The Nature of the Immune Reaction to Transplanted Cancer in the Rat.

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The purpose of the present paper is to extend to another species the investigation of the early history of tumour grafts carried out by Russell* in normal and immune mice, and to describe in detail the reactions taking place in and about fragments of the Flexner-Jobling† adeno-carcinoma of the rat after its transplantation into normal and resistant animals.

Immune rats were obtained by selecting those which had proved themselves resistant to one or two inoculations of the tumour in question, or by subjecting animals to previous treatment with 0·2—0·3 c.c. of an emulsion of rat embryo skin, and the introduction of the grafts destined to be excised for the study of early stages took place in all cases two or three weeks after the last immunising treatment.

Fragments removed after 24 hours show commencing degeneration of the stroma and of the parenchymal elements toward the central parts, while the tumour cells at the periphery have, on the contrary, preserved their vitality. There is no visible difference at this time between grafts removed from immune rats and those from normal animals.

The most interesting epoch in the history of a tumour nodule which is establishing itself in a new soil is the third day. In the majority of fragments removed from normal rats at this period the fibrinous exudate and the cleft, both formerly separating the graft from its host, have disappeared. The fibroblasts of the surrounding connective tissue have entered into the growth, and are engaged in the building of a new stroma, while penetrating capillaries can be discovered at the edge of the young tumour. The outermost cells of the parenchyma are in active mitosis, but the centre of the graft is quite necrotic. In fig. 1, representing the edge of a nodule which was removed 70 hours after implantation, the close connection between the growth and its host can be readily appreciated from the intimate commingling of tumour cells and connective tissue elements, as they are reproduced in the drawing. A new capillary, containing blood, has entered well into the fragment,

* Russell, B. R. G., 'Third Scientific Report, Imperial Cancer Research Fund, London,' 1908, p. 341.

† Flexner and Jobling, 'Monographs on Medical and Allied Subjects, Rockefeller Institute,' New York, 1910, No. 1, p. 1.

and is indicated toward the lower edge of the illustration to the right of the centre. The hyaline remains of the old stroma, its penetration by polymorphonuclear leucocytes, and the serious involvement of its connective tissue cells are also reproduced, as well as the active mitosis that is in progress among the elements of the parenchyma at the growing edge of the graft; but the necrotic tumour cells in the centre of the fragment are not included in the picture. The surviving cells of the parenchyma, which have hitherto been content merely to sustain life and to proliferate as best they may, now often show signs of an attempt to assume an acinous arrangement.

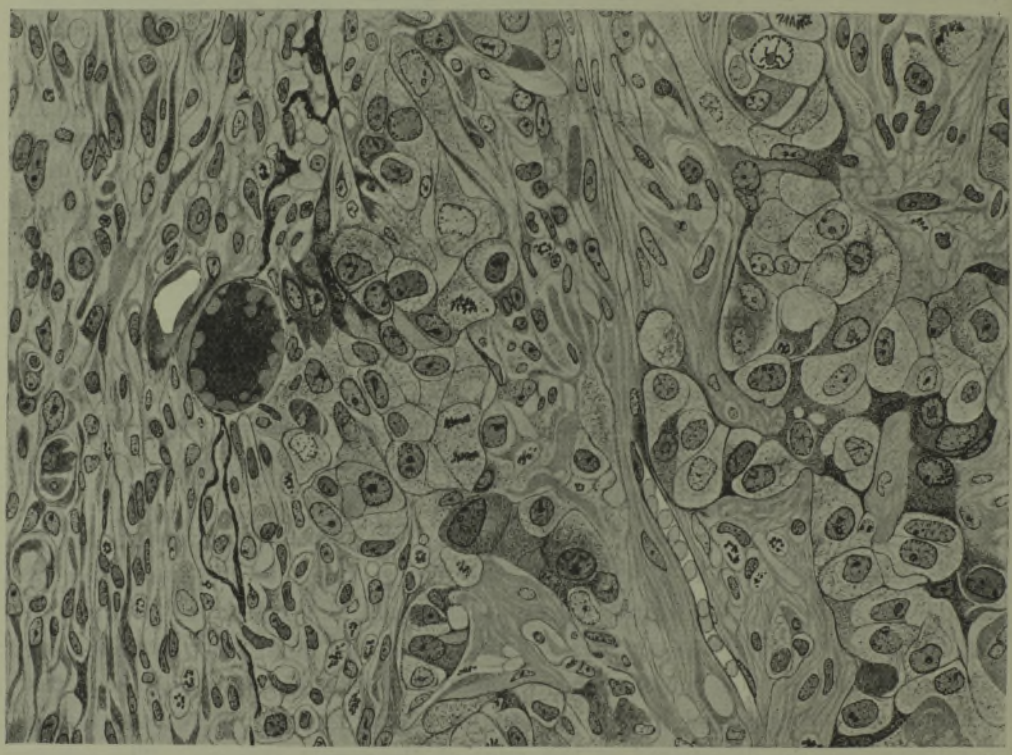
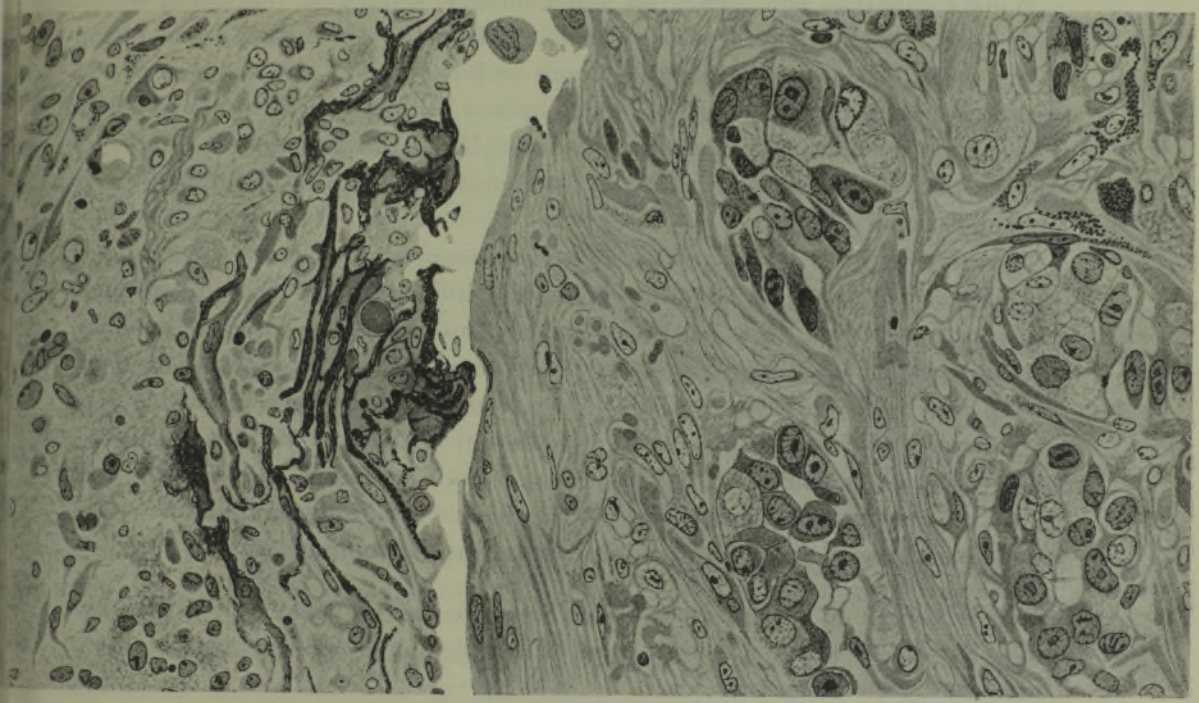


Fig. 1.—Flexner-Jobling adeno-carcinoma. Graft in normal rat 70 hours after implantation. Entrance of new blood vessels and fibroblasts from the host (on left). Mitoses in parenchymal cells, old stroma degenerated. Borrel, iron alum hematoxylin. × 410.

Whether the new framework is derived entirely from the connective tissue of the host, or whether certain cells of the transplanted stroma survive long enough to participate in its construction, is a question difficult of decision. Certain it is that all of the elements of the transferred stroma seem to be considerably damaged before the entrance of connective tissue corpuscles from the host; still the possibility cannot be eliminated that the damaged

cells may in some cases be able to recover and continue their proliferation for a time. Beyond reasonable doubt, however, nearly all of the introduced stroma perishes within the first few days, so that the framework of the new tumour is entirely, or almost entirely, the product of the host. This view coincides with that of Flexner and Jobling, who have expressed the opinion that only the epithelial cells of this growth survive transplantation, that the new tumour is the result of their proliferation, and that its stroma is furnished by the connective tissues of the host.

There is little need to insist upon the contrast between the condition just described and that represented in fig. 2, which reproduces a graft taken from



2.—Flexner-Jobling adeno-carcinoma. Graft in immune rat 72 hours after implantation. The graft is still separated from the host tissues by a cleft and layers of fibrin. No entrance of new blood vessels or fibroblasts from the host. Parenchymal cells at surface of graft still well preserved, connective tissues glassy and degenerated. Borrel, iron alum hæmatoxylin. × 410.

an immune rat 72 hours after inoculation. The outlying cells of the parenchyma are still well preserved at this period, and division figures are not infrequent, but there is no trace of acinous arrangement, and the cells lie either as irregular groups within the lacunæ of the stroma, or else in single layers at the edges of the cleft. The imbedded fragment is shrunken, it remains entirely separated by a space and a barrier of fibrin from the

neighbouring connective tissues of the host, and nowhere can there be detected that projection of fibroblasts between the cells of the tumour which invariably occurs in successful grafts. In many cases the fibrin barrier is even more persistent than in the specimen from which the drawing was made.

After the third day, the graft in a normal animal is the theatre of a progressive and orderly vascularisation and formation of stroma. By the fifth, an acinous arrangement of the parenchymal cells is practically completed, and at the seventh day, the production of collagen having commenced in the new stroma, the implanted tumour is well on its way toward maturity.

Widely different conditions, on the contrary, obtain in fragments which have been introduced into resistant rats. After the third day, degeneration of the graft becomes progressively more serious, and, in the absence of the specific stroma reaction, necrosis is complete by the tenth, although those cells more fortunately situated at the margin of the fragment are able to survive, and in a few cases even to proliferate, as long as eight days after transplantation.

The investigation leads inevitably to the conclusion that the phenomena described by Russell as characterising the immunity of mice to tumour implantation occur also in the case of the resistance offered by rats. Furthermore, as no difference could be detected between grafts taken from rats treated with embryo skin, and those removed from animals which had undergone a previous unsuccessful inoculation with tumour, it is concluded that resistance is similar in the two cases. Both types are the outcome of a failure on the part of the new host to furnish to the implanted fragment the proper blood vessel supply and connective tissue scaffolding.

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