IMPLANTATION OF RAT CARCINOMA AND SARCOMA WITHIN BENIGN FIBROADENOMA

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The results of transplanting mixtures of tumors of different varieties have been studied by Apolant (1, 4) and Ehrlich (1, 3) and by Haaland (2). A mixture of a sarcoma and a carcinoma was implanted into mice. The neoplasms grew together but each strain could be separated by growing it in animals susceptible to only one type of tumor. When tumors varying in viability and proliferative capacity were mixed and transplanted, the most energetic type overgrew the others in a few generations. None of these workers were able to produce an amalgamation of tumor strains into a new type, but obtained rather a mixture of two types of tumors, each retaining its morphological characteristics. The same phenomenon has been observable in the metastasis of complex human tumors, such as those of the testicle. The highly specialized tissues rarely appear in the secondary growths, but instead, sarcomatous, chondromatous or carcinomatous elements dominate in the metastases. In a rhabdosarcomata of the sternum of the rat, Bullock and Curtis (5) were able to observe muscle elements over a long period, but gradually these disappeared and the strain became a pure sarcoma. In the course of a study of benign tumors of the rat breast, which has been in progress in this laboratory for several years, the opportunity was offered to study the effects of inoculating into the center of a slow-growing benign tumor, neoplasms of a highly malignant variety. Ten adult white female rats, each with a large spontaneous fibroadenoma of the breast, and seventeen younger animals of the same breed, with transplanted fibroadenomata, were available as hosts. The spontaneous tumors were large, soft, lobulated growths,
situated over the anterior or posterior mammary regions, measuring about 9 x 7.5 x 6.5 cm., and weighing about 120 gms. The transplanted tumors (first generation) were 92 to 167 days old, with an average measurement of 4 x 3 x 2 cm. and average weight of 70 gms. Histologically these growths conform to the human type of fibroadenoma of the breast with a densely fibrous stroma interspersed with regularly growing or distorted or compressed glands arranged in lobules. Some of the transplanted tumors show a very cellular stroma, and some have entirely lost the glandular elements.

The neoplasms taken for implantation were the Flexner rat carcinoma (121st generation), and a sarcoma known as Rat 10 (93d generation). The carcinoma (0.003 gm.) was introduced by needle about 2 cms. from the lower pole of the benign growths.
At intervals the fibroadenomata were removed and examined grossly and microscopically. In six animals the carcinoma has been able to get sufficient nutrition to proliferate within the fibroadenomata. It grew in the depths of the benign tumor without visibly affecting the health of the animals, or appreciably modifying the development of the fibroadenoma. No change in the external appearance of the tumor was evident. The inoculated benign growths resembled outwardly the uninoculated controls. A section, however, through the former showed a striking difference between the outside benign and the circumscribed malignant tissue within. The outside was white fibrous, lobulated, with a firm elastic feel, while the inner growth within a growth, was soft smooth, pearl-gray, and very distinctly outlined from its fibrous shell. Histologic examination showed
no change in the structural characteristics of these individual tumors, growing in such close proximity. They each retained their identity.

In one old rat a large cyst formed at the site of the Flexner carcinoma inoculation in the bulky spontaneous fibroadenoma. The cyst wall closely adhered to the abdominal muscles, and

the cavity was filled with a thick pale-green, purulent fluid. The cyst margin showed microscopically a thick fibrous capsule rather plentifully but not closely infiltrated with carcinoma cells. Just beyond this margin the lobules of the original fibroadenoma retain their outlines, but an active fibrosis is replacing the necrotic and disintegrated glands. In many there is no epithelium, and hyalinization is very apparent. Other lobules, although highly sclerosed, show areas of infiltrating carcinoma.
implantation of rat carcinoma and sarcoma

cells, singly or in groups. These are obviously viable, lying entrenched within thick layers of dense fibrous coils.

Some of the early implants did not show on gross section. Microscopically, streaks of carcinoma cells are visible along the channel of inoculation. Most of these cells are necrotic.

Fig. 4. A Few Cells of Carcinoma Surviving about a Small Capillary in a Necrotic Area, 68 Days after Implantation of F. R. C. within a Transplanted Fibroadenoma Six Months Old.

Sections of later implants show the carcinoma cells growing in small colonies. At the margin of invasion there is a marked polymorphonuclear leucocytic infiltration. In general, however, there seems to be little reaction on the part of the benign growth.

Some of the animals lived three months and one lived four months after the implantation of carcinoma in the fibroadenoma. Of the four transplanted benign tumors in each rat, only one tumor was inoculated with carcinoma. The injected fibroadenoma did not vary from the controls in gross appearance. One rat
with a spontaneous tumor, enclosing carcinoma, weighed 260 gms., the growth alone being 60 gms., while another with a transplanted and later injected fibroadenoma, weighed 140 gms., the growth alone being 40 gms. No metastases were found of either the carcinoma or the fibroadenoma on autopsy.

A very malignant spindle cell sarcoma (Rat 10) was implanted similarly in spontaneous fibroadenomata of five rats. In 66 days two animals were killed and the benign growth disclosed a marked sarcomatous infiltration which extended also outside and around it. The soft grayish-yellow sarcoma had invaded the capsule surrounding the glistening white firm fibroadenoma, and had found a path through the abdominal and chest wall into the mesentery and mediastinum. The spleen and left axillary lymph nodes were enlarged.
The contrast between the mode of growth of carcinoma and sarcoma similarly implanted in the benign tumor is very striking. The first impression was that connective tissue exerts an inhibitory effect on the proliferation of carcinoma cells, and acts as an augmenting force on the sarcoma. If this were true, removal of the enclosed carcinoma and its reimplantation in

the same host or in other animals would hardly succeed. However, such transplants showed the same percentage of takes as controls and the same ultimate growth rate. Fragments of benign tumor containing carcinoma cells when transplanted showed a greater latent period, but eventually the carcinoma outstripped the other elements and became firmly established.

The transplanted carcinoma retains its identity though growing in the very heart of the benign tumor. The cells remain

![Image](image_url)
viable three to four months after implantation. In a few weeks a subcutaneous carcinoma transplant reaches double the size of one implanted for months in the benign tumor. Although subcutaneous transplants of F. R. C. metastasize six to eight weeks after implantation, the same tumor embedded for fifteen

weeks in the benign fibroma show no signs of gross or microscopic metastases in the lymph nodes or lungs.

An interesting corroboration of the virulence of the F. R. C. when unrestrained occurred under the following circumstances. On October 12, 1927, the experiments were repeated for verification. In the process of introducing the carcinoma within the tough, firm fibroma, the needle was accidentally forced clear through the fibroma, from the lower pole out and beyond the upper pole.

In 68 days the carcinoma, grew beyond the poles of the benign

Fig. 7. R 10 Sarcoma Growing through and around Fibroma 66 Days. This tumor ultimately invaded the mesentery and mediastinum.
fibroma which measured 22 x 12 x 10 mm. and was 258 days old. The malignant growth in 68 days reached a size of 41 x 28 x 12 mm. and had infiltrated the muscles of the chest and neck and had invaded the lung mediastinum, and pericardium.

There were metastases in the axillary lymph nodes. The fibroma showed no malignant growth within it, and there was a distinct necrotic zone between the two types of tumor.

It is plausible to assume that the poor vascularization of the benign tumor impedes the growth of the carcinoma. That the nutrition is poor, is evidenced by the fact that sclerosis and hyalinization occurs frequently in the benign fibroadenomata of the rat breast. Microscopically there are but very few small blood vessels present in the fibromata. How the few cancer cells, embedded in sclerosed fibrous strands, can maintain themselves is a problem for further investigation.

DISCUSSION

Inoculation of rapidly growing carcinomata or sarcomata of the rat in the center of large spontaneous or transplanted fibromata or fibroadenomata of the breast resulted in the growth of a malignant tumor, but with greatly reduced proliferative rate of the former. The carcinomata continued to remain encysted in the center of the benign tumor while the sarcomata seemed able to grow along the track of the needle infiltrating the fibrous tissue and ultimately escaping into the tissues of the host, but no other influence could be observed, the benign tumor seeming to play wholly a neutral part, even though highly malignant neoplastic cells were resident in its center. Although occasionally these fibromata or fibroadenomata are capable of changing their biology and becoming malignant, no such alteration was observed as induced by the presence of these grafted tumors. After a long residence in the host the carcinoma cells, when transplanted into a fresh animal, showed no change in their biology but grew as rapidly as control tumors did which had never been imprisoned in the connective tissues of a benign neoplasm. This result is another evidence against an organism being responsible for the growth of malignant tumors, for it
might be expected that if such an organism were present it would stimulate the benign tumor to become malignant. Very interesting implications of this experiment are that the conditions thus artificially produced resemble the clinical cures seen after radiation, in which tissue of the cervix or other connective tissue structures contain on microscopic examination neoplastic cells which are evidently viable, but these cells remain quiescent because, owing to the closure of the vessels, a wholly insufficient amount of nutrition reaches the malignant cells and thus their proliferation is prevented. But if the cells of the neoplasm are permitted to escape from the sheltering influence of a dense fibrous tissue by biopsy or other surgical intervention, it is well known that a recurrence is likely to take place. This furnishes additional evidence for the well-known fact that after a clinical cure has been produced by radiation no further surgical intervention should be permitted. The difference in behavior between carcinoma cells and the sarcoma cells has been observed also in the clinical treatment of such growths. The difficulty of influencing the spindle cell types of sarcoma by radiation as compared to carcinoma despite extreme scarring of the tissues about the sarcoma is well known to radiologists. It is also well known that broadly speaking unless the sarcoma is completely eradicated a local recurrence is much more rapid than with carcinoma.

REFERENCES