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HORMONAL THERAPY IN CANCER OF THE BREAST

I. The Effect of Testosterone Propionate Therapy on Clinical Course and Hormonal Excretion

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BENJAMIN N. HORBITT, PH.D., JOSEPH V. SCHLOSSER, M.D., and
PAUL J. MURISON, M.D.

It now appears well established that testosterone propionate has limited therapeutic effectiveness in patients with advanced mammary carcinoma. However, we are aware of only a few reports in which the effect of this therapy upon hormone excretion was studied. Hamburger and Kaas followed the 17-ketosteroid excretion in patients being treated for advanced mammary cancer with testosterone in various doses and by varying routes of administration. Taylor, Metke, and Twombly gave testosterone propionate to a normal control and to a patient with cancer of the breast recently operated upon and followed their estrogens and androgens excretion. In the present study, an attempt was made to evaluate the effect of testosterone propionate therapy on hormone excretion patterns, and, if possible, to correlate the effects with the clinical course.

Materials and Methods

All patients under study received 100 mg. of testosterone propionate in vegetable oil either daily or every other day.

Occasionally, a patient was unable to return for additional medication at the proper time so that therapy was interrupted for a week or ten days. In the majority of patients, during collection of urine for hormone studies, testo-

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The authors wish to express their thanks to Ciba Pharmaceutical Products, Inc., Summit, New Jersey, which supplied, through the courtesy of Mr. Fred Huntington, the testosterone propionate, in part with material set aside for the Committee on Research of the Council on Pharmacy and Chemistry of the American Medical Association, under schedule "C" of the Subcommittee on Steroids and Cancer.

Received for publication, October 20, 1950.

terone propionate was administered as 50 mg. daily in order to eliminate peaks and valleys that might be produced by therapy on alternate days.

In addition to clinical studies, roentgenograms were made before initiation of therapy and at approximately monthly intervals during therapy. Photographs and caliper measurements of accessible lesions were made both before and during therapy. In a few instances, serial biopsies were obtained. These observations were the means for determining objective changes.

An attempt was made to evaluate hormonal patterns before and during therapy. Urinary excretion of 17-ketosteroids, gonad-stimulating hormones, lactogenic hormone (prolactin), glycogenic corticoids, and urinary creatine-creatinine ratios were measured.

The 17-ketosteroid values were determined on the total neutral fraction by the Zimmerman reaction with aqueous sodium hydroxide, dehydroisoandrosterone being used as a standard. Gonad-stimulating-hormone excretion was measured by the mouse-uterine weight method of Klinefelter, Albright, and Grizzle; the charted value represented the highest positive value obtained. Urinary excretion of prolactin was assessed by the pigeon-crop method of Coppedge and Segaloff. Veming, Kazim, and Bell's method for glycogenic corticoids was used. Because of variations with different batches of mice, urinary extracts prepared from the urine of the same patient before and during therapy were kept in the dry state in the refrigerator and assayed simultaneously. Only these simultaneously assayed glycogenic corticoids are included in the final averages, although the other values are presented for completeness. Creatine and creatinine were measured by the alkaline picric acid reaction. Creatine was converted to creatinine by acid hydrolysis.
TABLE 1

<table>
<thead>
<tr>
<th>Response</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regressive</td>
<td>13</td>
</tr>
<tr>
<td>No change</td>
<td>2</td>
</tr>
<tr>
<td>Progressive</td>
<td>30</td>
</tr>
<tr>
<td>Unsuitable for evaluation</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>48</strong></td>
</tr>
</tbody>
</table>

CANCER March 1951

Forty-eight patients were treated with testosterone propionate. Their ages ranged from 25 to 75 years, with thirty-five more than 40 years of age. The majority had known of the presence of the tumor less than five years, although this period also varied considerably from less than one year to nineteen years. All but two patients had received surgical therapy, irradiation, or both, to the initial lesion. Prior to admission to the study, almost all patients had undergone the menopause either normally or by surgical or roentgenological castration. In instances in which castration produced regression in the metastatic lesions, treatment with testosterone propionate was initiated only after evidence of renewed progression of the metastases was found.

Patients were followed whether they had skeletal metastases, soft-tissue lesions, or both. In nearly all patients, testosterone propionate was the first steroid therapy administered. Three patients who had received other therapeutic agents while taking testosterone propionate and were considered unsuitable for evaluation are included in the final summary (Table 1) but have been omitted from Table 2. In all except two patients, administration of testosterone propionate was continued until there was unequivocal evidence of progression of the disease. These two patients, in whom there was definite regression of the lesions and who discontinued therapy against advice, were subsequently given an additional course of testosterone propionate when they returned with further growth of the lesions. All patients were treated for at least one month; the total duration of therapy varied from one month to more than one year.

RESULTS

Thirteen of the forty-eight patients, or 27 per cent, showed objective regression of the lesions. The few patients who showed evidences of both progression and regression were classified as showing progression (Table 1). The duration of regression extended over an average period of 31.5 weeks, the longest being fifty weeks. It is interesting that in none of the ten patients less than 40 years old was a good response obtained, whereas a third of those more than 40 years old showed improvement. The length of time the tumor was present prior to testosterone therapy was approximately the same for the group showing progression as for those who showed improvement. No correlation was noted between the type of menopause experienced and the therapeutic result obtained, except that the patients who were still menstruating gave uniformly poor results. The response of the patients according to the site of the lesion is shown in Table 2.

Tables 3 and 4 contain excretion data on the patients before and during therapy. Studies during treatment were all done after at least one month of therapy. Only data on patients in whom studies were obtained both before and during treatment are included in this presentation. In those tables, the averages are also expressed as percentage change from the initial value obtained before therapy. As expected, there was an increase in the 17-ketosteroid excretion as well as a decrease in the urinary gonad-stimulating-hormone excretion. In general, there was an increase in lactogenic hormone. These changes could not be correlated with the presence or absence of objective improvement. There was a decrease in the urinary glycogenic corticoids in the group that showed objective improvement, whereas there was an increase in the groups that did not show improvement. However, it is doubtful whether this difference is significant. The greatest difference was noted in urinary creatine excretion, which decreased in the patients who improved and increased in those who failed to improve. This difference is more uniform and more striking when expressed as the creatine-creatinine ratio.

TABLE 2

<table>
<thead>
<tr>
<th>Site</th>
<th>No. of cases</th>
<th>Regression</th>
<th>Progression</th>
<th>Unchanged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal</td>
<td>13</td>
<td>5 (38.5)</td>
<td>8 (61.5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>11</td>
<td>3 (27.3)</td>
<td>8 (72.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Both</td>
<td>24</td>
<td>8 (33.3)</td>
<td>14 (58.3)</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>45</strong></td>
<td><strong>13</strong></td>
<td><strong>30</strong></td>
<td><strong>2</strong></td>
</tr>
</tbody>
</table>

HORMON
### Table 3

**Urinary Excretions Before and During Testosterone Therapy in Patients with Carcinoma of the Breast Showing Objective Improvement**

<table>
<thead>
<tr>
<th>Case no</th>
<th>Creatinine, gm./24 hr.</th>
<th>17-Ketosteroids, mg./24 hr.</th>
<th>Gonad-stim.-born., m.u./24 hr.</th>
<th>Cortin, mg. C'p'd. A'T/24 hr.</th>
<th>Prolactin, I.U./24 hr.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>During</td>
<td>Before</td>
<td>During</td>
<td>Before</td>
</tr>
<tr>
<td>1</td>
<td>I.A.</td>
<td>0.087 (5)</td>
<td>0.051 (8)</td>
<td>0.639 (5)</td>
<td>0.608 (8)</td>
</tr>
<tr>
<td>6</td>
<td>A.D.</td>
<td>0.031 (5)</td>
<td>0.013 (5)</td>
<td>0.213 (5)</td>
<td>1.33 (3)</td>
</tr>
<tr>
<td>14</td>
<td>E.M.</td>
<td>0.072 (2)</td>
<td>0.180 (4)</td>
<td>0.210 (2)</td>
<td>0.504 (4)</td>
</tr>
<tr>
<td>15</td>
<td>A.M.</td>
<td>0.043 (3)</td>
<td>0.000 (4)</td>
<td>0.157 (3)</td>
<td>0.904 (3)</td>
</tr>
<tr>
<td>19</td>
<td>A.L.</td>
<td>0.006 (4)</td>
<td>0.043 (4)</td>
<td>0.708 (4)</td>
<td>0.830 (4)</td>
</tr>
<tr>
<td>20</td>
<td>A.L.</td>
<td>0.020 (4)</td>
<td>0.101 (7)</td>
<td>1.43 (4)</td>
<td>0.788 (7)</td>
</tr>
<tr>
<td>20</td>
<td>E.A.</td>
<td>0.152 (4)</td>
<td>0.185 (11)</td>
<td>1.95 (4)</td>
<td>1.78 (11)</td>
</tr>
<tr>
<td>31</td>
<td>R.P.</td>
<td>0.061 (4)</td>
<td>0.094 (8)</td>
<td>0.908 (4)</td>
<td>1.23 (8)</td>
</tr>
<tr>
<td>40</td>
<td>P.C.</td>
<td>0.182 (4)</td>
<td>0.009 (4)</td>
<td>0.904 (4)</td>
<td>3.05 (4)</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>0.175</td>
<td>0.060</td>
<td>0.783</td>
<td>1.045</td>
</tr>
</tbody>
</table>

*Numbers in parentheses indicate the number of determinations.
† Compound A.
‡ Assays not run in pairs; not included in averages.
§ The average creatinine-creatinine ratio before therapy was 0.223; during therapy, 0.053; the decrease in ratio is 72 per cent.

### Table 4

**Urinary Excretions Before and During Testosterone Therapy in Patients with Carcinoma of the Breast Showing No Objective Improvement**

<table>
<thead>
<tr>
<th>Case no</th>
<th>Creatinine, gm./24 hr.</th>
<th>17-Ketosteroids, mg./24 hr.</th>
<th>Gonad-stim.-born., m.u./24 hr.</th>
<th>Cortin, mg. C'p'd. A'T/24 hr.</th>
<th>Prolactin, I.U./24 hr.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>During</td>
<td>Before</td>
<td>During</td>
<td>Before</td>
</tr>
<tr>
<td>4</td>
<td>P.C.</td>
<td>0.171 (3)</td>
<td>0.158 (3)</td>
<td>0.478 (3)</td>
<td>0.570 (3)</td>
</tr>
<tr>
<td>5</td>
<td>L.G.</td>
<td>0.073 (2)</td>
<td>0.062 (2)</td>
<td>0.570 (2)</td>
<td>0.570 (2)</td>
</tr>
<tr>
<td>7</td>
<td>C.C.</td>
<td>0.344 (4)</td>
<td>0.253 (5)</td>
<td>0.858 (4)</td>
<td>0.917 (5)</td>
</tr>
<tr>
<td>13</td>
<td>J.M.</td>
<td>0.000 (4)</td>
<td>0.000 (4)</td>
<td>0.925 (4)</td>
<td>0.925 (4)</td>
</tr>
<tr>
<td>12</td>
<td>J.M.</td>
<td>0.187 (3)</td>
<td>0.166 (4)</td>
<td>0.225 (3)</td>
<td>0.225 (4)</td>
</tr>
<tr>
<td>16</td>
<td>A.M.</td>
<td>0.001 (4)</td>
<td>0.014 (5)</td>
<td>0.43 (4)</td>
<td>0.449 (5)</td>
</tr>
<tr>
<td>22</td>
<td>M.S.</td>
<td>0.016 (4)</td>
<td>0.154 (5)</td>
<td>1.1 (1)</td>
<td>1.01 (1)</td>
</tr>
<tr>
<td>30</td>
<td>A.R.</td>
<td>0.040 (4)</td>
<td>0.256 (5)</td>
<td>0.711 (4)</td>
<td>0.711 (5)</td>
</tr>
<tr>
<td>36</td>
<td>N.H.</td>
<td>0.077 (3)</td>
<td>0.301 (12)</td>
<td>0.583 (3)</td>
<td>0.494 (12)</td>
</tr>
<tr>
<td>38</td>
<td>D.A.</td>
<td>0.070 (3)</td>
<td>0.290 (2)</td>
<td>0.620 (3)</td>
<td>0.389 (2)</td>
</tr>
<tr>
<td>50</td>
<td>M.N.</td>
<td>0.043 (5)</td>
<td>0.137 (4)</td>
<td>0.748 (5)</td>
<td>0.249 (4)</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td>0.125</td>
<td>0.166</td>
<td>0.753</td>
<td>0.754</td>
</tr>
</tbody>
</table>

*Numbers in parentheses indicate the number of determinations.
† Compound A.
‡ Assays not run in pairs; not included in averages.
§ The average creatinine-creatinine ratio before therapy was 0.166; during therapy, 0.220; the increase in ratio is 33 per cent.
DISCUSSION

Early in this study it appeared that administration of testosterone propionate was leading to an increase in urinary excretion of glycogenic corticoids. These early assays (marked *) are shown in Tables 3 and 4 but were not included in the averages. However, realizing the importance of the animal factor, we began breeding our own assay mice as well as running the specimens before and during therapy in the same batch of mice at the same time. The great differences apparent in the early studies then disappeared. It is doubtful that the differences observed with these more stringent methods for assay of glycogenic corticoids are of any significance. It is to be recalled that administration of testosterone has been shown to decrease urinary glycogenic corticoids.10

Our original studies in the development of a method for the assay of urinary prolactin were undertaken because of our belief that prolactin might be involved in the development of mammary carcinoma. This is particularly borne out by the preponderance of nulliparous women in the present study (twelve of twenty-eight in whom information was obtained). This is merely confirmation of the observations of others.5 However, it does appear that there is neither consistent change in urinary prolactin observed in women with cancer of the breast, nor any distinct pattern of response of urinary prolactin to various types of hormonal therapy. We are now surveying various pathological entities and increasing our normal reference group so that the possible significance of these studies can be assessed. Nonetheless, it is of interest to note that there has been a definite trend toward increase of urinary prolactin excretion during testosterone propionate therapy in both the improved and unimproved groups.

The rise in 17-ketosteroid excretion observed in both groups was, of course, to be expected following the administration of testosterone propionate. The mean rise for both groups represents somewhat less than 20 per cent of the original steroid administered (calculated as free testosterone). The amount of increase in each patient varied from essentially nothing to 22.5 mg. per twenty-four hours. The latter figure represents a total recovery of 54 per cent in that patient. These are the expected results, and here again, it is particularly noteworthy that there is no substantial difference between the patients responding well and those not responding at all.

The one patient (case 6) who failed to show an increase was seen early in the study and was treated with 100 mg. three times weekly during the collection, and these 17-ketosteroid values are each only from a single determination.

The results with urinary gonad-stimulating hormone are equally interesting despite the well-known difficulties of lowering the urinary titer of gonad-stimulating hormones with more modest amounts of testosterone.6 The dosage administered here uniformly produced a decrease in the urinary excretion of gonad-stimulating hormone, which again was unrelated to the patient’s therapeutic response. However, the initial values obtained are of great interest in that the patients’ ages and endocrine status were such that extremely high titers of urinary gonad-stimulating hormone were expected. This was not at all true. It is our opinion that the cachexia resulting from the extensive disease in these patients produced an effect similar to that seen in the “pseudohypophysectomy” of starvation; i.e., the cachexia induced a sort of physiological hypophysectomy with respect to gonad-stimulating hormone. That this was not a complete type of pseudohypophysectomy is borne out by the lack of correlation between our usually measured gonad-stimulating hormones and the titer of lactogenic hormone, which is thought to be the third gonadotropic hormone or lutotropin.

Seven patients (cases 4, 15, 18, 22, 27, 36, and 50) showed this initial “pseudohypophysectomy.” The majority of these (six of the seven) fell in the group who failed to respond favorably to therapy. Two of these (cases 4 and 18) were in poor shape, were too young for spontaneous menopause, and had menstruated at least fairly regularly up to a few months before initiation of therapy. However, even if these are eliminated, there are still four patients (cases 22, 27, 36, and 50) in the unimproved group who manifested this phenomenon. It is of interest that in two (cases 4 and 18) of the patients, the low gonad-stimulating-hormone excretion was accompanied by a low 17-ketosteroid value but not by a low prolactin value.

The fairly uniform finding of creatininuria in patients in both groups is a reflection of the
HORMONAL THERAPY IN CANCER OF THE BREAST · 1 · Segaloff et al.

Summary

Forty-eight patients with advanced mammary carcinoma were treated with testosterone propionate. In thirteen of these, there was objective regression in the lesions, and in the others either progression or no change.

All patients showed the expected increase in 17-ketosteroid excretion as well as the expected decrease in gonad-stimulating-hormone excretion. In the patients who showed improvement, there was a decrease of doubtful significance in urinary corticoids, and conversely an increase in corticoids in the patients who did not show improvement. Prolactin excretion for both groups of patients increased.

In general, the patients who improved showed a decrease in urinary creatinine, whereas those who failed to improve showed an average increase in urinary creatinine. Many patients initially showed a lower urinary gonad-stimulating-hormone value than expected from their age and endocrine status. The significance of this is discussed.

REFERENCES


