Factors Affecting the Distribution of Tumor Metastases
Experiments with V₂ Carcinoma of Rabbits*

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In the study of tumor metastasis, a major problem is to account for the distribution of secondary tumors in different anatomic locations, and especially for the scarcity of metastases in certain organs, notably in the spleen and in the muscles.

One explanation that has been advanced is that some organs may afford a less favorable environment for the growth of embolizing tumor cells than do others. Thus Paget (1), in 1889, likened tumor emboli to "seeds" falling in "soils" of different degrees of fertility, and this concept of the "suitability of the soil" as favoring or inhibiting the establishment of tumor emboli and their development into secondary tumors has been accepted by many writers (2). By "soil" is meant the various chemical and physical factors that may differ from one part of the body to another. Thus in voluntary muscle it is conceivable that production of lactic acid or mechanical stress might be unfavorable to survival and growth of embolizing cells.

Another possible explanation is that metastases may fail to appear in certain organs because tumor emboli fail to reach them.

The present investigation was designed to test the validity of this hypothesis, which we may express as follows: tumor metastasis will develop in any organ that receives viable tumor emboli in sufficient numbers, so that scarcity of metastases in an organ is explainable by scarcity of emboli. This hypothesis may readily be tested by injecting cancer cells into the arterial blood supply of the organ. If, in consequence, metastases regularly develop there, the hypothesis of organ susceptibility or suitable "soil" would, at least for the tumor and species studied, be unnecessary.

MATERIAL AND METHODS

The tumor used in these experiments was a squamous cell carcinoma of rabbits, the V₂ carcinoma derived from the Shope virus papilloma.

This tumor is readily maintained in domestic rabbits; it metastasizes regularly to adjacent lymph nodes, occasionally to the lungs, rarely elsewhere, in this behavior resembling squamous cell carcinoma in man.

Cancer cells were prepared for injection by passing viable portions of tumor through a fine mesh metal sieve and suspending the cells in 5 volumes of saline (Gey's solution); 0.3 to 1.0 cc. of this suspension was injected intravascularly in rabbits.

RESULTS

Intra-arterial injections.—Since skeletal muscles are seldom the seat of spontaneous metastases, embolism to these organs, if it should regularly result in the development of metastases, would give strong support to the hypothesis being tested. Accordingly, a tumor cell suspension was injected into the femoral artery. In each of 8 rabbits at the time of sacrifice, 65 to 86 days later, there was found extensive infiltration of the leg muscles with confluent masses of neoplasm (Fig. 1). Evidently cancer cells, providing they are able to reach muscle, have no difficulty in establishing metastases there. In other words, there is no indication that muscle provides an unfavorable "soil."

Injections into the left side of the heart.—In order further to test the hypothesis that metastases will develop in any organ receiving an adequate number of tumor emboli, a suspension of tumor cells was injected into the left side of the heart. Cancer cells should in consequence be carried to all organs and metastases should appear everywhere. That is approximately what happened. In Table 1 is shown the distribution of metastases by organs. It is interesting to observe that muscles, skin, myocardium, and lungs head the list in frequency. In each of 6 rabbits, great numbers of secondary tumors appeared in voluntary muscles and skin, as well as in many other organs (Figs. 2 to 3). As shown in Figure 3, metastases were frequent in the musculature of the trunk. In muscles of the extremities, secondary tumors were less common and
occurred in greater numbers in the proximal than in the distal portions. As to visceral metastases, these are shown in Figure 2 in the liver, lungs, spleen, intestine, and kidneys. The histologic appearance of a metastatic tumor nodule in muscle is shown in Figure 4.

Thus it has been found that if cancer cells get into the left side of the heart they produce metastases everywhere. And yet, as mentioned earlier, this tumor rarely metastasizes spontaneously except to the regional lymph nodes and lungs. This is true, obviously, because few cancer cells reach the left side of the heart, having been trapped in the lungs.

**Injections into the right side of the heart and into the femoral vein.**—The question was now asked: How efficient are the lungs in preventing tumor cells from getting through into the systemic arteries?

![FIG. 1.—Hind leg of a rabbit showing massive infiltration of the musculature by neoplastic tissue following injection of a tumor cell suspension into the femoral artery.](image1)

![TABLE 1](table1)

**TABLE 1**

<table>
<thead>
<tr>
<th>Site*</th>
<th>Number of animals in which metastases were observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculature</td>
<td>6</td>
</tr>
<tr>
<td>Skin</td>
<td>5</td>
</tr>
<tr>
<td>Myocardium</td>
<td>5</td>
</tr>
<tr>
<td>Lungs</td>
<td>5</td>
</tr>
<tr>
<td>Kidneys</td>
<td>4</td>
</tr>
<tr>
<td>Eye (anterior chamber)</td>
<td>3</td>
</tr>
<tr>
<td>Liver</td>
<td>2</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2</td>
</tr>
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<td>Adrenals</td>
<td>1</td>
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<td>Bowel</td>
<td>1</td>
</tr>
<tr>
<td>Brain</td>
<td>1</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>1</td>
</tr>
<tr>
<td>Spleen</td>
<td>1</td>
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</tbody>
</table>

* The skeleton was examined in only one animal and was found to contain metastases in several of the long and flat bones.

![FIG. 2.—Viscera of a rabbit following injection of a tumor cell suspension into the left side of the heart. Nodules of tumor are seen in the intestine, liver, spleen, kidneys, lungs, and heart.](image2)

![FIG. 3.—A rabbit with skin reflected to show numerous metastatic nodules in the muscles of the trunk and legs and in the subcutaneous tissue, following injection of a tumor cell suspension into the left side of the heart.](image3)
To answer this question a heavy suspension of these cells was injected into the femoral vein or the right side of the heart. In each of 4 rabbits so injected and sacrificed from 35 to 40 days later, innumerable tumor nodules were found in the lungs (Fig. 5) but not a tumor in any other organ. Evidently the cells of this cancer were unable to pass through the lungs, and no secondary metastases arose from the primary metastases. It follows that when in the presence of a tumor metastasizing to the lungs, metastases do not develop elsewhere, it is because tumor cells do not pass in adequate numbers from the lungs into the systemic arteries.

SUMMARY

Scarcity of tumor metastases in certain organs, such as voluntary muscles, might be due to low tumor susceptibility (unfavorable "soil") or to failure of cancer cells to reach these organs. If the latter explanation is correct, secondary tumors should arise in all organs receiving an adequate number of embolizing tumor cells. This can be accomplished by injecting a suspension of tumor cells into the arterial blood supply of an organ. The tumor employed was the V2 carcinoma derived from the Shope rabbit papilloma. When suspensions of cells from this tumor were injected into the femoral artery of rabbits, massive neoplastic growths infiltrated the leg muscles, showing that skeletal muscles readily support secondary tumors.

If tumor cells are injected into the left side of the heart, they should be distributed to and produce metastases in all organs. This was verified experimentally. Hence scarcity of metastases in an organ is due to scarcity of tumor emboli in the systemic arterial blood, as the result of screening by the lungs. Screening of cells of this tumor was found to be highly efficient, as injection of cancer cells into the femoral vein was followed by a multitude of secondary tumors in the lungs but not one tumor was found elsewhere. It is concluded that scarcity of metastases in an organ is explainable by scarcity of tumor cells reaching that organ. Under the conditions of these experiments, no organ proved to be unfavorable soil.

REFERENCES

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