The Natural History of the Lakeland Sarcoma
(Leiomyosarcoma) *

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Recently, we reported a new transplantable tumor which we described as a sarcoma of undetermined type (3). The tumor was observed in the pelvic lymph nodes of a 2-year old Sprague-Dawley (S-D) rat, the liver of which had been irradiated with 4000 r of x-rays 1 year prior to death. The tumor encompassed the cervix and parts of both uteri. Subsequent microscopic study has shown that it originated in the smooth musculature of the uterus (Fig. 1). We wish to present here in greater detail the characteristics of this leiomyosarcoma in earlier and later transplant preparations.

MATERIALS AND METHODS

Transplantation.—The original tumor has undergone fourteen serial subcutaneous transplantations in S-D rats. In the first five generations cell suspensions of the tumor were injected into several sites in each host. In subsequent generations, the trocar method was employed, about 1 cu. mm. being grafted. Except for one group, the leftinguinal region was the only site used for the trocar grafts.

Measurements.—Tumor size was determined at autopsy by caliper measurements of the three diameters, and by weight. The rate of growth of the tumor was approximated in the F9 through the F14 generations by making weekly caliper measurements of two diameters, the arithmetic mean of which was considered the “average tumor diameter” (1).

RESULTS

Percentage of “takes.”—In the first five transplant generations, in which the cell-suspension method was used, only fourteen of 29 females (48 per cent) developed tumors. In the sixth through the fourteenth generations, by the trocar method, 77 of 88 females (88 per cent) and 56 of 48 males (75 per cent) developed tumors. The sex difference in susceptibility to transplantation is statistically significant at a 5 per cent level.

Regressions.—No regressions of the Lakeland tumor have been observed in S-D rats.

Rate of growth.—The post mortem size of the tumor, as determined by averaging the three main dimensions, was divided by the number of days between the grafting and death of the animal (5). The average daily increment in tumor diameter rose from 0.3 mm to 0.9 mm after the transformation which occurred in the tumor in the fourth and fifth generations.

In Chart 1 the “average diameters” (1), as derived from the two weekly measurements, are plotted against time for the ninth through the fourteenth generations, omitting the eleventh, which comprised only a few animals used as donors. It is evident from these graphs that, as measured, the average increase in the size of the Lakeland tumor was linear and that it was consistent for different generations in spite of wide individual variations. It is also apparent that sex did not significantly modify the rate of tumor growth.

Invasiveness.—Skin and muscle appear to be the only tissues invaded. The most frequent site of invasion was the musculature of the back adjacent to the pelvic lymph nodes. Frequently, the invasion of skin and muscle was accompanied by a massive gelatinous edema.

Metastases.—The use of multiple transplant sites in the first five generations interfered with a clear-cut differentiation between invasion and metastases. For this reason, only data from the grafts made by trocar will be presented.

Reference to Table 1 will show that 94 of 103 tumor-bearing animals (91 per cent) had metastases. Sex did not significantly alter the frequency of metastases. The fact that 33 per cent of males and 13 per cent of females had five to seven me-

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tastases was due to the fact that more of the females were sacrificed at the time when the first member of their group died.

In Table 1 the term “pelvic lymph nodes” is used to include both the caudal and the left lumbar (4), which were often so large that they fused.

Variability in the size of the metastases was very marked; many were exceptionally large for the rat. For example, both axillary and pelvic nodes reached an average diameter of 3.8 cm. with a weight of 47 and 33 gm., respectively, and the lungs of one animal weighed 154 gm.

As previously observed (5), all the metastases appeared in the lungs, lymph nodes, or muscle.

Survival time.—In the first three transplant generations the average survival time was 20 weeks—excluding one animal that died of pneumonia at 3 weeks. One animal of the second generation lived for 249 days after transplantation. After the fifth generation, when the trocar method was used, the average survival time was 10 weeks. Of the 103 tumor-bearing animals, only two died in less than 54 days, and only one survived longer than 118 days (181 days). These figures exclude animals used as donors.

Gross appearance of the tumor at autopsy.—Most of the tumors had well vascularized “capsules.” The tumor tissue was firm and pale gray in color. Central necrosis was observed in nearly all tumors, and cavitation was frequent in the larger ones. Hemorrhages into the central cavity were often extensive, but were rarely seen in the tumor tissue.

The histologic findings.—The histologic characteristics of the tumor are compatible with those of a leiomyosarcoma.

The original tumor and most specimens from the second, third, and fourth transplantations showed a rather uniform cell population. The neoplasm consisted of spindle-shaped cells of rather uniform size, which were arranged in sheets. In many areas, the long axes of the cells of two adjacent sheets were located at right angles to one another, thus producing a herringbone arrangement (Fig. 2). In other areas, the cells in one sheet are seen cut parallel to the long axis, and in the adjacent sheet in cross-section.

The neoplasm was well vascularized. Occasionally, one had the impression that the walls of the blood vessels were infiltrated by tumor cells. This was seen especially in metastases (Fig. 3). The cells were densely packed. The use of Mallory and Von Gieson stains did not demonstrate fibers between the cells. The shape and staining of the nuclei were uniform. They were oval or cigarette-shaped and showed a vesicular appearance. Nucleoli were not prominent. Mitoses were numerous, from one to two in a field of high magnification, most of them being typical.

The histologic picture from the fifth transplant generation (Fig. 5) and in one area of the specimen from the second transplant generation had an entirely different character. Only occasionally could
areas be seen which resembled the original tumor. Necrosis was a constant feature. Areas of tumor around blood vessels were vital but separated by sheets of necrosis.

After the fifth generation, the cells in general were larger and differed greatly in shape and size (Figs. 5, 6, and 8). They also formed no fibers. Owing to the histologic procedure, the cells became isolated in many areas. In such instances they were usually polygonal. Where they appeared spindle-shaped, they were much longer than the cells in the original neoplasm. A large percentage of the cells were multinucleated (Fig. 8). These seemed to predominate in the vicinity of necrotic areas. In some of these cells, one or two or more nuclei appeared to be dividing (Fig. 8). The nuclei were of different size but in almost all instances larger than in the original tumor. Their shape was irregular and varied from spheric to kidney-shaped. The chromatin in many nuclei appeared to be distributed as though arrested in a state of prophase, with a distinct nuclear membrane. The nucleoli also differed in size; they were prominent and occasionally of huge size. Normal mitoses were rare, atypical mitoses frequent.

**DISCUSSION**

Homburger et al. (2) have reported a transplantable leiomyosarcoma which originated in a hamster after the implantation of a cholesterol pellet. This tumor also metastasized frequently to the lung.

**SUMMARY**

A transplantable tumor which originated in the uterus of a Sprague-Dawley rat and appears to be a leiomyosarcoma is described. The tumor has been studied through fourteen transplant generations. After the fifth generation, the tumor grew more rapidly, became more anaplastic, and metastasized more frequently. The rate of growth was linear during the first 8 weeks, and no regressions have been observed. The transplants made by the trocar method grew in 94 per cent of females and 75 per cent of males. In the tumor-bearing animals, 91 per cent developed metastases; the axillary and pelvic lymph nodes were involved in 82 and 57 per cent of cases, respectively. The lungs were involved in 50 per cent of cases. In 127 tumor-bearing animals, no metastases have been found in any tissue except muscle, lymph nodes, and lungs. After the fifth generation, the average survival time has been 10 weeks, with a range of 6–19 weeks.

**REFERENCES**

Fig. 5.—Photomicrograph showing the tumor following the fifth transplantation (#2084). Note the polymorphism of the cells and hyperchromatism of the nuclei and the prominence of nucleoli (Mag. X550).

Fig. 6.—Photomicrograph showing a metastasis in the perirenal lymph node following the tenth transplantation (#2178A). Note the large spindle cells of varying shape and size, the hyperchromatosis and polymorphism of the nuclei and the multinucleated giant cell at the right upper corner (Mag. X550).

Fig. 7.—Photomicrograph of metastasis in a lymph node following the sixth transplantation (#2125A). Note the left half of the node invaded by the neoplasm (C) and a lymphocytic hyperplastic zone (B) separating the neoplasm from a still relatively normal portion (A) (Mag. X140).

Fig. 8.—Photomicrograph of an area of a metastasis in a lymph node following sixth transplantation (#2125A). Note the hyperchromatosis of one nucleus in the multinucleated giant cell, suggesting nuclear division (Mag. X850).
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