Many investigations have been carried out on the effects of cortisone on experimental tumors and on almost every aspect of tumor growth and behavior. However, most interest has centered around the action of cortisone on the growth, heterotransplantability, and metastatic diffusion of certain experimental tumors; some of the literature will be reviewed under these headings.

The action of cortisone on the growth of experimental tumors has been the most widely studied. Heilman and Kendall (12) appear to be the only authors reporting the complete inhibition of an established tumor, namely, a lymphosarcoma; others, studying the action of cortisone on tumors arising from the lymphopoietic system (7–9, 18, 16, 19, 22, 24), report a slight, inevitably temporary, inhibition. Results similar to these were obtained with certain transplantable sarcomas (24), a rhabdomyosarcoma (14), an ependymoma (6), and a mastocytoma (4) in the dog. On the other hand, following the administration of cortisone no effect on growth was noted with the Walker carcinoma in the rat (3, 17); Sarcoma 180, the Harding-Passey melanoma (24), various mammary adenocarcinomas (11, 24, 28), and castration-induced adrenal adenomas in NH mice (81). Two reports have been made of inhibitory action of cortisone on the Walker rat carcinoma (17) and mammary adenocarcinoma in mice (1) that seem at variance with the majority of recorded investigations. Thus, it would seem that cortisone has a general inhibitory action that is slight and temporary on transplantable tumors of an epithelial origin.

According to some workers, cortisone favors the growth of tumors in genetically alien strains of mice in a heterologous fashion (10, 15); others (27) have reported that human tumors may be grown successfully in cortisone-treated rats.

The action of cortisone on the metastatic diffusion of tumors is the most recently investigated aspect of this subject. Agosin et al. (1) and, subsequently, Molomut et al. (20) have reported an increase in the incidence of metastases in cortisone-treated tumor-bearing mice. Agosin et al. (1), in studies on transplantable mammary adenocarcinomas in C3H mice, did not find any metastases in untreated animals, whereas 40 per cent of those mice treated with cortisone had metastatic lesions. Molomut et al. found it possible to induce widespread metastases with cortisone treatment of mice bearing a sarcoma transplanted from Strain A mice to cortisone-treated C57BL mice. This report, however, is contradicted by another from Kaliss and Borges (18), using the same conditions and finding no more metastases in treated mice than in controls. Both heterologous growth and metastatic diffusion of tumors are matters of fundamental interest in studies of tumors. The literature thus far on this subject is confined to but few examples of different types of tumors, and some contradictory results have been reported. The present paper is concerned with both these results of treatment with cortisone on tumors, and, in addition, with its action on the chemical induction of tumors.

**MATERIALS AND METHODS**

Male and female DBA and Swiss strain mice were used for these experiments. The DBA mice originated from the stock of Dr. Albert Tannenbaum of Michael Reese Hospital, Chicago, and the Swiss mice from the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine. Both strains of mice were bred in this laboratory; they were housed in plastic cages, and given Rockland mouse diet and water ad libitum.

The tumor used for transplantation was a mammary adenocarcinoma originated in a DBA mouse and obtained through the courtesy of Dr. Kurt Stern of the Mount Sinai Medical Research Foundation and The Chicago Medical School, Chicago. The tumor was ground in saline until a heavy suspension was obtained. When 0.8 cc. of such a suspension was injected subcutaneously in the groin, the tumor
took in 100 per cent of the DBA mice, becoming visible from 6 to 8 days after the implantation, growing steadily and usually killing the animal between the 25th and 85th day following inoculation. Histologically, it is a very anaplastic carcinoma. Methylcholanthrene (Eastman Kodak, Rochester, New York) was used, either as a 0.5 per cent solution in acetone for skin painting or in 2-mg. doses in triacylglycerol for subcutaneous injection. Cortisone (Cortone Merck) was given in doses of 0.5 mg. in saline daily, except on Sundays, by intraperitoneal injection. The needle was inserted through the left lower quadrant of the abdomen, to avoid the tumor implant, which was always made in the right groin.

**EXPERIMENTAL**

**Tumor Transplantation**

One hundred DBA mice were given implants of the above-described tumor and divided into four groups:

*Group 1* received no further treatment and served as control. The other three groups received cortisone according to the following schedule: *Group 2* started cortisone treatment 10 days before the implant; *Group 3* started cortisone treatment 6 days after the implant; *Group 4* started cortisone treatment 15 days after the implant.

Some of the animals died early in the course of the experiment and will not be taken into consideration. The others died or were sacrificed between the 22d and the 35th day after the implant. Autopsy was performed in all cases, and specimens taken for microscopic examination.

In addition, 52 Swiss mice were given injections in the right groin of the same tumor described above and divided into three groups:

*Group 5* (26 mice) received no further treatment and served as control. *Group 6* (thirteen mice) started cortisone treatment 3 days before the implant. *Group 7* (thirteen mice) began cortisone on the same day as the inoculation.

The tumor growth was carefully observed until all the tumor had regressed or until the death of the animal. Autopsies were performed and specimens taken for microscopic examination.

*DBA mice.*—No differences were noted in the growth rate of tumors in mice of Groups 1, 3, and 4. However, in the mice of Group 2, which began receiving cortisone 10 days before the implantation, the tumors grew slowly for some days, and, after 10 days, were considerably smaller in size than the tumors of the other three groups. After the 10th day, the tumors started to grow faster, and, at the end of the experiment, no significant differences were noted in the sizes of tumors in all four groups. There was no noticeable difference in the average weight of cortisone-treated and control animals at the end of the experiment. All the animals were in good general condition, and no animal was found to be emaciated.

The action of cortisone on the metastatic diffusion of the transplantable tumor is illustrated in Table 1. No metastases were observed in 37 control animals of Group 1 not receiving cortisone. Of the 22 animals in Group 2 (in which cortisone was started before the implant), eight showed evidence of metastases, as did five out of the eight animals of the third group, which began receiving cortisone 6 days after the implant. Metastases were found in only one mouse of the eighteen animals of Group 4 receiving cortisone starting 15 days after the implantation. All metastases were confirmed microscopically and were found in various sites: lungs, liver, kidney, diaphragm, heart, peritoneum, ovary, etc. (Figs. 1, 3).

*Swiss mice.*—In all the Swiss mice given injections of mammary adenocarcinoma in the right groin, the tumors grew for a while, but no difference in the size of the tumors was noticed between cortisone-treated and control animals. After 2 weeks most of the tumors had regressed, except in three cortisone-treated and two control animals, in which a lump was still present at the site of inoculation. However, autopsy of these five mice disclosed that the "tumor" actually consisted of thick, necrotic material surrounded by an inflammatory capsule. No true tumor tissue was found on microscopic examination.

**Induced Tumors**

The action of cortisone on the induction of skin tumors.—Fifty-three Swiss mice were painted twice weekly with 0.8 per cent methylcholanthrene in acetone in the intrascapular region, which was clipped free of hair with scissors. Both groups received a total number of 38 applications of carcinogen. The individual tumors were recorded on graph paper as soon as they appeared and the mice numbered by ear clipping. The mice were divided into two groups: Group 1 consisted of sixteen animals which received cortisone treatment 6 days a week...
Throughout the experiment; Group 2 consisted of 37 animals which served as controls and were only given carcinogen treatment.

In this experiment the induction of skin tumors by methylcholanthrene was strikingly inhibited by cortisone administration. In Group 2 (control group), the first tumors appeared after 5 weeks, and after 10 weeks nineteen out of 37 mice (more than 50 per cent) had a total of 46 tumors. At the end of the experiment, 19 weeks following the first application of methylcholanthrene, 29 out of 31 survivors had a total of 90 tumors. Eventually, at least one tumor in each tumor-bearing mouse developed into a malignancy. In Group 1 (cortisone-treated mice) the first tumor, a sessile papilloma, appeared 18 weeks following the first application of the carcinogen. At this time, there were twelve survivors. No other tumor appeared in the following 6 weeks, and the papilloma remained stationary. At this point, the experiment was discontinued. The average weight, at the beginning of the experiment, was 22.5 gm. in Group 1 and 22.8 gm. in Group 2. At the end of the experiment, after 19 weeks of carcinogen applications and cortisone treatment, the average weight was 23.9 gm. in cortisone-treated mice and 25.8 gm. in the control group. The results were undoubtedly striking. However, the dosage of cortisone was high, and the toxic action marked enough to result in an over-all diminution in the average weight of the cortisone group as compared to the controls. This might certainly have played a significant part in these results.

The action of cortisone on the growth and metastatic behavior of induced skin tumors.—For the second part of this experiment the skin tumors induced in the control group of the first part of the experiment were used. These tumors were taken in pairs as soon as obvious, gross malignancy was seen, as noted by a greatly increased growth rate, infiltration of surrounding tissues, and often the development of an ulcerating lesion with eversion of the edges. Of the pair of malignancies taken, one was treated with cortisone and the other kept as control. In this manner eighteen tumors were treated with cortisone and seventeen kept as controls. No noticeable action on the growth rate and characteristics of these tumors was noted. However, at autopsy, as can be seen in Table 2, it was noted that six of the mice in the cortisone-treated group had metastatic lesions, whereas those in the other group had none. The metastases were all unquestionable secondary growths having the histological appearance of squamous-cell carcinoma and were seen mainly in the lungs and livers of these animals (Figs. 5, 6). The lack of metastases in the untreated animals is well in keeping with the behavior of squamous-cell carcinomas induced by painting with carcinogenic hydrocarbons in the skin of the mouse; a recent survey in this department of 100 squamous-cell carcinomas induced in the mouse with 9,10-dimethyl-1,2-benzanthracene painted repeatedly failed to reveal a single instance of a visceral metastasis. The average survival rate after the appearance of a malignant growth was the same in both treated and untreated animals. The earliest metastasis was found after 2 weeks of cortisone treatment.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. tumor-bearing mice</th>
<th>No. mice with metastases</th>
<th>metastases (days)</th>
<th>Av. survival rate after the appearance of a tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisone (0.5 mg. daily)</td>
<td>18</td>
<td>6</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>17</td>
<td>0</td>
<td>36</td>
<td></td>
</tr>
</tbody>
</table>

*Grossly malignant skin tumors induced with methylcholanthrene.
*Treatment with cortisone was begun in individual mice as soon as a tumor became grossly malignant.

Subcutaneously induced sarcomas.—Thirty-eight Swiss mice were given subcutaneous injections of 2 mg. of methylcholanthrene dissolved in 0.8 cc. of triacrylin. At the end of 3 months, 28 mice had evidence of tumor growth, and these were then divided into two groups. Twelve mice were treated continuously with cortisone, whereas the other sixteen served as controls. The length of cortisone treatment varied from a minimum of 3 weeks to a maximum of 2 months. However, most of the animals, except four which died earlier, were killed after 2 months of treatment. There was no evidence at all of any inhibition of the growth rate of these tumors, no differences in size being noted between the tumors of the cortisone-treated and control animals. However, it was noted that five of the twelve cortisone-treated mice had metastases, whereas no metastases were noted after a similar period in the sixteen control animals (Table 3). The metastases were seen in the lungs, liver, kidneys, adrenal glands, pleural and peritoneal surfaces, and reproduced the histological characteristics of the original tumor (Fig. 4). There was no significant difference in the average weight between cortisone-treated and control animals. When cortisone administration was begun, the average weight was 24 gm. for the mice which were undergoing cortisone treatment and 24.9 gm. for the control group. At the end of the experiment, after 2 months, the average weights were 23.1 gm.
in cortisone-treated animals and 26.1 in control mice.

**DISCUSSION**

In these experiments it has been found, paralleling the work of others, that metastatic diffusion from transplantable tumors is favored by administration of cortisone. In addition, it has been noted that the metastatic spread of both induced skin tumors and subcutaneously induced sarcomas is stimulated in a similar fashion. This observation is in keeping with clinical observations made by the American Medical Association Committee (25) on the action of steroids in cancer that stated “in several cases (of neoplastic disease treated with cortisone), despite the subjective response, and improved appearance of the patient, there was evidence of more rapid spread of neoplasm and autopsy later revealed that even the spleen was riddled with metastases.”

No inhibitory action on the growth rate of induced skin tumors or subcutaneously induced sarcomas was noted in the course of this investigation. This supports the general view in the literature that lymphoid tumors are the only neoplasms directly influenced by cortisone. However, a temporary inhibition of the growth rate was noted in a transplanted mammary adenocarcinoma in DBA mice treated with cortisone. Such inhibition lasted for only the first 10 days following the tumor implant, and then the tumors started to grow faster, reaching in a brief time the same size as in control animals. This may account for the positive results reported by Ingle et al. (17) in retarding the growth rate of a Walker carcinoma in the rat by cortisone treatment. In their experiment, cortisone treatment was given only for 10 days, after which the rats were killed and the growth rate determined.

The influence of cortisone on heterologous transplantation of tumors has been consistently negative in our experiments, which is at variance with the results reported by other authors. Probably the kind of tumors used, the strain of mice, and the dosage of cortisone may account for the difference in results. However, an inhibitory action on the induction by methylcholanthrene of skin tumors was noted. This finding is in keeping with that of Baker and Whitaker (2) but contrary to that of Boutwell and Rusch (5). It is possible that in this investigation the validity of attributing the action noted in this particular observation to cortisone is much hampered by the large dose of the drug used and the general systemic effects seen. It would appear unwise, therefore, to compare this particular finding to those of others.

The most interesting aspect of this experiment is the demonstration that injections of cortisone favor the metastatic spread of induced as well as transplantable tumors. This is a particularly striking phenomenon when seen in the skin tumors of the mouse. At present it is difficult to suggest hypothetical mechanisms as explanations for this phenomenon. It seems unlikely that any effect mediated through a general caloric restriction should be held responsible; Tannenbaum and Silverstone (26) have noted that dietary restriction, in fact, decreased the number of grossly visible lung metastases seen in C3H mice with mammary tumors. It would certainly seem that a good experimental tool is at hand for studies of mechanisms concerned in the metastatic spread of tumors.

**TABLE 3**

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>Av. Wt. (gm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cortisone</strong></td>
<td>26.1</td>
</tr>
<tr>
<td><strong>Control</strong></td>
<td>26.1</td>
</tr>
</tbody>
</table>

* Mice with palpable sarcomas induced subcutaneously with methylcholanthrene.

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**SUMMARY**

1. The action of cortisone has been studied on the heterologous transplantation, growth, and metastatic diffusion of a transplantable adeno-carcinoma in DBA mice, and on the genesis, growth, and metastatic diffusion of tumors induced in the skin and subcutaneous tissues of Swiss mice with methylcholanthrene.

2. Cortisone did not show any appreciable influence on the heterologous transplantation of a mammary adenocarcinoma from DBA mice and on the growth of methylcholanthrene-induced tumors in Swiss mice.

3. The growth rate of a transplanted adenocarcinoma in DBA mice was temporarily inhibited by the administration of cortisone.

4. The induction of skin tumors in Swiss mice by methylcholanthrene has been markedly inhibited by the administration of 0.5 mg. of cortisone daily.

5. Cortisone has been found to favor an increased metastatic spread of all the experimental tumors studied.

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1 It should be mentioned that, since this manuscript was submitted, Engelbreth-Holm and Asboe-Hansen (Acta Path. et Microbiol. Scand., XXXII:560—64, 1953) have also found that administration of cortisol inhibits the induction of skin tumors in mice by painting with 9,10-dimethyl-1,2-benzanthracene.
ACKNOWLEDGMENTS

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REFERENCES


FIG. 5.—Metastasis in the lung from a methylcholanthrene-induced tumor of the skin in a cortisone-treated mouse. X40.

FIG. 6.—Idem. X105.
The Action of Cortisone on Transplanted and Induced Tumors in Mice

Renato Baserga, Philippe Shubik and Jay Pass

_Cancer Res_ 1954;14:12-16.

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