jones DL, Beranek PA, Reed MJ, James VHT. The interrelationship between plasma 5-ene adrenal androgens in normal women. *J Steroid Biochem* 1984, **20**, 1353–1355.
18. Bonney RC, Scanlon MJ, Reed MJ, Jones DL, Beranek PA, James VHT. Adrenal androgen concentrations in breast tumours and in normal breast tissue. The relationship to oestradiol metabolism. *J Steroid Biochem* 1984, **20**, 501–504.
19. Meldrum DR, Davidson BJ, Tataryn IV, Judd HL. Changes in circulating steroids with aging in postmenopausal women. *Obstet Gynecol* 1981, **57**, 624–628.
20. Vermeulen-Meiners C, Benedek Jaszmann LJ, Haspels AA, Poortman J, Thijssen JHH. The endogenous concentration of estradiol and estrone in normal human postmenopausal endometrium. *J Steroid Biochem* 1984, **21**, 607–612.
21. Wiegerinck MAHM, Poortman J, Donker TH, Thijssen JHH. *In vivo* uptake and subcellular distribution of tritium-labelled estrogens in human endometrium, myometrium and vagina. *J Clin Endocrinol Metab* 1983, **56**, 76–86.
22. Benjamin F, Deutsch S. Plasma levels of fractionated estrogens and pituitary hormones in endometrial cancer. *Am J Obstet Gynec* 1976, **126**, 638–647.