Production of Metastases by Treatment with Carcinostatic Agents

I. Effects of Carcinostatic Agents on the Host

TATSUHEI KONDO* AND GEORGE E. MOORE
(Department of Surgery, Roswell Park Memorial Institute, Buffalo, N.Y.)

SUMMARY

The number of lung "metastases" that develop from intravenously injected tumor cells is modified by the administration of certain carcinostatic agents. The number is increased by post-treatment with small amounts of mechlorethamine (HN2) or actinomycin D, but is decreased by larger amounts. Pretreatment with HN2 results in increased numbers of lung metastases. Pretreatment with actinomycin D, HN2, or triethylenemelamine (TEM) results in an increased growth of transplanted ascites tumor cells. Increasing the dose of actinomycin D or HN2 reduces the minimum number of cells required for successful transplantation. Although experimental results like these cannot be directly applied to clinical work, they still serve as a warning that cancer chemotherapy that is inadequate because the dosage is insufficient or the drug is ineffective may sometimes be even less satisfactory than no chemotherapy at all.

Perhaps the greatest problem in the treatment of cancer is the general inadequacy of current methods of therapy when disseminated cells have resulted in distant metastases. A major step toward resolution of this difficulty has been the development of carcinostatic agents, since they provide a means for systemic treatment. Unfortunately, however, almost all of them are toxic, and dosage levels necessary to attain tumor inhibition often cause severe side effects. Successful balancing of the toxic and beneficial properties of these drugs in the treatment of each different kind of tumor requires experienced clinical judgment.

In addition, several groups of investigators have reported that the use of carcinostatic agents, x-rays, or hormones may be followed by an increase in the number and the growth rate of metastases. For example, Kondo and Tsukui (9) found that nitrogen mustard N-oxide, x-rays, and cortisone each "stimulated" the development of metastases from Yoshida sarcoma in the rat.

In the promotion of metastases, carcinostatic agents can be considered to have three general modes of action: (a) the tumor itself may be made
to release more cells into the blood stream, (b) invaded tissues may lose some of their local defenses against the survival of neoplastic cells, or (c) systemic host resistance may be reduced. In any particular instance, these modes may operate singly or in combination.

If a chemotherapeutic agent is toxic and relatively ineffective against experimental tumors, administration of the compound following tumor cell inoculation should demonstrate a reduction in host defenses. If, on the other hand, a compound is effective against tumor cells, the results of toxicity and chemotherapeutic activity can be separated only by administration of the drug before tumor cell inoculation. Still another kind of experiment involves delayed injection of chemotherapeutic agents in an attempt to find out whether latent or dormant cancer cells can be provoked to grow by changing their local environment. The purpose of experiments in which transplantable tumors are used, as in the present study, is to serve as models for experiments with spontaneous tumors and for clinical investigations.

EXPERIMENTAL DATA

Effect of post-treatment on occurrence of metastases.—Female Swiss mice, 2–3 months old, re-
received injections in the tail vein of $10^6$ 7-day-old Ehrlich ascites tumor cells. Chemotherapy was begun 2 weeks later and was continued for 1–5 days. Carcinostatic agents were given intravenously, and dosages were as follows: mechlorethamine (HN2), 0.5 mg/kg/day; actinomycin D, 50 μg/kg/day. Fifty days after tumor injection, the animals were sacrificed, and the gross lung metastases were counted. Microscopical studies were used for confirmation in selected instances.

Administration of either drug was followed by an increase in the number of metastases (Table 1). In the case of HN2, the number reached a maximum after the administration of two daily doses and was slightly less after three or four such doses. In the case of actinomycin D, the number reached a maximum after three daily doses and quickly dropped after further doses, attaining after five doses a count less than that for the control animals. It is assumed that the additional doses increased the therapeutic effect on the tumor growth, but further experiments are needed to elucidate this point.

**Effect of pretreatment on occurrence of metastases.**—Female Swiss mice received 1 mg/kg/day of HN2 intravenously for 1–4 days. On the day after the last dose of HN2, $2 \times 10^6$ Ehrlich ascites tumor cells were injected into the tail vein. Fifty days later, the animals were sacrificed, and the lung metastases were counted. The number of metastases was largest in the animals that would survive and uniformly establish tumor growth when transplanted into untreated mice. However, the minimum number of cells that would survive transplantation was reduced from $10^4$ to $10^3$ due to pretreatment with TEM, however, the minimum was as little as $10^3$. The use of actinomycin D, HN2, or TEM was followed by a striking increase in the rate of tumor growth. NMO and 6-MP gave less striking results, because their chemotherapeutic activity lasts for several days and therefore limited the growth of tumor cells injected within 3 days, regardless of any adverse effect on the host.

**Effect of pretreatment with larger doses.**—Parallel experiments were performed with double doses of carcinostatic agents: actinomycin D, 100 μg/kg; and HN2, 1 mg/kg. With these large doses, the minimum number of cells that would survive transplantation was reduced from $10^4$ to $10^3$.
(Table 2). This finding implies a direct relationship among tumor growth, tumor transplantability, and production of metastases. The mechanism of this relationship evidently involves host resistance as well as the balance between the chemotherapeutic effect of carcinostatic agents and the depression of host resistance by their toxicity.

**DISCUSSION**

When tumors are transplanted from one animal to another, metastases develop in different organs at different rates. This might be explained on the basis of mechanical factors influencing the vascular system (2). Nevertheless, the susceptibility of the local "soil"—as postulated in the "soil hypothesis"—should also be considered (12).

**TABLE 2**

**Transplantability of Tumor Cells after Pretreatment of Host with Chemotherapeutic Agents for 4 Days**

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DAILY DOSAGE PER KG.</th>
<th>1,000 cells S.C.</th>
<th>10,000 cells S.C.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td></td>
<td>0.03</td>
<td>0.36</td>
</tr>
<tr>
<td>Actinomycin D</td>
<td>50 µg.</td>
<td>0.01</td>
<td>0.11</td>
</tr>
<tr>
<td>Mechlorethamine</td>
<td>0.5 mg.</td>
<td>0.08</td>
<td>0.25</td>
</tr>
<tr>
<td>TEM</td>
<td>1.0 µg.</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>NMO</td>
<td>5.0 µg.</td>
<td>0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>6-MP</td>
<td>40 µg.</td>
<td>0.82</td>
<td>0.98</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>0.29</td>
<td>0.37</td>
</tr>
<tr>
<td>Actinomycin D</td>
<td>100 µg.</td>
<td>0.20</td>
<td>0.98</td>
</tr>
<tr>
<td>Mechlorethamine</td>
<td>1.0 mg.</td>
<td>0.28</td>
<td>3.07</td>
</tr>
</tbody>
</table>

Metastasis production following local exposure to x-rays has been reported by some investigators (8, 12). Pelner (11) has noted instances of apparently increased rates of tumor growth in patients on corticoid therapy. Some experimenters (1, 9) have reported that cortisone "stimulated" the development of metastases, whereas others (7, 10) have stated that its effect was inhibitory. Undoubtedly, no generalization is wise—each tumor-host relationship must be considered separately.

The carcinostatic agents now in existence have limited effectiveness and are more or less toxic to the host. Even though definitive proof of the existence of host resistance factors in human beings is scant, the danger that some carcinostatic agents may depress such factors should always be taken into consideration in the treatment of cancer patients.

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**REFERENCES**


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Tatsuhei Kondo and George E. Moore


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