ON THE EXCRETION OF ANDROGENS IN CARCINOMA OF THE PROSTATE

II. ESTROGEN THERAPY BEFORE AND AFTER ORCHIECTOMY

By

G. Birke, C. Franksson and L.-O. Plantin

Estrogens have won a prominent place in the treatment of carcinoma of the prostate. But although good results have been achieved, complete agreement has not yet been reached concerning the effective dosage. Some writers (Colston et al., 1947, Dean et al., 1944, Kearns, 1942, Nesbit et al., 1950) have stated that only moderate dosage is required, while others (Cox, 1946, Fergusson, 1946, Heckel, 1948) maintained that high dosage — «castration dosage» — is necessary. In order to elucidate the amount of estrogen which effects the greatest possible inhibition of androgen secretion in noncastrated cases and to determine if estrogen therapy after the operation has any inhibitory influence on the adrenal steroids, the pattern of 17-ketosteroid excretion was studied during estrogen therapy before and after orchiectomy.

OWN INVESTIGATIONS

Methods

As in earlier studies the micromethod of Zygmuntowicz et al. (1951) for separation of the 17-ketosteroids was supplemented by a similar separation technique permitting infrared spectrographic analysis of the various steroids. Pooled urinary extracts from each group of treated patients were subjected to chromatographic analysis and infrared spectroscopy before and during therapy. Prior to therapy the total 17-ketosteroid excretion was determined if possible in each patient from three consecutive twenty-four urine specimens and a mean calculated. The extracts were then pooled and the requisite quantity microchromatographed. The same procedure was carried out in as many cases as possible after some form of therapy had been introduced.
The effect of estrogen therapy prior to orchiectomy

7 patients with carcinoma of the prostate gland were given 5 mg. of stilbesterol daily for 5 days. In 4 cases followed by 30 mg. daily for 5 days. Orchiectomy was then performed. Stilbesterol therapy was continued post-operatively.

Table 1 and 2 show that when 5 mg. of stilbesterol was given the 17-ketosteroids androsterone and etiocholanolone showed distinct decrease, which in all cases was greatly accentuated when the dosage was raised to 30 mg. The total 17-ketosteroid excretion also showed a greater fall in response to the 30 mg. dosage. It is further shown that orchiectomy performed after administration of the latter dosage produced no further effect on the 17-ketosteroid and »androgen« excretion.

Fig. 1 illustrates the effect of treatment with 30 mg stilbesterol and ablation of testis. It demonstrates that no further effect is seen after ablation of testis when the patient is treated with 30 mg. stilbesterol per day.

Similar chromatograms were obtained in all cases.

As this stilbesterol therapy was of short duration, we also tried administration of 5 mg. for a longer period in order to avoid a »Hohlweg« effect. In one case as shown in figure 2 the initially achieved effect, which was noted after

Table 1.
The total excretion of 17-ketosteroids and »androgen metabolites« before and during treatment with 5 mg. stilbesterol.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Before treatment</th>
<th>During treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total excretion of 17-ketosteroids mg./24 hrs.</td>
<td>androsterone + etiocholanolone excretion mg./24 hrs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.</td>
<td>2.</td>
</tr>
<tr>
<td>JF</td>
<td>76</td>
<td>1.7</td>
<td>0.9</td>
</tr>
<tr>
<td>DG</td>
<td>70</td>
<td>1.5</td>
<td>0.9</td>
</tr>
<tr>
<td>VL</td>
<td>61</td>
<td>6.4</td>
<td>3.4</td>
</tr>
<tr>
<td>CE</td>
<td>67</td>
<td>2.2</td>
<td>1.0</td>
</tr>
<tr>
<td>TE</td>
<td>67</td>
<td>4.2</td>
<td>2.4</td>
</tr>
<tr>
<td>SU</td>
<td>75</td>
<td>1.2</td>
<td>0.7</td>
</tr>
<tr>
<td>HG</td>
<td>65</td>
<td>6.4</td>
<td>4.0</td>
</tr>
</tbody>
</table>

The difference in per cent between group 2 and 4 is 33 ± 5 (t = 6.22). Significance *** (P < 0.001).

Table 2.
The total excretion of 17-ketosteroids and androgen metabolites before and during treatment with 30 mg. stilbesterol and the effect of ablatio testis.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Before treatment</th>
<th>During treatment</th>
<th>Effect of ablatio testis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total excretion of 17-ketosteroids mg./24 hrs.</td>
<td>androsterone + etiocholanolone excretion mg./24 hrs.</td>
<td>Total excretion of 17-ketosteroids mg./24 hrs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.</td>
<td>2.</td>
<td>3.</td>
</tr>
<tr>
<td>JF</td>
<td>76</td>
<td>1.7</td>
<td>0.9</td>
<td>1.5</td>
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<td>VL</td>
<td>61</td>
<td>6.4</td>
<td>3.4</td>
<td>3.3</td>
</tr>
<tr>
<td>TE</td>
<td>67</td>
<td>4.2</td>
<td>2.4</td>
<td>2.2</td>
</tr>
<tr>
<td>SU</td>
<td>75</td>
<td>1.2</td>
<td>0.7</td>
<td>0.8</td>
</tr>
</tbody>
</table>

The difference in per cent between group 2 and 4 is 55 ± 7 (t = 7.40).
Significance ** (P < 0.005).
The difference in per cent between group 4 and 6 is 10 ± 11 (t = 0.85).
Not significant.
**Case: V. L.♂. Age: 61. D.: Cancer prostatae.**
Treatment: Stilbestrol 30 mg./day.
Ablatio testis.
- ○ Before treatment (17-KS 6.4 mg./24 hr.)
- ◯ After stilbestrol for 5 days (17-KS 3.3 mg./24 hr.)
- —— 5 days after op. Stilbestrol continued. (17-KS 3.0 mg./24 hr.)

![Graph showing 17-ketosteroid excretion before and after treatment with stilbestrol and castration.](image)

**Fig. 1.**
17-ketosteroid excretion before and after treatment with stilbestrol and castration.

Treatment: stilbestrol 5 mg./day.
- ○ Before treatment (17-KS 6.4 mg./24 hr. «Androgen metabolites» 4.0 mg./24 hr.)
- ◯ Treated 7 days (17-KS 4.7 mg./24 hr. «Androgen metabolites» 2.8 mg./24 hr.)
- —— Treated 60 days (17-KS 4.1 mg./24 hr. «Androgen metabolites» 2.1 mg./24 hr.)

![Graph showing Androgen metabolites before and after stilbestrol in a patient with cancer prostatae.](image)

**Fig. 2.**
Androgen metabolites before and after stilbestrol in a patient with cancer prostatae.
The total excretion of 17-ketosteroids and »androgen metabolites« before and during treatment with 5 mg. stilbesterol (orchiectomized patients).

<table>
<thead>
<tr>
<th>Case</th>
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<th>Before treatment</th>
<th>During treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total excretion of 17-ketosteroids mg./24 hrs.</td>
<td>androsterone + etiocholanolone excretion mg./24 hrs.</td>
</tr>
<tr>
<td>OL</td>
<td>62</td>
<td>2.1</td>
<td>0.8</td>
</tr>
<tr>
<td>KA</td>
<td>75</td>
<td>1.5</td>
<td>0.6</td>
</tr>
<tr>
<td>KJ</td>
<td>69</td>
<td>2.0</td>
<td>1.3</td>
</tr>
<tr>
<td>VS</td>
<td>61</td>
<td>3.5</td>
<td>1.8</td>
</tr>
<tr>
<td>KSN</td>
<td>53</td>
<td>1.8</td>
<td>0.9</td>
</tr>
<tr>
<td>HI</td>
<td>73</td>
<td>1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>KD</td>
<td>69</td>
<td>1.3</td>
<td>1.0</td>
</tr>
</tbody>
</table>

The difference in per cent between group 2 and 4 is $7 \pm 7$ ($t = 1.04$).
Not significant.

only a few days, showed a possible tendency to increase during the eight weeks of therapy. In another case this tendency could not be traced. Study of this question will be continued.

Table 4.
The total excretion of 17-ketosteroids and »androgen metabolites« before and during treatment with 30 mg. stilbesterol (orchiectomized patients).

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Before treatment</th>
<th>During treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total excretion of 17-ketosteroids mg./24 hrs.</td>
<td>androsterone + etiocholanolone excretion mg./24 hrs.</td>
</tr>
<tr>
<td>PR</td>
<td>82</td>
<td>3.0</td>
<td>1.5</td>
</tr>
<tr>
<td>OL</td>
<td>62</td>
<td>2.1</td>
<td>0.8</td>
</tr>
<tr>
<td>KA</td>
<td>75</td>
<td>1.5</td>
<td>0.6</td>
</tr>
<tr>
<td>KJ</td>
<td>69</td>
<td>2.0</td>
<td>1.3</td>
</tr>
<tr>
<td>VS</td>
<td>61</td>
<td>3.5</td>
<td>1.8</td>
</tr>
<tr>
<td>AF</td>
<td>75</td>
<td>2.0</td>
<td>0.8</td>
</tr>
<tr>
<td>BQ</td>
<td>60</td>
<td>1.4</td>
<td>0.3</td>
</tr>
</tbody>
</table>

The difference in per cent between group 2 and 4 is $4 \pm 11$ ($t = 0.34$).
Not significant.
Case V. S. ♂. Age: 61.
D.: Cancer prostatic (orchiectomized).
- Immediately after op. (17-KS 1.5 mg./24 hr. »Androgen metabolites« 0.7 mg./24 hr.)
- 5 months after op. (17-KS 3.5 mg./24 hr. »Androgen metabolites« 1.8 mg./24 hr.)
- After stilbestrol 30 mg./day for 3 days (17-KS 3.1 mg./24 hr. »Androgen metabolites« 1.5 mg./24 hr.)

Fig. 3.
»Androgen metabolites« in orchiectomized patient before and after treatment with stilbestrol.

In table 2 and 3 it is seen that following orchiectomy neither the 5 mg. nor the 30 mg. dosage of stilbestrol brought about further »androgen« decrease, whether therapy was begun shortly after the operation or a relatively long time after.

These chromatograms demonstrate that 30 mg. stilbestrol daily has no effect on a patient formerly orchiectomized. The same results are obtained regarding patients treated both with 5 and 30 mg. stilbestrol for up to 50 days.

DISCUSSION

In 1932 Moore & Price showed that the atrophic action of estrogens on the testes was produced by inhibition of gonadotrophin from the hypophysis. This has since been confirmed in many investigations (Byrnes et al., 1951. Gauren-
stroom et al., 1948, Greep et al., 1950, Jungck et al., 1947, Rowlands et al., 1950, Salhanick et al., 1952): The effect of estrogens in prostatic cancer, therefore, has good theoretic justification, as gonadotrophin (ICSH) stimulates the testicular androgen production. But the dosage by which the best clinical results can be achieved has been the subject of debate. The investigations herein presented have shown that 5 mg. of stilbesterol administered daily lowers the excretion of the 17-ketosteroids and »androgen metabolites«, and that 30 mg. has a stronger action in this respect. The latter dosage probably causes total inhibition of testicular androgen secretion, since subsequent orchiectomy resulted in no further decrease of androsterone and etiocholanolone. Thus 30 mg. of stilbesterol daily per os may be regarded as true castration dosage. Whether or not the same effect may be achieved by somewhat lower dosage will be a matter for further investigations.

In this connection it should be pointed out that, when the indications for orchiectomy in carcinoma of the prostate are doubtful, 30 mg. of stilbesterol daily should be given for a short period, and the effect on the 17-ketosteroids and preferable also on the »androgens« studied. If no distinct decrease is observed, it can scarcely be presumed that orchiectomy will be beneficial. In such patients the testicular production of androgens plays an insignificant rôle. Should an obvious reduction appear, however, it may reasonably be considered that the testes have greater significance for the growth of the tumour.

In patients with intact testes and adrenals, estrogens appear to inhibit the gonadotrophin of the hypophysis and the consequent effect on the testes is expressed as a pronounced fall in the excretion of androsterone and etiocholanolone. The picture becomes considerably more complicated when estrogens are given to patients in whom the testes have been removed. Whether or not estrogens then affect the excretion of 17-ketosteroids has hitherto been studied in detail by Hamburger (1951), who could find no change in this respect. Estrogens inhibit the secretion of gonadotrophin, and Reifenstein et al. (1945) considered the excretion of adrenal androgens to be influenced by ICSH. Christensen (1944), however, reported inhibition of the gonadotrophin, growth and thyrotrropic hormones of the hypophysis, but no atrophy of the adrenals: this despite the fact that the dosage of estrogen was so high as to produce chromophobe adenoma. Several writers have expressed the opinion that estrogens may produce adrenal hypertrophy and that this necessitates an intact hypophysis (Burrows, 1936, Castillo et al., 1937, Ellison et al., 1936, Golla et al., 1941). Some investigators could not verify this observation (Clausen et al., 1939, Selye et al., 1942). The process by which this hypertrophy develops is outside the scope of the present study. But theoretically it would perhaps seem more conceivable that the stimulating effect of estrogens on adrenocorticotropic hormone, which has been demonstrated by many writers (Christensen, 1944, Gemzell. 1952, Long et al., 1945, Lurie, 1950), should be the cause of adrenal
hypertrophy. Gemzell (1952) described increased ACTH in the blood of laboratory animals which had received estrogens. A significant point in this connection, however, is that in most of the studies which showed adrenal hypertrophy the estrogen dosage was high enough to have been capable of causing purely nonspecific stress according to Selye (1950).

If then, estrogens in high and relatively high dosage produce increased secretion of ACTH, it would seem scarcely rational to give estrogens after orchiectomy when, according to this reasoning, one may anticipate only a heightened excretion of the 17-ketosteroids. We therefore considered it important to study the effect of estrogen therapy following orchiectomy. But no significant change was observed in either the total or the relative 17-ketosteroid excretion. A possible explanation may be that the therapeutic dosage of stilbesterol given for a fairly short time produced no noteworthy rise in the secretion of ACTH, and therefore no change in the 17-ketosteroids. No difference was noted between the results of 5 mg. and 30 mg. dosage. It is, of course, desirable that the present investigation should be supplemented by a study of more protracted estrogen therapy, and this is now in progress. The absence of direct action by therapeutic doses of stilbesterol on the postorchiectomy excretion of 17-ketosteroids and of androsterone and etiocholanoione would seem to make such therapy of doubtful value. Additional negative evidence is supplied by the fact that gonadotrophin has at least no pronounced effect on the 17-ketosteroid or androgen excretion of orchiectomized men. But it is obvious that, as Huggins et al. (1940) has pointed out, a direct action of estrogens on the cancerous tissue is conceivable, and this would warrant stilbesterol therapy after castration. Seen solely as a question of androgen excretion, however, the present study has shown that estrogens, in the dosage used, are without effect in orchiectomized men.

Nesbit et al. (1950) found that an estrogen dosage of 1–5 mg. daily was better than no treatment at all. The five-year survival rates showed that orchiectomy and estrogen therapy together were most effective in patients without metastases. Orchiectomy was considered superior to estrogens when metastasization had occurred. In these latter cases combined therapy seemed to provide no advantage to orchiectomy alone.

In the present investigation many of the chromatograms showed an increase in fraction 5 during estrogen therapy. This steroid was isolated, but its infrared spectrum could not be identified, as it did not confirm to any steroid spectrum available to us. Chemical identification was precluded by the small amounts of the steroid. Its isolation from a large pool of urine is being performed. The significance of its increase in some patients undergoing therapy is, of course, difficult to assess at this stage.
SUMMARY

The effect of estrogen therapy before and after orchiectomy for carcinoma of the prostate was studied by separation of the various 17-ketosteroids, and analysis with infrared spectrography. The results were as follows.

1. Prior to orchiectomy 5 mg. of stilbesterol given daily for 5 days reduced the urinary excretion of androsterone and etiocholanolone by about 34 per cent. and of the 17-ketosteroids by an average of 17 per cent.

2. In 2 patients given 5 mg. of stilbesterol for a longer period, no certain further reduction of the 17-ketosteroids or of androsterone and etiocholanolone was observed.

3. A daily dose of 30 mg. stilbesterol for five days brought about a decrease of 42 per cent in the 17-ketosteroid excretion. Androsterone and etiocholanolone excretion fell by 63 per cent, i. e. a considerably stronger effect than that of the 5 mg. dosage.

4. In patients given 30 mg. of stilbesterol preoperatively, orchiectomy produced no further decrease of the 17-ketosteroids or of androsterone and etiocholanolone.

5. Postorchiectomy medication with 5 mg. and 30 mg. of stilbesterol was also ineffective in reducing the excretion of the above steroids.

6. The clinical aspects of the question are discussed.

REFERENCES


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