The Action of Cortisone and ACTH on Transplanted Mouse Tumors

RAYMOND G. GOTTschALK* AND ARTHUR GROLLMAN

(Department of Experimental Medicine, Southwestern Medical School of the University of Texas, Dallas, Tex.; and Veterans Administration Hospital and Department of Pathology, Baylor University College of Medicine, Houston, Tex.)

The inhibition of the growth of normal (1) and malignant (5, 7) lymphocytes of mice and rats by cortical secretions is paralleled by the remissions obtained with cortisone and ACTH in human lymphomas (8). Some other types of tumors are inhibited in mice by maximal doses of these products (11) but are not affected in man by the tolerated amounts of the drugs (2). Early attempts of therapy against varied human tumors (12) prompted us to test the effect of ACTH and cortisone on two nonlymphoid tumors of mice. Experiments were also performed which demonstrated that these products do not modify the growth of Rous sarcomas induced in chickens by inoculation of the virus (4).

MATERIALS AND METHODS

The tumors were implanted in BALB/c mice obtained from the Jackson Memorial Laboratory and fed a commercial diet (Rockland Farms Pellets) supplemented with carrots. The mammary carcinoma arose spontaneously in a mouse (B 324) of this strain. Two subcutaneous passages prior to this experiment resulted in 100 per cent takes. When the tumors reached a large size, they became in part necrotic or ulcerated. Metastases to the lungs and liver were frequent. The growth consisted of solid strads and cords of neoplastic cells occasionally forming acini or lining vascular spaces. The stroma was scanty.

For this experiment 0.1 ml. of a suspension of pooled mammary tumors in an equal volume of Locke's solution was injected under the skin of both flanks of eighteen 6-month-old female mice. One mouse of each group was injected in sequence. The size of the tumors was determined at intervals by palpation and plotted on a semi-logarithmic scale as the product of the three maximal dimensions. All mice were allowed to die.

The "ascites sarcoma" developed in mouse B 52 following an intraperitoneal implant of a pellet of paraffin impregnated with 0.5 mg. methylcholanthrene. After 101 days, the abdomen was distended by slightly bloody straw-colored fluid. A retroperitoneal nodule of fibrosarcoma, 8×5×5 mm., was also found at necropsy. The ascites was transferred by intraperitoneal injection of 0.4–0.5 ml. of acetic fluid, with 22.

*This work was conducted during the tenure by R. G. G. of a Public Health Service Special Research Fellowship of the National Cancer Institute. Present address: Veterans Administration Hospital, Houston 31, Tex.

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takes out of a total of 25 mice injected in four passages prior to the present experiment. Small sarcomatous nodules were often found attached to the peritoneal surfaces or floating in the fluid. Injection of the fluid into soft tissues resulted in local fibrosarcomas. Smears of the ascitic fluid contained red blood cells, lymphocytes, macrophages, and a small number of round, presumably malignant cells isolated or in clumps; these cells varied in size and had dense nuclei.

For this experiment nine female 6-month-old mice each received intraperitoneal injections of 0.5 ml. of heparinised acetic fluid 381. Eleven mice of the same age had injections of 0.5 ml. of pooled fluid 302 (from two mice of a different subtransfer of fluid 58). The mice were observed for abdominal swelling or tumors, and the diagnosis was confirmed at necropsy. Mice that developed no tumors were observed for 8 months.

Intramuscular injections of cortisone acetate (Merck) or of ACTH (Wilson) were given daily until death (mammary carcinoma experiment) or until the 105th day. The treatment was started on the day of the implants at the "low level," 0.075 mg. of ACTH or 0.15 mg. of cortisone. At the "high level," 0.5 mg. of ACTH or 1 mg. of cortisone was injected daily only after tumors had developed (seventh day for the mammary tumor, 88th day for the ascites sarcoma). Groups of untreated mice were kept as controls.

RESULTS

All transfers of mammary carcinomas were successful and were fatal to the mice (Table 1). The tumors during their early stage followed an exponential rate of growth, and the untreated mice gained in total weight. As the tumors became necrotic or ulcerated, there was a flattening or even a recession of the growth curves, and the mice lost weight.

High levels of cortisone slowed the growth of the transplants and increased the survival time; the

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>SIZE* AT 50 DAYS</th>
<th>SURV.</th>
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</thead>
<tbody>
<tr>
<td>ACTH 0.5</td>
<td>5.0 (2.1–5.4)</td>
<td>4.4</td>
</tr>
<tr>
<td>ACTH 0.075</td>
<td>5.1 (2.6–3.6)</td>
<td>64</td>
</tr>
<tr>
<td>Cortisone</td>
<td>1.5 (1.1–2.8)</td>
<td>90</td>
</tr>
<tr>
<td>Cortisone</td>
<td>2.8 (2.5–5.2)</td>
<td>67</td>
</tr>
<tr>
<td>Control</td>
<td>3.2 (2.3–5.7)</td>
<td>52</td>
</tr>
</tbody>
</table>

* Log. of product of 5 dimensions in mm.
treated mice lost considerable weight before the implants became very large. With low levels of cortisone there was a lesser body weight loss, which was compensated by the bulk of the tumors; inhibition of the neoplastic growth appeared doubtful.

ACTH at both levels seemed without effect on the growth of the tumors or on the weight of the mice.

The results with the ascites sarcoma are given in Chart 1. The percentage of takes was higher and the latent periods shorter in transfers of ascites 881 than of ascites 882. The divided condition of the injected malignant cells and their prolonged contact with the peritoneum of the host during the latent period appeared favorable to chemotherapy. Nevertheless, ACTH and cortisone were without effect on the number of takes or on the latent periods of both subtransfers. Weight losses of the mice injected with cortisone were moderate at the low level, severe at the high level.

## DISCUSSION

On a weight basis the lower amounts of ACTH and cortisone given to mice (about 3.75 and 7.5 mg/kg/day) were similar to the largest human therapeutic doses (100–200 mg/day of ACTH and 200–400 mg/day of cortisone); these are, however, toxic for continued treatment (2, 8). The larger amounts of cortisone (about 50 mg/kg/day) are about the maximum dose tolerated by mice, reducing their food intake and producing marked anemia (11). Only at this high level was one of the two mouse tumors definitely inhibited, as were certain nonlymphoid mouse tumors reported in other studies (11).

The inhibition of the mammary carcinoma was probably not due to a physiologic balance, like the lymphoid-adrenal system, since comparable levels of ACTH did not affect the tumor. Divided doses of ACTH might, however, have been more effective. Cortisone is probably more “toxic” than the endogenous hormones released by corticotrophin.

Although cortical hormones inhibit fibroblasts in inflammatory reactions (9) and can decrease the reaction around various human tumors (8), they were ineffective in checking the growth of the ascites sarcoma and of various human sarcomas (2, 8).

The adverse effect of maximal amounts of cortisone on the mammary carcinoma and the weight loss of the mice appear to be nonspecific “toxic” effects. Both could, however, be the result of an increase of protein catabolism and gluconeogenesis (cf. 5), or of a general inhibition of growth, as observed by Karnofsky in chick embryos, newly hatched chicks, and baby mice, with high levels of cortisone or smaller amounts of Compound F (6, 11). Conversely, an increase of body weight and an acceleration of growth of a transplanted mammary carcinoma have been recently observed in mice injected with pituitary growth hormone (10).

The inhibitory effect of cortisone on the growth of the mouse mammary carcinoma, observed in these experiments, is of no clinical significance, since it required the use of toxic doses of the drug.

## SUMMARY

The rate of growth of a transplanted mouse mammary carcinoma was reduced by very large doses of cortisone, while the effect was doubtful at the usual human therapeutic level. ACTH did not affect this tumor. Neither product inhibited the growth of an ascites-producing sarcoma.

## ACKNOWLEDGMENTS

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Raymond G. Gottschalk and Arthur Grollman


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