Experimental Inhibition of Carcinoma by Lymphosarcoma*

ANDRÉ BRUWER,† THOMAS C. DONALD, JR., ‡ GEORGE M. HIGGINS, JOHN R. MCDONALD, AND EUGENE T. LEDDY

(Mayo Foundation, University of Minnesota, and Mayo Clinic, Rochester, Minn.)

It has been our impression that patients with a lymphosarcoma rarely have an associated carcinoma. There are reports (8) which describe multiple primary malignant lesions, but the lymphomas, because of their "controversial nature," have been deliberately omitted from consideration. Of patients who die of malignant lesions, 2 to 4 per cent disclose multiple primary malignant lesions. From reports which do include the lymphomas, it is apparent that the combination of carcinoma with a lymphosarcoma is extremely rare.

Warren and Gates (9) studied 794 cases of multiple primary malignant lesions. Ten of these were of carcinoma associated with lymphosarcoma. Owen (6), in a study of 148 multiple malignant lesions, did not record a single association of the two types of neoplasm. Schreiner and Wehr (7) reported 307 cases of multiple primary malignant lesions, 4 of which showed a lymphosarcoma coupled with a carcinoma. Burke (1) analyzed data on 27 cases of primary multiple malignant lesions, none of which were associated with lymphosarcoma. The same was true for the 25 cases detailed by Kirshbaum and Shively (3).

Furthermore, the infrequency of metastatic involvement of the spleen by a carcinoma is a clinical observation which is pertinent to our inquiry. Willis (10) has stated that the incidence of splenic metastasis in malignant lesions which have come to necropsy has ranged from 1 to 4 per cent.

Experimentally, the controversial literature dealing with this presumed antagonism between the spleen and other lymphatic structures on the one hand, and the growth of a carcinoma on the other, has been reviewed by Woglom (11). In his study of 600 papers dealing with resistance to transplantable tumors, the role of the lymphocytes was extensively cited. It was shown by some that the development of immune reactions to transplanted tumors was always associated with the presence of lymphocytes. These cells were regarded, not as scavengers, but as an integral part in the development of this immune reaction. Some accessory factor was postulated, however, because satisfactory tumor growth was obtained in some rats with extraordinarily high lymphocyte counts; whereas others, with subnormal counts, were immune. Certain workers were quoted as having reduced the immunity of rats to tumors by lowering the lymphocyte counts with roentgen rays.

It would thus appear that there are conflicting opinions regarding the role of the lymphatic system in its association with carcinoma. One view is that the lymphatic system may be regarded as a sort of permanent "open house," facilitating the spread of the cancer cells. The contrary view holds that the lymphatic system is antagonistic to invading cancer cells and that it succumbs to them only after a struggle.

In view of the clinical observations recorded in the previous paragraphs and of the conflicting opinions which abound in the literature, we proposed an experiment whereby the influence, if any, exerted by a growing transplanted lymphosarcoma on the growth of a transplanted carcinoma, and vice versa, could be observed.

MATERIALS AND METHODS

In an initial study, 48 weanling male rats of the Sprague-Dawley strain were arranged into 4 groups of 12 rats each.

Group 1.—Each rat was given a subcutaneous injection, in the region of the thigh, of 0.5 cc. of a suspension of cells of Murphy-Sturm lymphosarcoma (5) in an isotonic saline solution.

Group 2.—Each rat was given a subcutaneous injection, along the back, of 0.2 cc. of a suspension of cells of the Walker rat carcinoma 256, in an isotonic saline solution.

Group 3.—Each rat was given injections of comparable amounts of the suspensions of both the lymphosarcoma and the carcinoma, subcutaneously, in regions identical to those selected for Groups 1 and 2.

Group 4.—Each rat was given a subcutaneous

* With the technical assistance of Mary J. Woods.
† Fellow in Radiology.
‡ Fellow in Medicine.

Received for publication August 1, 1951.
injection of 0.7 cc. of a mixed cellular suspension, composed of both the lymphosarcoma cells and the carcinoma cells, so prepared as to provide amounts of each tumor suspension comparable to those provided separately to animals comprising Group 3.

These tumors were measured in centimeters along their largest diameters on alternate days.

RESULTS

Group 1.—The Murphy-Sturm lymphosarcoma, after transplantation, exhibits a pattern of growth which is often followed by subsequent regression. One of us¹ has studied the growth patterns of this tumor and has observed this tendency toward regression. The percentage of tumors which regress, following a period of growth, is inversely proportional to the biologic age of the donor tumor. Whereas this tendency toward regression of transplanted tumors would be disappointing in certain types of experiments, it proved of interest to us in our present study. In our experience these lymphosarcoma transplants grew rapidly for 11 days after implantation and then regressed (Chart 1).

Group 2.—Transplants of the Walker carcinoma likewise grew rapidly and exhibited continuous growth until the death of the animal at about 23 days (Chart 1).

Group 3.—In this group of twelve rats, these tumors were implanted in different sites in the same animal. The growth patterns of the carcinoma and of the lymphosarcoma were essentially like those displayed by these tumors when they had been implanted into separate animals (Groups 1 and 2). The lymphosarcomas were not so large, however, and regression was obvious 2 days earlier than in those of Group 1 (Chart 1). In general it seemed obvious that each tumor had grown independent of the other and that the one had not exerted any significant influence on the growth of the other. These results, therefore, did not sustain the impression we had gained from reported clinical data that a natural antagonism between lymphosarcomas and carcinomas did exist.

Group 4.—The fourth group, in which the two tumor suspensions were thoroughly mixed and then implanted subcutaneously in amounts comparable to those which had been injected separately, presented some growth patterns which were of interest (Chart 1). Some of the tumors in this group grew rapidly following implantation and then regressed permanently. These tumors appeared to follow the growth pattern originally displayed by the lymphosarcoma implants. One group of five animals given the mixed suspension was of particular interest in that the implant continued to grow in a manner suggesting a pattern of growth characteristic of the lymphosarcoma. Following the growth period, there was a regression of each tumor, and in one case complete regression was observed (Chart 1). The regression of these five tumors was only temporary, however, and was followed in 4 days by a second period of uninterrupted growth.²

It seemed to us that the first two stages, those of growth and of subsequent regression, represented the period when the lymphosarcomatous constituents of the mixed suspension were dominant, since necropsy performed during this initial period of growth of some of the mixed implants showed that the tumors were almost exclusively composed of lymphosarcomatous cells. It was noted that sections of tumors obtained during the second phase of rapid growth—that which took place after the initial regression—were then very largely composed of carcinomatous cells. The cytologic structure was then predominantly typical of the Walker carcinoma. Since the initial growth was largely lymphosarcomatous and the second period of growth predominantly carcinomatous, an inhibitory effect of the former on the latter may be conjectured. It was not until regression of the rapidly growing lymphosarcoma

¹ Note that the first three curves in Chart 1 represent averages. The fourth curve represents the most striking case in this group. In the other 4 cases mentioned in Group 4, the temporary regression was not complete.
had occurred that the extensive growth of the carcinoma took place.

Since the initial experiment showed that, when mixed suspensions were implanted the growth of the carcinoma was invariably delayed, we repeated our study. Forty young rats were selected and arranged into four groups of ten animals each, and implantations of cellular suspensions were made as before. Results of the second experiment were essentially the same as those obtained in the first. The combined survival data in the two experiments 23 days after implantation have been condensed into Table 1. Of the 22 animals given a lymphosarcoma implant, 11 were living. Of these, the implant in 1 had failed to grow and in 10 all tumors had regressed. Of the 11 dead, 6 had died from the effects of the tumor and 5 had been killed to obtain viable tissue for study. Of the 22 animals inoculated with cellular suspensions of the carcinoma, 4 were living. One tumor had regressed, but 3 were growing; 15 animals had died, and 3 had been killed to obtain tissue. In Group 3, only 2 animals had survived, 17 had died, and 3 had been killed. In Group 4, animals which had received mixed suspensions of both tumors, 12 were still living and only 5 had died from the effects of the tumor. This group also had a greater number of growing tumors than any other group at the end of 23 days.

It appears from these data that the lymphosarcoma may have moderated the degree of malignancy of the carcinoma in those animals into which the mixed suspensions of these two types of neoplastic tissue had been injected. The separate implantation of cellular suspensions of these two tumors into different sites in the same animal had failed to reveal any such attenuated pattern of response of the carcinoma. Furthermore, we did not observe any significant difference between the growth patterns of these two tumors when they were implanted into the same animals (Group 3) and when they were implanted separately, as in Groups 1 and 2.

By the 23d day following implantation, 15 (68 per cent) of the 22 animals that were treated with carcinoma alone (Group 2) had died of the lethal effects of the tumor, and 17 (77 per cent) of the 22 animals inoculated with both carcinoma and lymphosarcoma in separate sites (Group 3) had died of the effects of the tumor. But 6 (27 per cent) of the 22 animals bearing the implanted lymphosarcoma had died, and only 5 (25 per cent) of those bearing the mixed tumor cell growths had died. When these mortality data are contrasted with those set forth previously—68 per cent in Group 2 and 77 per cent in Group 3—it is obvious that some inhibitory influence, presumably exerted by the lymphosarcoma on the carcinoma, extended survival times of animals of Group 4.

**TABLE 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>No.</th>
<th>Condition</th>
<th>Examined at Necropsy</th>
<th>Of Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphosarcoma</td>
<td>11</td>
<td>1 no take</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>4</td>
<td>1 regressed</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Both, different sites</td>
<td>2</td>
<td>1 regressed</td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td>Both, same site</td>
<td>12</td>
<td>4 regressed</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

**RESULTS AT THE END OF 23 DAYS, WITH 22 ANIMALS IN EACH GROUP**

COMMENT

One may postulate from the data assembled on the growth of implants within Group 4 that, when suspensions were mixed and implanted into the same site, the organism permitted only one of the two neoplasms to demonstrate detectable growth at any one time. It may be that cellular constituents of the one neoplasm were destroyed or kept in abeyance; or that growth factors essential for its nutrition were withheld. It may well be that certain enzyme systems either in the host or in the tumor tissue play a part in the growth of both the lymphosarcoma and the carcinoma cells, favoring at times lymphosarcoma cells when both lymphosarcoma cells and carcinoma cells are present in suitable numbers for individual growth. An analogous situation is thought to occur in diabetes. The oxidation of fats is accomplished by the same enzyme system, which, in the normal nondiabetic animal, would favor the oxidation of carbohydrates (4). And, again, when para-aminobenzoic acid is present, a micro-organism such as Staphylococcus will take it up and thrive. But, when sufficient sulfonamide is available, it will be favored by the same enzyme system hitherto allied to the micro-organism, and thus to the latter's detriment (9). Bacteriologists call this "competitive inhibition." Perhaps there is a substance in the lymphosarcoma cell which competes successfully for the enzyme system of the host essential for the growth of carcinoma when both are trying to grow at the same site. When the lymphosarcoma regresses, the enzyme system could then become available for the growth of carcinoma.

**SUMMARY AND CONCLUSIONS**

A study has been made of the effects obtained in experimental animals when suspensions of lym-
phosphatidylcholine cells and carcinomatous cells are implanted, separately and in mixtures.

The results showed that, of 22 rats implanted with lymphosarcoma, tumors grew rapidly in 21 animals for a certain period of time and then regressed. All tumors grew rapidly in the 22 animals which received implants of the carcinoma. When cell suspensions were implanted in separate sites on the same animal, the resulting tumors followed growth patterns which were more or less like those obtained when implantations were made into separate animals. When mixed suspensions of the two tumors were implanted, however, tumor growth patterns suggesting certain inhibitory relationships were seen. A period of rapid growth, a period of regression, and a subsequent period of growth were observed. Sections of the tumor obtained during the initial growth showed that the tissue was predominantly lymphosarcomatous, whereas sections obtained during the second period of rapid growth showed that the tissue was then predominantly carcinomatous.

Our study would seem to support the opinion that lymphosarcoma and carcinoma, when growing independently in separate locations in the same animal, display no antagonistic growth patterns. However, when lymphosarcoma cells and carcinoma cells are implanted together and subjected to identical environmental factors provided by the host, there appears to be a preferential development of the lymphosarcoma. Significant growth of the carcinoma cells did not take place until growth and regression of the lymphosarcoma had occurred. Possible explanations for this sequential development are offered.

REFERENCES

Experimental Inhibition of Carcinoma by Lymphosarcoma
André Bruwer, Thomas C. Donald, Jr., George M. Higgins, et al.


Updated version  Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/11/12/922

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.