Observations on the Ketosteroid Content of Urine from Patients with Prostatic Carcinoma and Adenoma*


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The relation of sex hormones to enlargement of the prostate was reviewed by Dodds (2). Observations by Huggins and associates (5) led to the conclusion that androgens stimulate activity of the prostate and that estrogens have a depressing effect. Dean (1) reported observations on the androgen content of urine from cases of prostatic carcinoma before and after treatment by castration and by administration of estrogens. Urinary levels prior to castration appeared to be low. Data on urinary excretion of androgens have been reported by Fraser and associates (3), mainly for normal subjects and for persons with endocrine disorders. The content of 17-ketosteroids in the urine of patients with prostatic cancer was determined before and after castration by Scott and Vermeulen (6). Normal values have been given also by Venning and Kazmin (7). Since there has been a wide-spread assumption that sex hormones were involved in the production of carcinoma of the prostate, it seemed advantageous to determine urinary excretions of ketosteroids by patients having carcinomas or adenomas of the prostate.

METHODS

The quantity of 17-ketosteroids was determined chemically by a modification of the procedure of Holtorff and Koch (4), involving an adaptation of the Zimmerman color reaction (8). Briefly, the method involves hydrolysis to liberate the ketosteroids from esters, extraction of the ketosteroids with benzene, removal of phenolic material with sodium hydroxide, and the development of color by combination of ketosteroids with m-dinitro benzene in the presence of aqueous potassium hydroxide. Color determinations were made in the Coleman universal spectrophotometer set at 520 m\(\mu\), using pure androsterone as a standard. Neutral 17-ketosteroids were calculated as androsterone. Recovery of known amounts of androsterone added to urine samples averaged 94 per cent.

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Except in special cases noted below, 24-hour specimens of urine were used. Usual preservatives, such as toluene and chloroform, which are solvents for ketosteroids, are unsatisfactory for this analysis. Benzoic acid was found to be suitable since it preserved the urine and did not interfere with the determination. It was employed in a concentration of 2 gm. per collection bottle (0.1 to 0.2 per cent weight by volume). Urine specimens were kept cool whenever possible, and analyses were made shortly after collection was complete.

Under prevailing conditions of staff shortages in hospitals, there was some difficulty in collecting 24-hour specimens. It was suggested that morning specimens would give sufficient information. Analyses of samples from 2 normal subjects, obtained thrice daily for 4 consecutive days, showed considerable variation in 17-ketosteroid content. Contrary to expectation, the morning specimen did not always have the highest concentration. Because of the variability found in these specimens, it seemed advantageous to use only 24-hour samples.

Observations on cases of prostatic carcinoma and adenoma.—About 200 specimens were obtained from 32 cases of carcinoma and from 39 cases of adenoma. The levels were contrasted with those found in specimens from 19 normal males. Data are given in Table I. The range of values found for normal subjects is in agreement with the observations for similar persons reported by Fraser and associates (4), by Scott and Vermeulen (6), and by Venning and Kazmin (7). It should be noted that normal subjects were appreciably younger than persons in the carcinoma and adenoma groups. It was not possible to obtain specimens from normal men of older ages. Total 24-hour excretion of ketosteroids by cases of carcinoma and adenoma of the prostate were fairly similar and were definitely lower than values found for younger normal persons. If prostatic carcinoma results from, or is coincident with, an abnormal secretion of androgenic hormones, an increased output in the urine would be expected.
This was not the case in the patients on whom observations were made. The lower values actually found were similar to the preaccretion data reported by Dean (1) and are probably a reflection of the ages of the subjects. They are intermediate between the values for older subjects found by Fraser and associates (3) and by Venning and Kazmin (7).

**Table I: 24-Hour Excretion of 17-Ketosteroids**

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>19</th>
<th>39</th>
<th>32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>20–60</td>
<td>48–82</td>
<td>56–89</td>
</tr>
<tr>
<td>Range</td>
<td>10.1–23.2 mgm.</td>
<td>18.2 mgm.</td>
<td>16.8 mgm.</td>
</tr>
<tr>
<td>Average</td>
<td>16.2 mgm.</td>
<td>10.2 mgm.</td>
<td>10.0 mgm.</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>4.02 mgm.</td>
<td>4.00 mgm.</td>
<td>4.12 mgm.</td>
</tr>
<tr>
<td>Correlation (r)</td>
<td>0.4930*</td>
<td>0.1370</td>
<td>0.4732†</td>
</tr>
</tbody>
</table>

*Significant at the 5 per cent level.
†Significant at the 1 per cent level.

**Relation of ketosteroid output and urine volume.**—In considering the data shown in Table I it was observed that there was some indication of a relation of the total amount of ketosteroids to the volume of urine. Calculation of correlation coefficients showed that the relation was significant at the 5 per cent level for normal subjects and at the 1 per cent level for carcinoma patients. The relation was not significant for adenoma patients.

To obtain further information on a correlation between volume of urine and output of ketosteroids, 24-hour specimens were obtained, for 13 consecutive days, from a normal male, 45 to 50 years of age. During the first 9 days no attention was paid to ingestion of fluids and the variation in output was small. The correlation coefficient for this period was very slightly less than significant at the 5 per cent level. During the remaining 4 days, the subject took large amounts of fluids. Urinary volume and content of 17-ketosteroids were markedly increased, the latter by about 50 per cent. For this entire series of specimens, the correlation between volume and total output of 17-ketosteroids was significant at the 1 per cent level. The data are given in Table II.

**Table II: 17-Ketosteroid Excretion of a Normal Male, 45–50 Years of Age**

<table>
<thead>
<tr>
<th>Range</th>
<th>9 consecutive days</th>
<th>13 consecutive days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>14.6–18.7 mgm.</td>
<td>14.6–24.0 mgm.</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>1.70</td>
<td>2.66</td>
</tr>
<tr>
<td>Correlation (r)</td>
<td>0.5369</td>
<td>0.7669†</td>
</tr>
</tbody>
</table>

†Significant at the 1 per cent level.

**Relation of ketosteroid concentration to specific gravity.**—Arising from the observations on the relation between volume and the total daily excretion of ketosteroids, it seemed advantageous to determine if there was also a relation between specific gravity of urine and the concentration of ketosteroids (i.e., the amount per unit of volume).

For this series of samples from a normal subject referred to in the previous section, there was a highly significant correlation. The data are given in Table III. This correlation was not suspected until after analyses had been made on a considerable number of the hospital specimens and for these earlier samples specific gravity was not measured. Hospital specimens on which specific gravity was determined showed an indication of the same correlation, as determined by plotting specific gravity against ketosteroid concentration.

**Table III: 17-Ketosteroid Excretion of a Normal Male, 15–50 Years of Age**

<table>
<thead>
<tr>
<th>Range</th>
<th>9 consecutive days</th>
<th>13 consecutive days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>1.18–1.84</td>
<td>0.88–1.84</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>0.26</td>
<td>0.29</td>
</tr>
<tr>
<td>Correlation (r)</td>
<td>0.8723†</td>
<td>0.9012†</td>
</tr>
</tbody>
</table>

†Significant at the 1 per cent level.

**DISCUSSION**

The data given in Table I show that in a series of 32 patients, in whom a diagnosis of prostate carcinoma was definitely made, there was not an abnormally high output of 17-ketosteroids in the urine. In fact the output was less than that observed in normal males of younger age. The amounts observed were probably compatible with the ages of the patients. The data are in agreement with the report of Scott and Vermeulen (6). It is concluded that the estimation of 17-ketosteroids in the urine is of no value as a guide to hormone therapy in the treatment of carcinoma of the prostate.

The observed relations between daily output of ketosteroids and urinary volume and between urine specific gravity and ketosteroid concentration cause doubt to arise as to the value of determinations of ketosteroids in urine for diagnostic purposes. The assumption is made frequently that estimation of a constituent of urine is an indication of the amount of the constituent in the blood and in the body. The data here recorded give an impression that the daily excretion of ketosteroids varies with the amount of urine.
and that the concentration of ketosteroids parallels the amount of solids in the urine. These data indicate that, in some cases at least, the excretion of ketosteroids is dependent upon kidney function and is not a reflection of the amount of ketosteroids available in the body. Some indications are available, however, which lead us to think that the two relations described above hold only when the metabolism of 17-ketosteroids is approximately normal. Specimens from young children and from cases of adrenal tumor and of pituitary tumor have not shown these relations. These observations suggest an approach to the interpretation of analyses of ketosteroids in urine. If values for a series of normal specimens are available, a curve showing either the relation of total output to urine volume or of concentration to specific gravity can be plotted. An observation failing to fit the curve, within the limits of error, may be regarded as abnormal. On this basis the values for carcinoma patients shown in Table I may be considered as "normal." In our opinion data regarding ketosteroids in urine should be considered in conjunction with urinary volume or specific gravity, depending upon whether total excretion or concentration is measured. Unless this is done, misleading conclusions may be drawn.

SUMMARY

Colorimetric estimations of 17-ketosteroids in urine specimens from cases of prostatic carcinoma and adenoma gave values for daily output less than those found for normal males of younger age. The low values are probably normal for the ages of the patients. In these patients the estimation of urinary ketosteroids was of no value in the diagnosis of carcinoma of the prostate and was not useful as a guide to hormone therapy. For the normal controls and for the carcinoma patients there were correlations between the daily output of ketosteroids and the volume of urine, and between the concentration of ketosteroids in the urine and its specific gravity. It is suggested that these correlations, indicative of the effect of kidney function, should be kept in mind in estimations of ketosteroids in urine.

REFERENCES
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