INTRATESTICULAR IMPLANTATION OF THE FLEXNER-JOBLING RAT CARCINOMA.

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PLATE 26.

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It is generally agreed that the propagable tumors of mice and rats will proliferate in practically all the organs[1] of the body, including the testis, though the transplantability of the Flexner-Jobling rat carcinoma into this gland has not yet been definitely proved. Thus, Flexner and Jobling[2] said that their attempts to transplant this tumor into the testis had met with but indifferent success, while Levin[3]

[1] The bibliography up to 1913 is to be found in Woglom, W. H., Studies in Cancer and Allied Subjects. The Study of Experimental Cancer, New York, 1913, i. Other references are: Kraus, R., Ranzi, E., and Ehrlich, H., *Wien. klin. Wchnschr.*, 1909, xxii, 1653 (liver, omentum, and testis). Graf, R., *Centralbl. f. allg. Path. u. path. Anat.*, 1910, xxi, 723 (various organs, including the bones). Stumpf, R., *Beitr. z. path. Anat. u. z. allg. Path.*, 1910, xlvii, 571 (kidney). Levin, I., *Jour. Exper. Med.*, 1911, xiii, 604; 1912, xvi, 155 (various organs, including the brain and the bone marrow). Brancati, R., *Tumori*, 1911, i, 189 (various organs). Ruben, L., *Arch. f. Ophth.*, 1912, lxxxi, 199. Da Fano, C., *Folia neuro-biol.*, 1912, vi, 109 (brain). Uhlenhuth, P., *Deutsch. med. Wchnschr.*, 1913, xxxix, 1859 (testis and brain). Keysser, F., *Wien. klin. Wchnschr.*, 1913, xxvi, 1664; *Ztschr. f. Chemotherap., Ite Teil, Orig.*, 1914, ii, 188 (various organs, including the eye). Citron, H., *Ztschr. f. Immunitätsforsch., Orig.*, 1912, xv, 1; *Centralbl. f. Bakteriol., Ite Abt., Orig.*, 1914, lxxii, 328 (wall of stomach). Happe, *Ber. ü. d. xxxix. Versamml. d. ophthalmol. Gesellsch.*, Heidelberg, 1913, 407 (eye). Grignolo, F., *Gior. d. r. Accad. di med. di Torino*, 1914, lxxvii, 285 (eye). Ebeling, E., *Ztschr. f. Krebsforsch.*, 1914, xiv 151 (brain). A detailed account of Keysser's work is given by Hegner, C. A., an ophthalmologist in *München. med. Wchnschr.*, 1913, lx, 2722.

[2] Flexner, S., and Jobling, J. W., *Monographs of The Rockefeller Institute for Medical Research*, 1900, No. 1, 35.

[3] Levin, I., *Jour. Exper. Med.*, 1912, xvi, 149, 155; 1912, xv, 163.

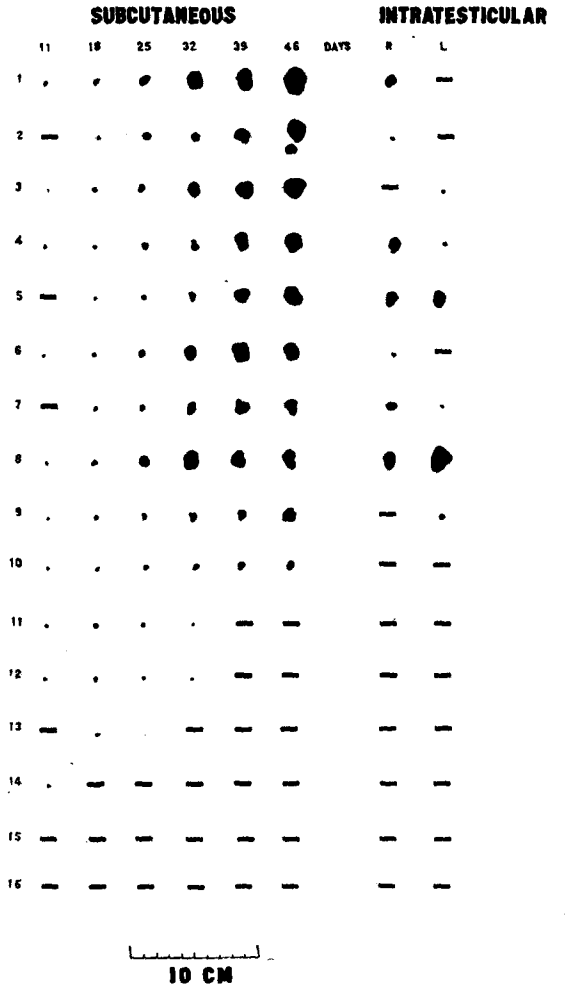
wrote that he had failed entirely to inoculate it into this organ. The failure can not be ascribed to any technical factor, because the Jensen rat sarcoma, transplanted by the same method, grew vigorously in the testis.

Since so many authors have reported the successful inoculation of other tumors at this site, it would appear from the experiments just cited that the Flexner-Jobling carcinoma is an exception to a general rule. Actually, however, it is not, since the experiments about to be described prove that this tumor grows well in the testis. A series of preliminary transplantations, which it is not necessary to reproduce here, demonstrated that the inoculation percentage of the Flexner-Jobling tumor in this gland is almost equal to the subcutaneous inoculation percentage, and that subcutaneous and intratesticular grafts in the same rat generally tend to fail or succeed together.

Although grafts do succeed, therefore, in proliferating in the testis, the resulting tumors do not attain quite the dimensions of those growing in the subcutaneous tissues. Why this should be so, it is impossible to explain. It is not true of all the parenchymatous organs, at any rate, for tumors inoculated into the kidney, for instance, attain dimensions equal to those of axillary neoplasms, as has been pointed out by Woglom.[4] The greater size of the subcutaneous growths is not apparent merely (explicable, that is, by the inclusion of skin at the weekly measurements), for in several experiments where the subcutaneous tumors were measured at autopsy, the skin was found to make but a negligible difference. The testis can not be regarded, in itself, as an unfavorable soil, for the ingrowth of blood vessels and fibroblasts during the first few days following implantation is not less marked than in the subcutaneous tissues (Fig. 1); yet it is possible, of course, that the blood supply in this gland finally becomes inadequate to satisfy the incessant requirements of a rapidly growing tumor. The presence of a growth in the axilla will not account for the smaller size of intratesticular neoplasms, since both tumors were inoculated at the same time; and ample evidence has been accumulated to show that two grafts, simultaneously implanted, do not affect one another. The question of age does not arise, for

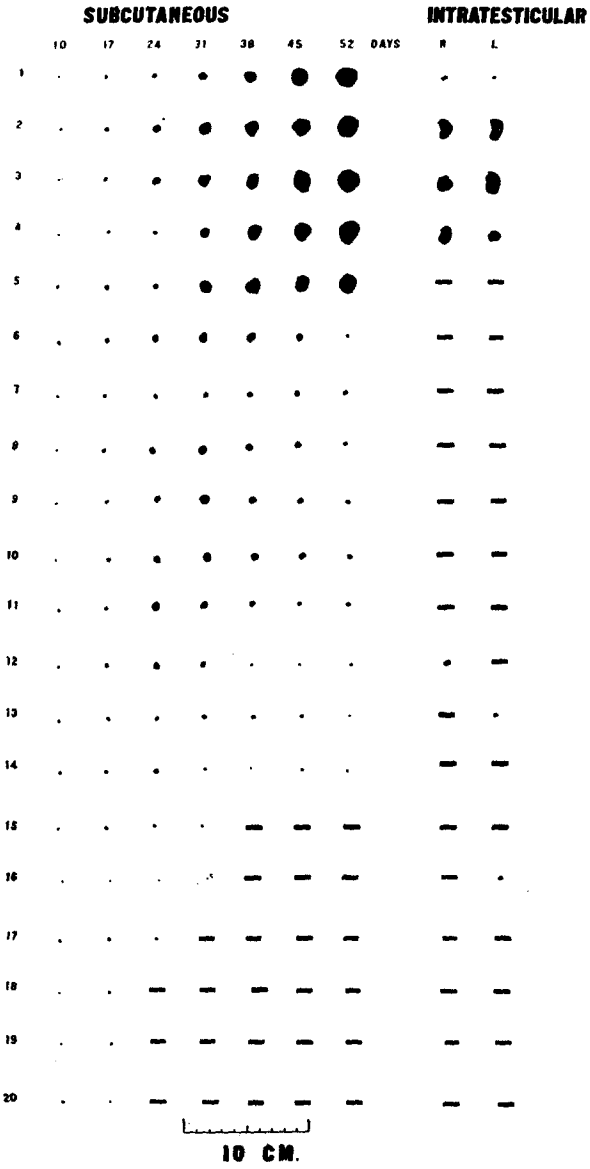
[4] Woglom, W. H., *Lancet*, 1911, ii, 92.

the animals were all young adults. The pressure of the tunica albuginea is the only remaining possibility among those that come readily

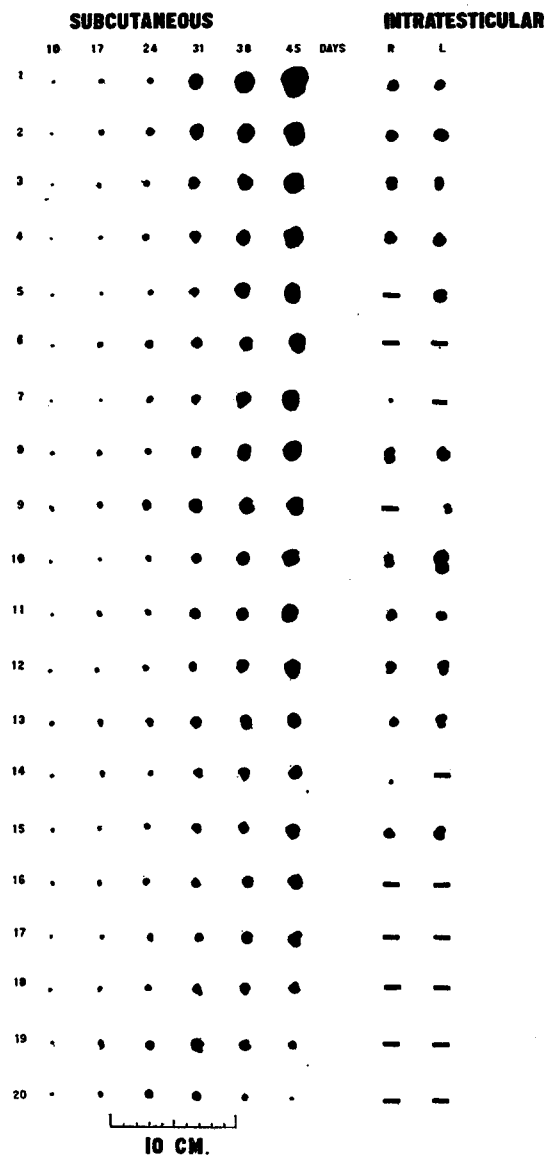


TEXT-FIG. 1. $\frac{FRC}{13E}$. Average weight of rats, 99 gm.

to mind; but the following experiments (Text- figs. 1 to 6) prove that this factor does not explain entirely the smaller size of intratesticular growths.

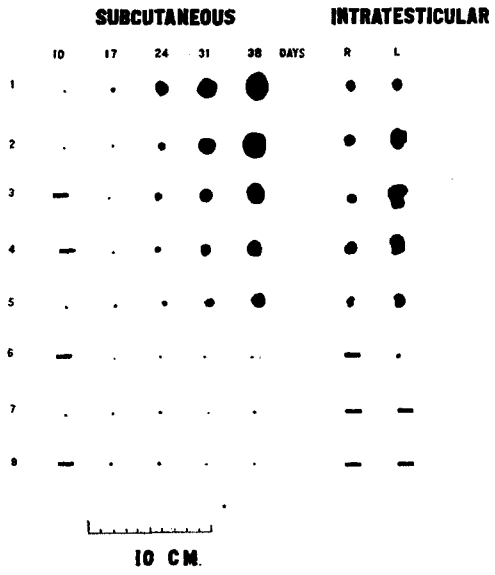


TEXT-FIG. 2. $\frac{\text{FRC}^1}{14\text{GG}}$. Average weight of rats, 79 gm.



TEXT-FIG. 3. $\frac{FRC}{14Z}$. Average weight of rats, 76 gm.

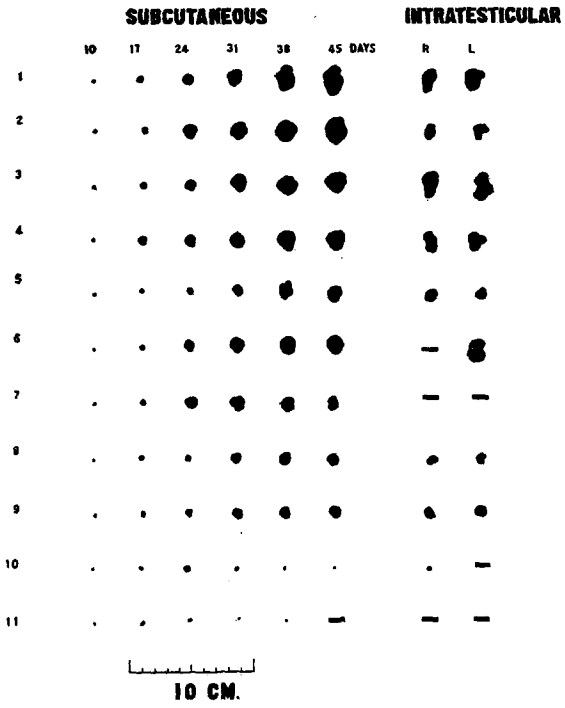
Six groups of young adult rats averaging 77 gm. in weight (except in experiments $\frac{FRC}{13\ E}$ where the weight was 99 gm., and $\frac{FRC}{13\ O}$ where the rats were not weighed), were inoculated in both testes and in the right axilla, each series at the same sitting and with an equal dose (0.01 gm. by the needle method) of the same tumor. From three to seven days afterward, the tension in the left testis was lowered by incising the tunic through an abdominal incision under ether anes-



TEXT-FIG. 4. $\frac{FRC}{13C}$. Average weight of rats, 77 gm.

thesia, while the right testis was left undisturbed as a control. The figures show the results when the rats were autopsied, from thirty-eight to fifty-two days after inoculation, the two columns to the right representing the growths in the right and left testes. The tumors in the opened (left) gland were not invariably larger than those in the unopened, as they would be were tension alone responsible for the smaller size of intratesticular growths. That the release of pressure may occasionally exert some slight favorable influence, however, is suggested by the fact that neoplasms in the opened testis had in

several cases grown through the incision in the tunic; furthermore, these growths were sometimes larger than those in the opposite testis. That is to say, in thirty-nine rats where grafts succeeded in both testes, a distinctly larger tumor was found in the opened gland in twelve, while in only six was the nodule on this side smaller than that in the intact organ; in twenty-one rats, the intratesticular growths were of uniform size.



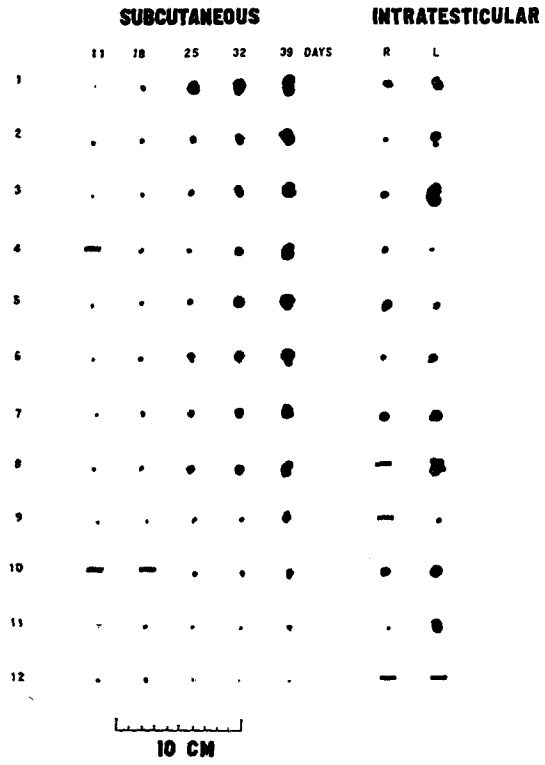
TEXT-FIG. 5. $\frac{FRC}{14V}$. Average weight of rats, 78 gm.

The absence of metastases in the abdominal cavity supports the observation of Jones and Rous,[5] that the peritoneum, in animals at least, is not susceptible to metastatic attack unless the subendothelial connective tissues have been injured.

The perfect receptivity of the various organs for inoculated tumors throws some light upon the rationale of metastasis in man. The

[5] Jones, F. S., and Rous, P., *Jour. Exper. Med.*, 1914, xx 404.

belief so long held, that the spleen, for example, actively antagonizes the growth of secondary neoplasms, has been proved untenable by the observation that tumor cells are well able to proliferate in this organ, among the lower animals at least, provided only that they succeed in reaching it. There is no reason to suppose that the human spleen enjoys a higher immunity; indeed, two authors (Kettle[6] and von



TEXT-FIG. 6. $\frac{FRC}{130}$. The rats in this experiment were not weighed.

Hansemann[7]) have but recently asserted that the resistance offered by this organ in man is not nearly so efficient as has been supposed. It is highly probable, therefore, that such exemption as it does possess

[6] Kettle, E. H., *Jour. Path. and Bacteriol.*, 1912–13, xvii, 40.
[7] von Hansemann, D., *Deutsch. med. Wchnschr.*, 1915, xli, 633.

is to be ascribed, not to the exhibition of an antagonism to the tumor cell higher than that opposed by other organs of the body, but chiefly to some mechanical factor. Such an explanation has been advanced recently by Kettle, who suggested that the contractions of the spleen force tumor emboli out of the organ again, and even prevent the growth of a large number of those that have become impacted in the capillaries.

In comparing natural metastasis with artificial metastasis, that is, with inoculation into the various organs, one distinction must not be overlooked; in the former, the tumor cells come to rest in a blood- or a lymph-channel, while in the latter process they are deposited by the needle directly in the tissues. Here they are under more favorable conditions for growth than they would be in the vessel, for a large proportion of natural emboli, unable to establish vascular connections with the vessel wall, perish in consequence, as Schmidt[8] has shown.

The work of Takahashi[9] upon artificial pulmonary metastasis, which he brought about by introducing emulsions of transplantable mouse tumors into the circulation, proves that the cells of certain of these neoplasms are unable to furnish themselves with a stroma from the vessel wall. Belonging, in general, to tumors of slow growth, they die before they have had time to effect the necessary union.

As in the experiments of Weil,[10] the tumor cells did not pass through the lungs, except in one instance. One sarcoma among the fourteen tumors employed by Takahashi (eleven carcinomata and three sarcomata) having done so, seemed to show some predilection for certain sites, resembling in this latter respect carcinomata of the prostate and the thyroid in man, which are especially apt to involve the skeletal system. Whether chemical peculiarities have any part in determining such a selective metastasis is still a disputed question; at present, however, the mechanical influences emphasized by von Recklinghausen and his pupils certainly appear to play the major rôle.

When the recent investigations of metastasis are recapitulated, it

[8] Schmidt, M. B., Die Verbreitungswege der Karzinome und die Beziehung generalisierter Sarkome zu den leukämischen Neubildungen, Jena, 1903.

[9] Takahashi, M., *Jour. Path. and Bacteriol.*, 1915, xx, 1.

[10] Weil, R., *Jour. Med. Research*, 1913, xxviii, 497.

appears that the process is governed by several factors. If a secondary tumor is to be produced, the cells of the primary neoplasm must have the power to establish vascular connections; secondly, they must remain undisturbed in the vessel long enough for this process to be completed. Thirdly, if these two conditions have been fulfilled, the organ in which they happen to lie is probably a matter of indifference in the large majority of cases.

CONCLUSIONS.

The Flexner-Jobling adenocarcinoma of the rat is easily transplantable into the testis of this animal.

The resulting growths in the intact testis do not often attain the size of subcutaneous tumors.

The smaller size of intratesticular nodules can not be explained solely by the pressure to which they are subjected during their growth; other factors, which cannot be determined, appear to be concerned.

EXPLANATION OF PLATE 26.

FIG. 1. Five day graft of the Flexner-Jobling tumor in the testis. Tumor below; testis above. Two capillaries are shown, one cut longitudinally, the other transversely. The old stroma in this field has disappeared, and its place has been taken by fibroblasts from the host. The condition is identical with that of subcutaneous grafts at the fifth day. Magnified 388 diameters.

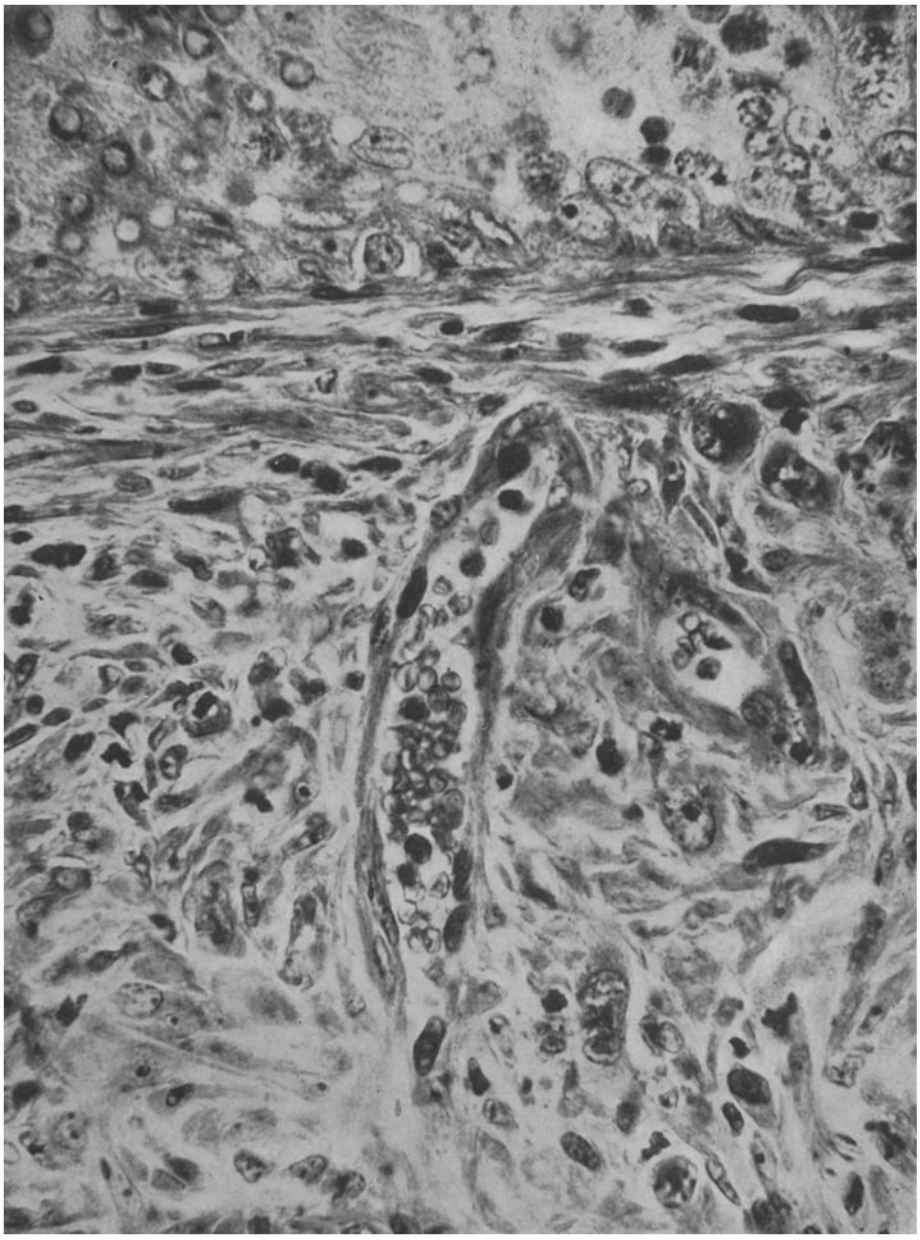


FIG. 1.

(Woglom: Flexner-Jobling Rat Carcinoma.)