In a recent article Parsons (1) said that lymph nodes from mice with various sarcomas would elicit tumors when subcutaneously implanted in other mice, and gave an extensive description of certain changes in these nodes. Running from hyperplasia of the reticulum to its malignant transformation, the alterations were referred to some unknown agent in the neoplasm which can act with such rapidity that even nodes of normal microscopic appearance, removed from mice bearing tumors only five days old, may on occasion give rise to sarcomas. This observation, highly important if it can be substantiated, was one of her reasons for dismissing metastasis as an explanation.

As sarcoma 37, one of the growths employed by Parsons, has been under cultivation at the Crocker Institute for some fifteen years, an opportunity was given to test her conclusion with a strain of the tumor that has been propagated under conditions more or less different from those obtaining in England.

In repeating her experiment the nodes selected for investigation were removed from mice bearing this neoplasm in the right flank, cut into fragments to allow the extracellular agent, if any such were present, to escape without hindrance, and implanted subcutaneously in normal mice without delay. Incidentally, this subdivision facilitated the aspiration of large nodes into the inoculating needle. No portion was reserved for microscopic examination lest the presence of a few tumor cells in the part transplanted and not in that kept for histological sections, or vice versa, might give rise to erroneous conclusions.

For a microscopic control reliance was placed upon corresponding nodes from mice bearing sarcoma 37 at the same site and of similar age, namely five to twenty-six days. All these nodes were examined in serial sections after they had been fixed in Zenker’s fluid and stained with hematoxylin and eosin.

The nodes employed were among those chosen by Parsons: the right and left axillary; the right and left inguinal; and the right and left aortic, lying behind the peritoneum and on either side of the aorta near its bifurcation.

Reference to Table I will show that 216 nodes, from 36 mice, were transplanted, and that 27 (12 per cent) of them gave rise to tumors. As these 27 nodes came from 14 mice, somewhat over one-third of the animals bearing sarcoma 37 furnished one or more nodes capable of transmitting this neoplasm. The earliest successful transplantation derived from the right inguinal node of a mouse with a tumor only five days old, and in one notable instance all six of the nodes removed from an animal with an eleven-day old sarcoma gave rise to tumors.

In this small series of animals, hardly adequate for definite conclusions, it appeared that the growth speed of a neoplasm, rather than its age, determined whether nodes from the host would transfer it. Thus the two sarcomas just mentioned were by far the largest of their groups, and other cases supporting
Table 1: Results of Transplanting Lymph Nodes from Mice Bearing Sarcoma 37

(+= Tumor developed. -= No tumor developed)

<table>
<thead>
<tr>
<th></th>
<th>Left</th>
<th>Left</th>
<th>Left</th>
<th>Right</th>
<th>Right</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>inguinal</td>
<td>axillary</td>
<td>aortic</td>
<td>inguinal</td>
<td>axillary</td>
<td>aortic</td>
<td></td>
</tr>
<tr>
<td>5 days</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>13</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>14</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>26</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

This supposition were observed, though there were a few exceptions also. The failure of successful implantation to rise with the age of the neoplasm may have been due to the use only of mice with tumors which had not yet ulcerated; that is, in the case of the older tumors, of mice with slowly growing neoplasms.

An experiment much more extensive than that here described had been
planned, but the histological examination of 134 nodes from 48 mice with
growths similar in respect of age and site to those borne by the animals whose
nodes were inoculated gave such a convincing explanation for the development
of neoplasms from a high proportion of implanted nodes that the investigation
was carried no further.

In brief, 31 nodes (23 per cent) from 20 mice (42 per cent) contained
manifest tumor cells, usually in the subcapsular sinus but often in the medul-
lar sinus, and more than one node was frequently found involved
even though all six were not always examined (Table II).

Fig. 1 shows how extensively a lymph node may be invaded, even by the
seventh day after tumor inoculation, while Fig. 2, a more highly magnified
view of the same node, illustrates the ease with which the malignant cells may
be recognized. It is conceivable that a single degenerating tumor cell might
be confused with a swollen cell detached from the wall of the sinus, but such a
desquamated littoral cell could hardly be mistaken for a well preserved tumor
cell. Indeed the authors of several recent articles have commented on the
ease with which the one can usually be distinguished from the other, and in
the material now under discussion, where metastatic cells were present in con-
siderable number if at all, the great majority were so vividly stained that there
was little room for doubt. The resemblance between them and the isolated
elements of sarcoma 37 at the margin of a subcutaneous growth (Fig. 3) is
obvious.

The desquamated littoral cells of chronic lymphadenitis are of quite dif-
ferent appearance (Fig. 4). These are much smaller, pink in hematoxylin-
eosin sections, and have indefinite serrate edges and poorly stained nuclei,
whereas the sarcoma cell has a distinctly purplish tinge, sharply defined con-
tours, and prominent nuclei which are often found in mitosis.

In conformity with Parsons’ experience, it was impossible to predict from
the size of a node whether or not it would give rise to a tumor. Nor, again,
did there seem to be any uniformity in the nodes involved, save that those on
the right side contained metastatic cells, and elicited sarcomas, more often
than those on the left, as was to have been expected since the neoplasm occu-
pied the right flank.
In the case of sarcoma 37 growing in the strain of mice used for these experiments, it is clear that the development of a tumor from an implanted node implies the presence of metastatic cells therein. No hypothetical non-cellular etiological agent need be invoked.

This explanation accords well with the experience of many other investigators. To mention but a few of those who have discussed the question in
recent years, Flaks (2) found that, of various organs from rats inoculated in the thigh with the Jensen sarcoma, only the lungs and the lumbar nodes would transmit the growth. As he had discovered metastatic cells in these nodes a few days after tumor implantation, and only those containing metastatic cells would reproduce the growth, there could be no reason for ascribing the neoplasms elicited by lungs and lymph nodes to an extracellular agent. Moreover, if such an agent did exist it would be curious indeed were it confined to the two sites just mentioned.

Kuschfeldt (3), after remarking that the cells of the mouse carcinoma which she employed could be distinguished by their slightly basophilic cytoplasm from swollen and desquamated littoral cells, said that she had found them in some of the nodes examined nine, twelve, and fourteen days after tumor inoculation. In one instance they appeared in a regional lymph node as early as twenty-four hours after the injection of fluid from mice with peritoneal carcinosis. This unusually early metastasis may have been due to the presence of isolated cells in the transudate, though Schmidt (4), who used
a similar material for his injections, found metastatic cells in the nodes only after a subcutaneous tumor was visible, that is from the ninth day onward. There were virtually no proliferative changes in the reticular cells like those described by Parsons, and he thought that her proposal of a non-cellular etiological agent should be received with considerable skepticism.

Ever since Blumenthal and Auler (5) reported, more than a decade ago, that they had produced neoplasms by implanting spleen from tumor-bearing animals, and raised once more the question of an extracellular agent, this possibility has been under almost constant examination. Yet the agent, if such there be, has consistently eluded discovery, and the prevailing opinion is that the development of new growths from inoculated organs means the presence of tumor cells therein, and nothing more.

**Conclusion**

Growths following the implantation of lymph nodes from a strain of American mice bearing sarcoma 37 arise from metastatic cells in these nodes. It is therefore unnecessary to invoke the participation of an extracellular etiological agent.
BIBLIOGRAPHY