The Heterologous Transplantation of Human Lung Cancer*

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In the routine heterologous transfer of unselected human tumors, approximately one-half of the growths are found to be in a dependent phase of development at the time of operation, and takes are not obtained (3). Analysis of the incidence of transplantability in relation to the primary site of the tumor shows a consistent variation with respect to several organs, and notable among these are the breast and the lung. At the time of first surgical approach, the majority of breast cancers are in a dependent phase and are not transplantable, while all the lung cancers studied have been autonomous, or transplantable. The present paper concerns the series of lung cancers. The results of transplantation are reported in relation to the fate of the patient, and corresponding data derived from the study of tumors of similar morphological type arising in other organs are presented for purposes of comparison.

MATERIALS AND METHODS

The anterior chamber and the brain of the guinea pig were used as transplantation sites in the primary transfers of the tumors. In a number of cases, corresponding sites in the mouse were also employed, and the transplantation reactions to several of the tumors carried serially were studied in this species as well as in the guinea pig. The technic of transfer has been described in detail (1, 2).

The tumors were derived from the operating room of the New Haven Hospital, and their transfer was undertaken as part of a general study of the heterotransplantability of human cancer. They do not represent a consecutive series of all the lung cancers removed during the period of study, and selection for transfer was made on a purely random basis. The tumor tissue, obtained from the primary lesion, involved lymph nodes or metastasis, was used immediately after operation or stored in sterile containers at ice-box temperature for short intervals of time. The material for transfer was selected for viability and cellular content after careful gross examination, and in many cases frozen sections were employed.

As a rule, each tumor was transferred to eight guinea pigs, but in the case of desmoplastic growths as many as twelve pigs were used. The selection of the eye or brain as a transplantation site was also based on the amount of desmoplasia, for in past experience it has been noted that the reaction to adult human connective tissue was less pronounced in the brain.

It is important in the present connection to emphasize the importance of care in the selection of fragments for transfer in heterologous transplantation experiments, particularly those involving human tumors. Human tumors, unlike mouse tumors, usually contain a large amount of desmoplastic connective tissue. This is an adult tissue and will not survive heterologous transfer. Furthermore, when present in quantity it appears to inhibit the growth of transplantable cancer cells, and, in a large series of heterologous experiments, it was found that the incidence of takes varied inversely with the proportion of desmoplastic connective tissue present in the tumor. Growth in laboratory animals is not associated with the desmoplasia characteristic of growth in man, and this factor can be neglected in subsequent animal passages.

The ability to select suitable fragments varies with the experience of the operator and determines the number of animals necessary to validate the experiment. In the present case, it has been found that, with the aid of frozen sections, at least one out of eight fragments selected from a highly scirrhus carcinoma contains a preponderance of parenchyma, and for this reason a minimum of eight animals are used in each test.

The point to be emphasized is that the incidence of takes in the first-generation passage of a heterologous tumor reflects its content of desmoplasia and the experience of the operator rather than any essential character of the neoplastic cells. From this point of view a single take is as expressive of the true nature of the tumor as a 100 per cent incidence, and, unless a complete uniformity of transplanted fragments with respect to desmoplasia and parenchyma is assured, a tabulation of the incidence of takes is not subject to meaningful interpretation. Accordingly, in the tables accompanying this paper the occurrence of takes following the transfer of a tumor is signified by a plus (+) sign and their nonoccurrence by a minus (—). In point of fact, the incidence of takes varied from one out of eight to eight out of eight, but this difference disappeared on second-generation transfer and thus denotes the action of an element present in the fragments obtained from the operative specimen but absent from those derived from the first-generation growth.

RESULTS

The results of heterologous transfer of the thirteen lung cancers in this series are shown in Table 1. It will be noted that all the tumors proved to be transplantable and that all the patients died within a few months of operation.

Morphologically, the tumors were all epidermoid in character: three were classified as pleomorphic in cell type, five as poorly differentiated, and five as anaplastic. The tissue used for transfer was obtained from the primary growth in three
cases, from regional nodes in five, from distal nodes in four, and from a brain metastasis in one case.

Neither histological type nor derivation of the tissue used appeared to influence the behavior of the transplanted tumor. With the sole exception of Case No. 11, growth in the eye was apparent by the 10th day after transfer, and the anterior chamber was filled with tumor by the end of a month. The tumor in Case No. 11 showed the highest degree of differentiation in the series and grew slowly on transfer. Growth was first observed on the 8th day, and the chamber was not replaced until the 7th month. Serial transfer was not associated with an accelerated growth rate in this or in other cases.

The behavior of transplants in the brain was comparable to that of other tumors. Neurological signs were not apparent until the transplant had grown to occupy approximately half a cerebral hemisphere, and their appearance was rapidly followed by death of the animal. In general, death occurred in from 40 to 60 days after transfer, and different tumors were not associated with consistent variations in survival time.

Morphologically, the transplants were similar to the tissue used for transfer (Figs. 1–18). The degree of differentiation was comparable in the human tumor and the transplant, and, even in the case of the more anaplastic or "oat-cell" tumors, no indication of differentiation in the direction of an epidermoid structure was found. This is in contrast to experience with anaplastic tumors of other organs where transplants generally show a higher degree of differentiation and the possibility is suggested that the "oat-cell" tumor may be an entity in itself rather than an anaplastic epidermoid carcinoma.

The results obtained on the heterologous transfer of a series of epidermoid carcinomas derived from organs other than the lung is shown in Table 2. The tumors include three of the larynx, two of the hypopharynx, two of the skin, and one each of the lip, tongue, breast, cervix, urethra, and urinary bladder. The tissue used was obtained from a primary growth in one case, from regional nodes in eleven cases, and from a distant node in one.

Approximately one-half (six of thirteen) of these tumors proved to be heterotransplantable. This proportion is in general agreement with that obtained in the routine transfer of tumors derived from the operating room and in sharp contrast to the results described in the case of the lung.

**DISCUSSION**

Heterotransplantability does not characterize tumors from their inception but is an attribute attained late in the course of development and ap-
FIG. 7.—Undifferentiated epidermoid carcinoma of lung from Case No. 9. ×275.

FIG. 8.—Mouse anterior chamber transplant of tumor shown in Figure 7. ×400.

FIG. 9.—Pleomorphic epidermoid carcinoma of lung from Case No. 10. ×275.

FIG. 10.—Guinea pig anterior chamber transplant of tumor shown in Figure 9. ×275.

FIG. 11.—Undifferentiated epidermoid carcinoma of lung from Case No. 11. ×275.

FIG. 12.—Guinea pig anterior chamber transplant of tumor shown in Figure 11. ×275.
Fig. 13.—Pleomorphic epidermoid carcinoma of lung from Case No. 12. ×275.

Fig. 14.—Guinea pig brain transplant of tumor shown in Figure 13. ×275.

Fig. 15.—Mouse brain transplant of tumor shown in Figure 13. ×135.

Fig. 16.—Anaplastic epidermoid (oat-cell) carcinoma of lung from Case No. 13. ×275.

Fig. 17.—Guinea pig brain transplant of tumor shown in Figure 16. ×275.

Fig. 18.—Mouse brain transplant of tumor shown in Figure 16. ×275.
pears to coincide with the attainment of the property of metastasizability (3). The results of the experiments reported in this paper represent the and may be interpreted as meaning either that the developmental advance from dependency to autonomy is more rapid in lung tumors than in

Table 2

The Results of the Heterologous Transfer of a Series of Epidermoid Carcinomas Derived from Organs Other Than the Lung

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Patient</th>
<th>Primary Site</th>
<th>Date</th>
<th>Tissue Used</th>
<th>Result</th>
<th>Present Status of Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B.S.(f)</td>
<td>Tongue</td>
<td>3/31/43</td>
<td>Cervical node</td>
<td>+</td>
<td>Died 7/20/45</td>
</tr>
<tr>
<td>2</td>
<td>C.P.(m)</td>
<td>Urethra</td>
<td>5/16/44</td>
<td>Inguinal node</td>
<td>+</td>
<td>Died 9/1/45</td>
</tr>
<tr>
<td>3</td>
<td>L.A.(m)</td>
<td>Hyopharynx</td>
<td>11/6/47</td>
<td>Cervical node</td>
<td>-</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>D.P.(m)</td>
<td>Skin</td>
<td>1/8/48</td>
<td>Primary</td>
<td>-</td>
<td>Alive</td>
</tr>
<tr>
<td>5</td>
<td>E.L.(m)</td>
<td>Hyopharynx</td>
<td>10/15/48</td>
<td>Cervical node</td>
<td>+</td>
<td>Died 9/21/40</td>
</tr>
<tr>
<td>6</td>
<td>D.B.(m)</td>
<td>Larynx</td>
<td>11/50/49</td>
<td>Cervical node</td>
<td>-</td>
<td>Died 9/21/51</td>
</tr>
<tr>
<td>7</td>
<td>D.D.(m)</td>
<td>Larynx</td>
<td>9/8/50</td>
<td>Cervical node</td>
<td>-</td>
<td>Died 9/22/50</td>
</tr>
<tr>
<td>8</td>
<td>G.C.(m)</td>
<td>Breast</td>
<td>7/6/50</td>
<td>Axillary node</td>
<td>+</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>9</td>
<td>D.C.(m)</td>
<td>Lip</td>
<td>7/91/50</td>
<td>Cervical node</td>
<td>-</td>
<td>Died 12/4/50</td>
</tr>
<tr>
<td>10</td>
<td>L.W.(f)</td>
<td>Cervix</td>
<td>7/98/50</td>
<td>Inguinal node</td>
<td>-</td>
<td>Alive</td>
</tr>
<tr>
<td>11</td>
<td>R.P.(m)</td>
<td>Bladder</td>
<td>8/3/50</td>
<td>Cervical node</td>
<td>+</td>
<td>Died 7/14/51</td>
</tr>
<tr>
<td>12</td>
<td>K.H.(f)</td>
<td>Larynx</td>
<td>10/6/50</td>
<td>Cervical node</td>
<td>+</td>
<td>Died 12/91/50</td>
</tr>
<tr>
<td>13</td>
<td>M.D.(f)</td>
<td>Skin</td>
<td>10/12/50</td>
<td>Axillary node</td>
<td>-</td>
<td>Alive</td>
</tr>
</tbody>
</table>

status of the tumors studied with respect to heterotransplantability and reflect their developmental state at the time of first surgical approach. In the great majority of cases this date closely approximates that of clinical discovery, and, in view of the disproportionate incidence of heterotransplantability in the two groups, it is apparent that, at this date, the tumors of the lung had reached a more advanced stage of development than those of other organs. This finding is of clinical significance tumors of other organs or that the developing neoplasm is present in the lung for a longer period of time before clinical discovery.

References
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