The Influence of Exercise on the Growth of Transplanted Rat Tumors*

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SUMMARY

Growth of the Walker 256 tumor in vigorously exercised male Wistar rats was compared with that of control animals confined in small, individual cages, permitting a minimum of movement. In each instance the weight of the tumor in the control group significantly exceeded that in the exercised group. In several instances there was complete tumor regression in the exercised animals.

Rat muscles were suspended in a 0.85 per cent NaCl bath and electrically stimulated to "fatigue." An extract of this bath (F-Substance) inhibited the growth of the Walker 256 and Murphy lymphosarcoma when injected either at the tumor site or on the opposite side. An extract prepared in a similar manner from nonfatigued muscle was found to be ineffective.

Bullough (1) reported that the number of mitoses in the skin was significantly diminished in mice forced to exercise vigorously; this was interpreted in terms of a diminished source of energy, specifically carbohydrates, available for the mitotic process. Heilbrunn (2) found that cleavage did not occur in fertilized sea urchin eggs kept in sea water in which lobster muscle had been stimulated to fatigue. He interpreted these results as the effect of a mitosis-inhibiting substance produced by fatigued muscles. S.N. Most (4), working in Heilbrunn's laboratory, stimulated frog muscles to fatigue in a Ringer bath; when another frog muscle was suspended in the "fatigue Ringer bath" fatigue occurred earlier than in a normal Ringer bath. Heilbrunn also exercised tumor-bearing mice and obtained a moderate increase in survival time of the exercised mice (3). Similar experiments with transplanted tumors and tumors induced by methylcholanthrene were performed by Rashkis (5), who used exercise as a form of "stress." Rusch and Kline (6) also demonstrated diminished tumor growth in exercised animals; their results were interpreted from the standpoint of energy or food supply available for tumor growth in exercised animals as compared with tumor growth in starved animals. The present experiments were performed to determine whether a substance produced by fatigued muscle may inhibit tumor growth.

MATERIALS AND METHODS

Exercise experiments.—Walker 256 tumors were transplanted by injection of 2 cc. of a standard tumor cell suspension subcutaneously into the right thigh of 150-gm. male Wistar rats which were maintained on a diet of Purina Laboratory Chow and tap water ad libitum. Immediately following tumor transplantation 24 of the animals were exercised daily for 3 weeks, as follows: (a) the animal was first conditioned by electric shock to run continually in a 20-foot runway; (b) after a brief rest the animal was forced to swim, starting with a 20-minute period and increasing 20 minutes per day to a maximum of 4 hours; (c) finally, the animal was placed in a revolving drum where he ambulated each night for a recorded distance of 5.4 miles per 12 hours. Serving as controls were fifteen tumor-bearing animals which were confined in individual cages, 8" high and 5" in diameter, to keep activity at a minimum. All animals were sacrificed on the 21st day following tumor transplantation.

* Supported in part by the Damon Runyon Memorial Fund for Cancer Research, Inc. (DRG Grant 618).
† Deceased January 27, 1961.

Received for publication November 29, 1961.
Injection experiments.—In this group, 150-gm. male Wistar and Sprague-Dawley rats, maintained on a diet of Purina Laboratory Chow and tap water ad libitum, were given inoculations of the Walker 256 tumor or the Murphy lymphosarcoma as described above. The amount of “fatigue substance” (F-Substance) for each injection per rat was prepared as follows: one rectus femoris muscle of a rat was suspended in a 30-ml. 0.85 per cent NaCl bath kept at a constant temperature (37° C. to 39° C.). Electric stimulation was applied to produce contraction to the point of fatigue, as evidenced by lack of response to further stimulation. The bathing fluid was then dialyzed in a liter bath (distilled water), which was changed 4 times over a 24-hr. period, and the residue was lyophilized. The dried material, weighing 0.31 ± 0.19 mg., was dissolved in 2 ml. distilled water and injected subcutaneously. The injections were begun when the smallest tumor in the control animals reached a size of 2 cm. in diameter, 7-10 days following transplantation. All animals were sacrificed when the control animals began to show signs of distress due to presence of the tumor, 14-21 days after tumor transplantation. One group of tumor-bearing animals was treated with F-Substance, which had been prepared as described previously but stored for 1 year at −10° C.

RESULTS AND DISCUSSION

Exercise experiments.—The tumor weight (Walker 256) in control rats exceeded that of the exercised animals in every instance (P = 0.01). In several cases there was complete tumor regression in the exercised animals. The mean tumor weight of the exercised rats was 2.3 gm. (range: 0.0 [regression] to 11.5 gm.) as compared with a mean tumor weight of 66.9 gm. (range: 16.8 to 175.7 gm.) in the control animals. The average change in carcass weight of the exercised animals was +61.2 gm., whereas that of the control animals was +36.6 gm.

F-Substance experiments.—The pertinent findings are presented in Table 1. The weight of the tumors of the control animals in every instance exceeded that of the animals given injections; the smallest difference between the control group and the injected group had a P value of less than 0.05. There was complete tumor regression in several animals which had been given injections. There was no significant difference in carcass weight in the Walker 256 tumor experiments. However, in the Murphy lymphosarcoma experiment the change in carcass weight of the control animals (+8.3 gm.) was noticeably less than that of the treated animals (+31.7 gm.). F-Substance which was stored for 1 year in the frozen state also exhibited inhibition of tumor growth.

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TABLE 1

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Tumor</th>
<th>Tumor transplant site</th>
<th>Control animals</th>
<th>Experimental animals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No. rats</td>
<td>Tumor weight* (gm.)</td>
</tr>
<tr>
<td>I</td>
<td>Walker</td>
<td>Right thigh</td>
<td>8</td>
<td>12.2–53.3 (27.7)</td>
</tr>
<tr>
<td>II</td>
<td>Walker</td>
<td>Right thorax</td>
<td>10</td>
<td>0.9–44.2 (28.7)</td>
</tr>
<tr>
<td>III</td>
<td>Walker</td>
<td>Right thorax</td>
<td>26</td>
<td>0.9–54.5 (8.9)</td>
</tr>
<tr>
<td>IV</td>
<td>Lympho.</td>
<td>Right thorax</td>
<td>19</td>
<td>1.2–18.9 (17.7)</td>
</tr>
<tr>
<td>V</td>
<td>Walker</td>
<td>Right thorax</td>
<td>12</td>
<td>4.3–54.8 (14.7)</td>
</tr>
<tr>
<td>VI</td>
<td>Walker</td>
<td>Right thorax</td>
<td>21</td>
<td>2.0–44.3 (18.7)</td>
</tr>
</tbody>
</table>

* The tumor weights are presented as a range from the smallest tumor to the largest; the mean tumor weight for the group is given in parentheses.

† The change in carcass weight is the difference between the initial weight of the animal (at the time of transplantation) and the final weight of the animal following surgical removal of the tumor.
Experiments with nonfatigued muscle extract.—
The material obtained from the bath fluid of non-
stimulated muscle was found to be ineffective in
decreasing tumor weight (Table 1).

These data support the conclusions of Heilbrunn
(3) and Most (4) that a tumorstatic factor may
be produced by a contracting muscle. It does not
appear from these data that the tumorstatic effect
of exercise is due entirely to a divergence of energy
from tumor growth during exercise, as proposed
by Rusch and Kline (6). Food intake was not
measured. The increment of weight gain during
the experimental period was approximately the
same for the control and experimental groups,
except in the experiment in which the lymphosar-
coma was used.

Neither the nature of the substance nor the
mechanism of its action in retarding tumor growth
is known at this time. Histological examination
of the tumors did not indicate depression of mitotic
activity.

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