Steroid Hormones and Tumor-Host Relations*

R. W. BEGG†

(Cancer Research Laboratory, Department of Biochemistry, Dalhousie University, Halifax, N.S.)

It has been demonstrated that testosterone propionate in oil causes an increase in hemoglobin and liver catalase activity in the normal rat but that the administration of the steroid in large doses could not overcome the characteristic anemia and loss of liver catalase activity in the tumor-bearing rat (2). It was of interest to see if these effects might be moderated by the administration of a more potent androgen.

The use of pellets of testosterone propionate provided another approach to the problem. Implanted in the subcutaneous tissues, these would give a slow steady absorption of the hormone which might be of greater effect than daily injections in oil.

A pattern of the systemic effects of tumors has been described and evidence presented to suggest that rats in the terminal stage of cancer may be in a state of adrenal cortical insufficiency (3). If this reasoning were valid, it might be anticipated that an exogenous supply of hormones of the adrenal cortex would modify the response of the host to the tumor.

METHODS

As test animals, a group of young, male Sprague-Dawley (Holtzman) rats bearing intramuscular grafts of the Walker 256 carcinoma in both thighs was used. On the ninth day of growth, when the tumors had attained a diameter of 10 mm., injections were begun or pellets implanted. The animals were maintained on Purina Fox Chow and tap water in a room controlled to 72°–78° F.

Testosterone cyclopentylpropionate (TCP) was given in two 5.0-mg. doses, one on the ninth and one on the fourteenth day of tumor growth. Lipo-Adrenal Cortex (LAC) was administered in daily injections of 0.5 ml., increasing to 1.5 ml., with different groups receiving 240, 360, and 420 rat units as total dose. Control animals were given appropriate amounts of cottonseed oil. Pellets of testosterone propionate (TPP) were implanted over the scapular region, five pellets per rat, each placed at a discrete site. At autopsy the pellets were removed, dried, and reweighed for the determination of total absorption.

Hemoglobin was estimated on tail blood the afternoon preceding sacrifice on the twentieth day of tumor growth, control rats being killed at the same time. The two androgen groups were given access to food and water until the end of the experiment, but the LAC group was starved for 16 hours and given 400 mg. glucose intraperitoneally 2 hours before sacrifice.

Tissues were removed under nembutal anesthesia and analyzed by methods previously described (3).

Tumors were measured in two diameters of each tumor and are expressed as the mean of the four diameters. In these experiments the tumor weight corresponds to approximately 25 per cent of the body weight.

RESULTS

Testosterone cyclopentylpropionate.—Table 1 indicates that the only significant difference between the control and treated groups is increased thymus atrophy in the rats given TCP. The mean adrenal weight is smaller in the treated group, but the variation considerable; a similar response is noted in adrenal cholesterol. The failure to influence

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* Aided by grants from the National Cancer Institute of Canada and the Nova Scotia Division of the Canadian Cancer Society.

† Research Associate, National Cancer Institute of Canada. Present address: Department of Medical Research, University of Western Ontario, London, Canada.

1 Testosterone cyclopentylpropionate was provided by the Upjohn Co. through the kindness of Dr. H. F. Halmian. The Upjohn Co. report that this compound has a more potent and prolonged androgenic activity than testosterone propionate.

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ence hemoglobin and liver catalase activity is evident.

**Testosterone propionate pellets.**—As indicated in Table 2, there is no apparent effect on adrenal ascorbic acid, but adrenal weight and cholesterol are both significantly lower in the treated group. A marked involution of the thymus was noted in the pellet-treated rats, but no significant effect on liver catalase activity or hemoglobin. The average absorption of testosterone propionate from the pellets was 0.99 mg/rat/day.

**Lipo-Adrenal Cortex.**—Table 3 demonstrates that the injection of adrenal cortical extract produced significant changes only in thymus weight, hemoglobin, and body weight. The mean weight of the two groups was the same at the beginning of the injections. It is difficult to interpret the decreased gain in body weight in the treated group, as the animals were not tube-fed, and the reduction in weight gain may be a reflection of a decreased food consumption. The characteristic loss of sudanophilia in the adrenals of tumor-bearing rats was not as marked in the treated as in the control group. Tumor growth was not inhibited by this treatment, and histological examination of the tumors from the treated animals did not reveal any variation from the control group.

**DISCUSSION**

The magnitude of a systemic effect is related to the size of the tumor (3). For this reason it is essential in an attempt to modify systemic effects that there be no difference in the growth rate and size of the tumors in the control and treated groups.

### TABLE 1

**EFFECT OF TESTOSTERONE CYCLOPENTYLPROPIONATE ON TUMOR-BEARING RATS**

<table>
<thead>
<tr>
<th>Control*</th>
<th>TCPP*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, gm.</td>
<td>245.1 ± 7.3(10)</td>
<td>282.8 ± 8.4(9)</td>
</tr>
<tr>
<td>Tumor diameter, mm.</td>
<td>39.0 ± 1.0(10)</td>
<td>39.1 ± 1.5(11)</td>
</tr>
<tr>
<td>Adrenal weight, mg.</td>
<td>28.5 ± 0.7(8)</td>
<td>28.5 ± 2.1(11)</td>
</tr>
<tr>
<td>Thymus weight, mg.</td>
<td>193.4 ± 20.7(9)</td>
<td>105.2 ± 14.0(11)</td>
</tr>
<tr>
<td>Hemoglobin, g/m/100 ml</td>
<td>8.05 ± 0.44(10)</td>
<td>7.67 ± 0.78(11)</td>
</tr>
<tr>
<td>Liver catalase, K×10⁴</td>
<td>1,064 ± 146(10)</td>
<td>2,053 ± 218(11)</td>
</tr>
<tr>
<td>Adrenal cholesterol, mg/100 mg</td>
<td>2.84 ± 0.28(8)</td>
<td>1.73 ± 0.20(11)</td>
</tr>
<tr>
<td>Adrenal ascorbic acid, mg/100 mg</td>
<td>0.315 ± 0.020(8)</td>
<td>0.315 ± 0.017(11)</td>
</tr>
</tbody>
</table>

* Number of observations in parentheses; ± standard error of the mean.
† Probability in t-test: <0.05—significant; <0.01—highly significant.

### TABLE 2

**EFFECT OF TESTOSTERONE PROPIONATE PELLETS ON TUMOR-BEARING RATS**

<table>
<thead>
<tr>
<th>Control*</th>
<th>Pellet*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, gm.</td>
<td>245.1 ± 7.3(10)</td>
<td>290.2 ± 8.8(11)</td>
</tr>
<tr>
<td>Tumor diameter, mm.</td>
<td>39.0 ± 1.0(10)</td>
<td>38.6 ± 1.0(11)</td>
</tr>
<tr>
<td>Adrenal weight, mg.</td>
<td>28.5 ± 0.7(8)</td>
<td>28.5 ± 0.7(11)</td>
</tr>
<tr>
<td>Thymus weight, mg.</td>
<td>193.4 ± 20.7(9)</td>
<td>50.8 ± 4.0(11)</td>
</tr>
<tr>
<td>Hemoglobin, g/m/100 ml</td>
<td>8.05 ± 0.44(10)</td>
<td>5.39 ± 0.70(11)</td>
</tr>
<tr>
<td>Liver catalase, K×10⁴</td>
<td>1,064 ± 146(10)</td>
<td>2,590 ± 118(11)</td>
</tr>
<tr>
<td>Adrenal cholesterol, mg/100 mg</td>
<td>2.84 ± 0.28(8)</td>
<td>1.09 ± 0.20(10)</td>
</tr>
<tr>
<td>Adrenal ascorbic acid, mg/100 mg</td>
<td>0.315 ± 0.020(7)</td>
<td>0.306 ± 0.018(11)</td>
</tr>
</tbody>
</table>

* Number of observations in parentheses; ± standard error of the mean.
† Probability in t-test: <0.05—significant; <0.01—highly significant.

### TABLE 3

**EFFECT OF LIP0-ADRENAL CORTEX ON TUMOR-BEARING RATS**

<table>
<thead>
<tr>
<th>Control*</th>
<th>LAC*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, gm.</td>
<td>233.4 ± 7.2(11)</td>
<td>299.3 ± 5.1(12)</td>
</tr>
<tr>
<td>Tumor diameter, mm.</td>
<td>46.3 ± 2.0(12)</td>
<td>45.8 ± 1.8(12)</td>
</tr>
<tr>
<td>Adrenal weight, mg.</td>
<td>29.4 ± 1.8(11)</td>
<td>97.4 ± 1.5(10)</td>
</tr>
<tr>
<td>Thymus weight, mg.</td>
<td>207.6 ± 17.6(11)</td>
<td>58.0 ± 6.9(10)</td>
</tr>
<tr>
<td>Hemoglobin, g/m/100 ml</td>
<td>8.5 ± 0.4(11)</td>
<td>10.4 ± 0.2(12)</td>
</tr>
<tr>
<td>Liver catalase, K×10⁴</td>
<td>953 ± 94(11)</td>
<td>759 ± 183(10)</td>
</tr>
<tr>
<td>Adrenal cholesterol, mg/100 mg</td>
<td>2.64 ± 0.30(11)</td>
<td>3.88 ± 0.44(10)</td>
</tr>
<tr>
<td>Adrenal ascorbic acid, mg/100 mg</td>
<td>0.314 ± 0.018(11)</td>
<td>0.291 ± 0.016(10)</td>
</tr>
<tr>
<td>Liver glycogen, mg/100 mg</td>
<td>0.44 ± 0.05(11)</td>
<td>0.45 ± 0.06(10)</td>
</tr>
</tbody>
</table>

* Number of observations in parentheses; ± standard error of the mean.
† Probability in t-test: <0.05—significant; <0.01—highly significant.
‡ Determined on a liver extract prepared by grinding with sand in a mortar. This procedure gives lower results than an extract prepared in a Waring Blender, as in the androgen experiments, but the ratio of the activity in the livers of control and tumor-bearing rats is the same in both methods.
§ Expressed as glucose, 3 hours after 400 mg. glucose intraperitoneally.
Steroid hormones have been shown to affect the growth of mammary tumors in the human and the response of the host to the tumor (11). In a rat bearing the Walker 256 carcinoma there is no effect on the tumor and only a slight influence on tumor-host relations. Haddow has directed attention to this discrepancy of the effect of chemotherapeutic agents in the laboratory and in the clinic (5).

Although TCP is a more potent androgen than testosterone propionate, this does not necessarily mean that it would have a greater effect on hemoglobin and liver catalase activity. Studies on the metabolic effects of the androgenic hormones have not yet established a correlation between action on enzyme systems and protein synthesis and the effects on the seminal vesicles and prostate of the castrate, immature rat. Kochakian has demonstrated that some steroids with a very weak or absent androgenic activity may have a moderate influence on alkaline phosphatase and thymus involution (8).

The thymus involution in tumor-bearing rats implanted with pellets of testosterone propionate is the greatest that has been observed. The gland is reduced in most instances to a small thread-like structure. This marked involution is produced by the absorption of 1 mg. per day from the pellets and exceeds that resulting from the injection of 2 mg. a day of the same steroid in oil.

The degree of adrenal hypertrophy was reduced by pellets of testosterone propionate, and it might be inferred that the release of ACTH from the pituitary was inhibited by testosterone (1,4). If this were true, an increase in adrenal ascorbic acid might have been expected but was not demonstrated.

The extract of adrenal cortex was able to reduce the degree of anemia but had no influence on the loss of liver catalase activity. It has been reported that an aqueous extract of the adrenal increases hemoglobin in the rat (12).

There appears to be some variation in the response of tumors to steroids of the adrenal cortex (10), but an inhibition of growth of the Walker 256 carcinoma has been reported (7). This occurs in the presence of an inhibition of body growth more marked than in this series.

The failure of LAC to affect the adrenal may not have been evident because of the design of the experiment. The mean weight of the adrenal in the treated group is smaller, and the cholesterol content higher, than in the control. If the series were expanded to include larger numbers of animals, the differences might become significant. Such a possibility is supported by the fact that LAC did have a sparing action on the loss of adrenal sudanophilia, which has been correlated with cholesterol content (9).

The failure to produce anticipated effects may be more fundamental, and concerned with an inadequate dosage of LAC. It has been estimated that the daily output of the adrenals in the rat is the equivalent of 25 ml. of an aqueous extract of the adrenal cortex, based on the amount required to permit normal performance of the work test in the adrenalectomized rat (6).

SUMMARY

Pellets of testosterone propionate reduce adrenal hypertrophy in the tumor-bearing rat, and an extract of the adrenal cortex diminishes the degree of anemia. No effect was noted on the growth of the Walker 256 carcinoma.

ACKNOWLEDGMENTS

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REFERENCES

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R. W. Begg

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