Hormonal pattern in prostatic cancer
I. Correlation with local extent of tumour, presence of metastases and grade of differentiation

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Abstract. In 32 subjects with histologically and/or cytologically verified prostatic cancer the hormonal pattern was studied by assaying 18 plasma and urinary hormones or groups of hormones. The tumours were classified according to the UICC classification system and the hormone values were correlated to the local extent of the tumour (T classification), the presence of metastases (M classification) and the differentiation grade (G classification). It was found that patients with metastases had significantly higher plasma oestradiol and lower testosterone/oestradiol and testosterone/oestrone plus oestradiol ratios as compared to those subjects without metastases. In subjects with moderately or poorly differentiated tumours plasma oestrone + oestradiol was significantly higher and the testosterone/oestrone + oestradiol ratio was significantly lower than in the subjects with well differentiated tumours. In the various TNM classification groups no obvious trends were found with regard to urinary hormones and no significant differences between the groups for plasma FSH, LH, prolactin, progesterone and cortisol were observed. It is concluded that in more advanced cases with metastatic cancer and when tumours are less well differentiated the androgen/oestrogen ratio may be decreased. These alterations have no diagnostic significance because of great overlapping of individual results between the various groups of patients.

Studies on urinary and plasma hormones in human subjects with prostatic cancer have revealed controversial results and there does not seem to be any clear difference in sex hormone production or metabolism or sex hormone binding globulin binding capacity (SHBG) between these subjects and normal individuals other than possible differences due to changes in the general condition of the carcinoma patients (for literature see Voigt & Krieg 1978). The results obtained would suggest that at least the sex hormone pattern prevailing before the development of cancer has no influence on the formation of the cancer. However, recent results showing significantly different hormonal pattern in two histological groups of cancer (Bartsch et al. 1977a) seem to suggest that the hormonal milieu could influence the further development of the cancer cells.

In order to study the correlation of the hormonal pattern in prostatic cancer with local extent of tumour, presence of metastases and grade of differentiation, 18 hormones or groups of hormones were assayed in the plasma and urine of patients classified according to UICC classification system. The results indicate that a low plasma testosterone/oestrogen (T/Oe) ratio is typical for patients with poorly and moderately differentiated advanced prostatic carcinoma.

Materials and Methods

Subjects

The series consisted of 32 patients with histologically and/or cytologically verified prostatic cancer (mean age

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68.0 ± 7.0 years; range 51–81). The mean body mass index (BMI) (Goldbourt & Medalie 1974) was 24.4. To study the influence of age the series was divided into two groups with ages below and above 70 years. Fifteen patients were under 70 years of age (mean 61.8 ± 5.7 and mean BMI 25.0) and 17 patients were aged 70 or over (mean 73.4 ± 2.9 and mean BMI 23.8).

The tumours were classified according to the Union Internationale Contra le Cancer system (UICC 1974). The local extent of the tumour (T classification) based on digital rectal palpation divided the patients into two groups: T1-2 (intracapsular) (8 subjects), mean age 66.3 ± 7.9 years (BMI 24.8) and T3-4 (extracapsular) (24 subjects), mean age 68.5 ± 7.2 years (BMI 24.3). The presence of metastases (M classification) was distributed as follows: M0 (15 subjects) mean age 68.0 ± 7.2 years (BMI 24.6) and M1 (17 subjects) mean age 67.9 ± 7.7 years (BMI 24.2). The differentiation grade (G classification divided the subjects as follows: G1 (well differentiated) (8 subjects), mean age 65.4 ± 9.9 years (BMI 24.8) and G2-3 (moderately and poorly differentiated) (24 subjects), mean age 68.8 ± 6.3 years (BMI 24.4). N categories were not recorded. In the T classification group a borderline case was classified into the more extensive group and in the M classification a borderline case was classified into the M1 category. In the case of discrepancy between the grades (G classification) based on histological and cytological examinations the highest grade was recorded.

None of the patients had received any therapy for prostatic cancer before the hormonal studies. Twelve patients were taking digitalis for congestive heart failure, and 3 patients took a sulphonylurea for diabetes mellitus.

Some patients had taken drugs, like indomethacin, for pain, when needed. The majority of the subjects was not under regular medication of any kind. None of the patients gave a history of liver disease and all had normal liver function tests. Serum creatinine was slightly elevated (range 110–200 μmol/l) in 6 patients. No correlation was found between the creatinine level and TMG classification. In 22 patients the erythrocyte sedimentation rate was elevated above 10 mm/h, but no correlation with TMG classification was observable. Nine patients were anaemic with haemoglobin below 125 g/l, 5 of them belonged to the T3-4 M1 G2-3 group.

Methods

Blood samples for hormone analyses were obtained between 7.30 and 9.30 a.m. a few days before orchidectomy or starting oestrogen therapy. The samples were taken from the cubital vein into heparinized tubes and the plasma was stored at −20°C if not immediately analyzed. Urine collection for hormone analyses was performed during the 24 h before taking the blood sample. The urine samples were analyzed immediately. Regular quality control samples were included in all series of assays. All analyses were done in duplicate.

Plasma follicle stimulating hormone (FSH) and luteinizing hormone (LH) were determined by radioimmunoassay (RIA) using a double antibody solid phase (DASP) method principally according to den Hollander & Schuurs (1971). The modifications introduced and the evaluation of the procedures have been described in detail (Karonen et al. 1978a). The antisera and the reference preparations of the peptide hormones were obtained from the National Pituitary Agency (NIAMDD,

Table 1.
Plasma hormone levels (geometric mean and 95% confidence interval)
in patients with carcinoma of the prostate, by age.

| Hormone | Age group (years) | | | | Significance |
| | < 70 (n = 15)* | | ≧ 70 (n = 17)* | | |
	Mean	95% CI	Mean	95% CI	
FSH (IU/l)	4.8	1.5–15.0	6.7	2.3–18.9	NS
LH (IU/l)	9.7	1.1–41.1	17.1	10.2–31.8	$P < 0.05$
Prolactin (mU/l)	207.0	90.7–472.0	267.0	143.0–686.0	NS
Testosterone (nmol/l)	18.8	8.2–29.3	16.9	6.4–35.4	NS
Oestrone (pmol/l)	145.0	34.8–324.0	198.0	61.1–509.0	NS
Oestradiol (pmol/l)	73.2	18.0–189.0	72.8	21.7–243.0	NS
Oestrone + oestradiol (pmol/l)	230.0	64.2–827.0	287.0	120.0–686.0	NS
Progesterone (nmol/l)	1.1	0.7–2.8	1.5	1.2–2.5	NS
Cortisol (μmol/l)	0.4	0.2–0.8	0.4	0.2–0.8	NS

* A few values are lacking due to loss of specimens.

Hormone	Age group (years)				Significance
	< 70 (n = 15)*		≧ 70 (n = 17)*		
	Mean	95% CI	Mean	95% CI	
17-KS (μmol/24 h)	24.7	12.2−51.9	21.9	8.5−71.0	NS
Androsterone (μmol/24 h)	2.9	1.2−7.7	1.7	0.5−6.4	$P < 0.025$
Aetiocholanolone (μmol/24 h)	4.4	1.5−10.6	2.2	0.4−9.7	$P < 0.01$
DHEA (μmol/24 h)	0.6	0.05−7.1	0.3	0.02−2.4	$P < 0.05$
17-KGS (μmol/24 h)	34.8	19.5−78.2	24.0	7.4−58.0	$P < 0.025$
Pregnanediol (μmol/24 h)	1.5	0.8−3.5	1.1	0.5−3.3	NS
Pregnanetriol (μmol/24 h)	1.8	0.5−4.8	1.8	0.6−5.7	NS
Oestrone (nmol/24 h)	22.8	8.0−56.0	21.5	5.0−110.0	NS
Oestradiol (nmol/24 h)	11.1	4.5−31.0	8.4	2.3−30.0	NS
Oestriol (nmol/24 h)	82.9	24.3−210.0	73.0	18.5−236.0	NS

* A few values are lacking due to loss of specimens.

NIH, Bethesda, Maryland). Plasma (Prl) was also determined with a similar technique using the same source for antisera and reference preparations. The slightly modified procedure and its evaluation has been described in detail previously (Karonen et al. 1978b). Plasma cortisol was assayed by a specific fluorometric procedure according to Clark et al. (1971) and plasma progesterone by RIA (Haukkamaa 1974). Plasma testosterone (T) was determined by a RIA method modified from that of Ismail et al. (1972) and described in detail (Kuoppasalmi et al. 1976). Plasma oestrone (Oe$_1$) and oestradiol (Oe$_2$) were assayed by RIA using a chromatographic method (Sephadex LH-20) similar to several published procedures and previously described in detail including all references to previous work (Kuoppasalmi et al. 1976).

The colorimetric methods for urinary 17-ketosteroids (17-KS), 17-ketogenic steroids (17-KGS) (Adlercreutz et al. 1967a), the gaschromatographic (GC) method for urinary androsterone (A), aetiocholanolone (Aet) and dehydroepiandrosterone (DHEA) (Adlercreutz & Schauman 1976) have been described previously. Pregnanediol and pregnanetriol were assayed by GC. The method is unpublished, but has been used in routine assays for more than 10 years. It is based on solvent extraction of the steroid conjugates, enzymatic hydrolysis, separation of the two steroids on a partially deactivated alumina column and GC of the trimethylsilyl ether derivatives of the steroids. The specificity of the GC methods was defined by combined GC-mass spectrometry. The urinary 'classical' oestrogens were determined with a colorimetric method and including enzymatic hydrolysis of the oestrogen conjugates with helix pomatia extract followed

by a procedure similar to that of Brown (1955). The method has been described previously (Adlercreutz et al. 1967b; Adlercreutz & Luukkainen 1968).

The given mean values are geometric means with confidence interval of 95% (95% CI), except for age which is given as arithmetic mean (± SD). Statistical comparisons were made using the *t*-test of de Jonge (1964) utilizing the logarithmic values. This *t*-test is designed for group comparisons when the variances of the groups differ considerably.

Results

Correlation of hormonal pattern with age

The mean plasma hormone levels in the two age groups are presented in Table 1. The only statistically significant difference was found for the mean LH level, which was higher in the older group ($P < 0.05$). The mean levels of Prl and Oe$_1$ tended to be higher in the older age group, but the differences were not statistically significant. The mean T and Oe$_2$ levels were almost identical.

The mean urinary hormone excretion in the two age groups is given in Table 2. No significant difference could be found in the excretion of total 17-KS. However, the excretion of 11-deoxy-17-KS (A, Aet and DHEA) was significantly lower in the older age group. There was no difference between the cortisol levels in plasma (Table 1), but the

Table 3.

Urinary hormone excretion (geometric mean and 95% confidence interval) in patients with carcinoma of the prostate, by local extent of the tumour (T classification).

Hormone	T classification				Significance
	T1-2 (n = 8)*		T3-4 (n = 24)*		
	Mean	95% CI	Mean	95% CI	
17-KS (μmol/24 h)	33.5	26.5−46.0	20.5	8.5−59.4	$P < 0.005$
Androsterone (μmol/24 h)	2.6	1.4−7.2	2.1	0.5−6.6	NS
Aetiocholanolone (μmol/24 h)	4.9	2.5−10.6	2.8	0.5−9.7	$P < 0.025$
DHEA (μmol/24 h)	0.9	0.2−7.1	0.3	0.02−2.4	$P < 0.05$
17-KGS (μmol/24 h)	36.4	22.4−58.0	26.3	8.1−85.7	$P < 0.025$
Pregnanediol (μmol/24 h)	1.3	0.8−2.2	1.3	0.5−3.9	NS
Pregnanetriol (μmol/24 h)	1.8	0.9−2.8	1.8	0.5−5.8	NS
Oestrone (nmol/24 h)	26.1	10.1−52.0	20.6	5.0−106.0	NS
Oestradiol (nmol/24 h)	12.8	5.6−31.0	8.6	2.3−30.0	NS
Oestriol (nmol/24 h)	71.3	16.0−210.0	80.1	22.9−236.0	NS

* A few values are lacking due to loss of specimens.

excretion of 17-KGS was significantly lower in the older age group (Table 2). The urinary excretion of oestrogens was on the same level in both age groups. The plasma T/Oe_2, $T/Oe_1 + Oe_2$, T/Prl and urinary A/Aet, $Oe_1 + Oe_2/Oe_3$ and $A + Aet + DHEA$/total 17-KS ratios were the same in both age groups (values not shown)[1].

Correlation of hormonal pattern with T classification

There were no significant differences in the plasma hormone levels between the two T groups, but the mean LH, Prl and Oe_2 levels tended to be higher in the locally more extended group (values not shown). No difference could be seen in mean plasma T levels. Urinary excretion of total 17-KS, Aet and DHEA was significantly lower ($P < 0.05 - 0.005$) in the locally more extended cases (Table 3). The urinary excretion of oestrogens was similar in both T classification groups investigated.

As expected on the basis of plasma hormone levels, the mean ratios of plasma T to Oe_2 and to Prl tended to be lower in the T3-4 group compared to the T1-2 group, but without statistical significance (values not shown). Due to unchanged excretion of A and decreased excretion of Aet the ratio of urinary A to Aet was significantly higher (0.9) ($P < 0.025$) in the T3-4 group as compared to the T1-2 (0.5).

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[1] All values can be obtained from the authors.

Correlation of hormonal pattern with M classification

The plasma levels of LH, Prl and oestrogens tended to be higher in the more advanced cases (M1 category), but only the difference between the Oe_2 levels was statistically significant ($P < 0.05$) (Table 4). The urinary excretion of hormones in the two M categories was similar (values not shown). The ratios of plasma T to Oe_1 plus Oe_2 and to plasma Oe_2 were significantly lower ($P < 0.05$ and < 0.025) in the M1 category (Table 5).

Correlation of hormonal pattern with G classification

The only significant difference in plasma hormone levels between the two G groups was found in plasma level of Oe_1 plus Oe_2; in consistency with the results for T and M classification it was higher (282.0 pmol/l as compared to 191.0 pmol/) ($P < 0.025$) in the less differentiated group (G2-3). The Prl, gonadotrophin and T mean values were very similar in both catetories, no differences were observed in urinary hormone excretion. In accordance with the difference in plasma levels of Oe_1 plus Oe_2 the ratio of plasma T to Oe_1 plus Oe_2 was significantly lower ($P < 0.025$) in the less differentiated group (Table 5).

Discussion

The main criticism which can be directed towards the design of this study is the fact that only single

Table 4.

Plasma hormone levels (geometric mean and 95% confidence interval) in patients with carcinoma of the prostate, by presence of metastases at the time of diagnosis (M classification).

Hormone	M classification				Significance
	M0 (n = 15)*		M1 (n = 17)*		
	Mean	95% CI	Mean	95% CI	
FSH (IU/l)	6.2	2.1–17.1	5.3	1.9–15.3	NS
LH (IU/l)	11.4	1.2–33.1	14.7	6.8–36.6	NS
Prolactin (mU/l)	211.0	78.3–484.0	263.0	163.0–592.0	NS
Testosterone (nmol/l)	19.6	8.1–35.4	16.3	6.6–34.2	NS
Oestrone (pmol/l)	143.0	37.8–347.0	202.0	51.5–509.0	NS
Oestradiol (pmol/l)	59.6	19.5–181.0	87.1	21.7–258.0	$P < 0.05$
Oestrone + oestradiol (pmol/l)	216.0	85.6–546.0	303.0	96.3–956.0	NS
Progesterone (nmol/l)	1.5	1.0–2.7	1.2	0.7–2.5	NS
Cortisol (µmol/l)	0.4	0.2–0.6	0.4	0.2–0.8	NS

* A few values are lacking due to loss of specimens.

plasma samples and one 24-h urinary collection were taken. The problem is greatest with regard to plasma T because of its rapid fluctuation (Murray & Corker 1973; West et al. 1973; Smith et al. 1974; Rowe et al. 1974; Leymarie et al. 1974; Goldzieher et al. 1976). However, taking several samples at short intervals would probably not eliminate the problem as there is considerable day-to-day (Rowe et al. 1974) and also regular rhythmic variation (Doering et al. 1975; Reinberg et al. 1975; Smals et al. 1976) over longer periods of time. These variations were unknown at the time when this work was initiated (1973). Sex hormone binding globulin capacity (SHBG) measurements would have been of value, however, these were not available at the time this study started.

In the more advanced cases with tumours extending beyond the capsule (T3-4 category) and with metastases (M1 category) mean plasma LH, Prl, Oe_1 and Oe_2 tended to be higher and the mean plasma level of T lower. However, only plasma Oe_2, T/Oe_2 ratio and $T/Oe_1 + Oe_2$ ratio were significantly different between the M1 and M0 categories. Young & Kent (1968) observed that patients with stage 4 (metastasized) carcinoma have significantly lower plasma T values than those with stage 3 (non-metastasized) or normal subjects, but because of different grouping those results are not comparable with ours. The mean Oe_1 plus Oe_2 level was significantly higher and the mean T/Oe_1

+ Oe_2 ratio was significantly lower in the G2-3 category compared to the G1 category. Thus the tendency with regard to the oestrogens and the T/Oe ratio was the same for the moderately and poorly differentiated tumour cases and those with tumours extending beyond the capsule and with metastases.

The above-mentioned decrease in T/Oe ratio should theoretically be reflected in increased serum SHBG level. Bartsch et al. (1977b) did not find any significant differences in plasma level of T, Oe_2, Oe_1 and SHBG in prostatic cancer patients as compared to normals. However, they did not classify the patients into groups as in the present study. Also Dennis et al. (1977) did not observe any difference in SHBG concentration between normal subjects and prostatic cancer patients; the mean level tended, in fact, to be lower in the cancer patients.

Plasma FSH, LH, progesterone and cortisol did not show any differences between the various categories in the TNM classification groups. Hammond et al. (1977) found lower plasma LH values in both benign prostatic hyperplasia and prostatic carcinoma as compared to controls whilst Bartsch et al. (1977a) found lower plasma LH values in carcinoma patients as compared to hospitalized controls. Our values in prostatic carcinoma patients also tended to be lower (12.7 ± 2.3 IU/l) than those observed in 10 hospitalized male subjects (18.0 ±

Table 5.

Hormone ratios (geometric means) in patients with carcinoma of the prostate, by the presence of metastases at the time of diagnosis (M classification) and by differentiation grade of the tumour (G classification).

Hormone ratio	M classifiaction			G classification		
	M0 (n = 15)* mean	M1 (n = 17)* mean	Significance	G1 (n = 8)* mean	G2-3 (n = 24)* mean	Significance
P-testosterone** / P-oestradiol	1.2	0.7	$P < 0.025$	1.3	0.8	NS
P-testosterone / P-(oestrone + oestradiol)	0.3	0.2	$P < 0.05$	0.4	0.2	$P < 0.025$
P-testosterone / P-prolactin	0.09	0.06	NS	0.08	0.07	NS

* A few values are lacking due to loss of specimens. ** P = plasma.

2.1 IU/l) with no subjective symptoms from the urinary tract and with a mean age of 69.2 ± 6.3 years, but the difference was not statistically significant ($P < 0.30$). Most, if not all, of these control subjects had benign prostatic hyperplasia (but no signs of prostatic carcinoma); in this age 'normal' subjects with regard to the prostata can hardly be found.

With regard to plasma Prl there was only a tendency to higher mean values in the more advanced cases (T3-4 and M1 categories) which may be due to the higher mean oestrogen levels seen in these cases. Bartsch et al. (1977a,b) observed higher than normal Prl levels in 15−20% of the subjects with prostatic cancer, the bioassay values showing more clearcut differences. However, our group of 10 hospitalized male subjects mentioned above had the same frequency of pathological Prl values as the prostatic cancer group. Hammond et al. (1977) did not observe any significant differences with regard to plasma Prl between normals and subjects with prostatic cancer. Thus, it seems that results of radioimmunological plasma Prl assays do not give any evidence indicating a role for Prl in prostatic cancer formation or progress despite the fact that Prl has a stimulating effect on the prostate (Grayhack et al. 1955; Farnsworth 1972; Lasnitzki & Franklin 1972).

The observed decrease of the excretion of some urinary neutral steroids (Table 3) is frequently seen in debilitating diseases and can hardly have any significance for the development of the cancer. Bulbrook et al. (1959) could not find any differ-ence between prostate cancer patients and controls with regard to urinary excretion of oestrogens, 17-KS and 17-KGS.

Thus it seems that in more advanced cases with metastatic cancer and with less differentiated tumours the plasma oestrogens tended to increase and the T/Oe ratio tended to decrease (statistically significant in the M and G classification groups). Because our classification system (UICC 1974) was different from Bartsch et al. (1977a) the present findings are not directly comparable with theirs. They found higher plasma T, dihydrotestosterone (DHT) and Oe_1 in subjects with carcinomas having cribriform and/or solid growth as compared to those without this type of growth.

The observed change in the ratio of plasma T and Oe_2 in the more extended and malignant cases is not due to difference in the age of the groups studied. Aging results in a decrease in this ratio (Pirke & Doerr 1970; Kley et al. 1974; Hallberg et al. 1976) and a decrease in free T due to increased binding of T to SHBG. Because the BMI values were similar in all groups an increased extraglandular conversion of androgens to oestrogens in fat tissue as seen in obese women (see MacDonald et al. 1978) and men (Schneider et al. 1979) is also an unlikely explanation.

Decreased T production has been observed in debilitating diseases (Young & Kent 1968) but also in prostatic cancer (Isurugi 1967) and this could result in a decreased T/Oe ratio. The similar BMI values in all groups studied did not suggest any definite difference with regard to general physical

health in the more extended and malignant cases as compared to the less extended and malignant cases. However, our data do not definitely exclude the possibility that the patients with a lower mean T/Oe ratio were more sick than those with a higher mean ratio even if this was not clinically obvious.

The other and more exciting possibility is that the changed ratio is causal with regard to the extent and malignancy of the disease. The change in the ratio is mainly due to increased oestrogen levels and therefore it is of interest to note that specific Oe_2 receptors have been found in the cytosol of benign hypertrophic human prostate (Bashirelahi et al. 1976). However, this could not be confirmed by Ekman et al. (1979a) and in addition oestrogen receptors were not found in metastatic carcinoma of the prostate (Ekman et al. 1979b). In the dog prostate cytoplasmic DHT binding is increased by Oe_2 (Moore et al. 1979) and may in this way influence the prostatic cell growth. On the other hand, oestrogens inhibit 5α-reductase in vitro, but it is not clear whether this also occurs in vivo (see Voigt et al. 1975). There is no doubt that oestrogens act synergistically with androgens on prostatic cell growth (see Mawhinney & Neubauer 1979) and a highly significant increase of prostate stroma was associated with higher individual Oe_2 concentrations in men with benign prostatic hypertrophy (Seppelt 1978). However, there is no evidence whatsoever that the growth of malignant prostatic cells is stimulated and thus the possible role of a decreased T/Oe ratio on the degree of malignancy and spread of prostatic carcinoma remains obscur. Our observations should be regarded as preliminary and further studies including assay of free T and SHBG seem to be indicated. However, the great overlapping of individual results between the various groups shows that hormone assays are of no diagnostic value in prostatic carcinoma.

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