The Brown-Pearce Carcinoma in the Hyperergic Rabbit*

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The voluminous literature on the subject of tumor immunity contains little information on the subject of tumor growth in the hyperergic or hypersensitive state. Neither Woglom (92) nor Spencer (1), in their very exhaustive reviews on the subject of tumor immunity, makes any mention of the effects of the hyperergic state of the host on the growth of malignant tumors. The importance of hypersensitivity in the pathogenesis of many diseases such as rheumatic fever, glomerulonephritis, and periarteritis nodosa has been very thoroughly studied, but the relationship of this phenomenon to tumor growth has been ignored. The following study was therefore undertaken to determine the effect of the experimentally induced hyperergic state on the growth of a transplantable malignant tumor.

METHODS

The Brown-Pearce rabbit carcinoma was used for this study. This is a highly malignant, readily transplantable tumor of the rabbit which metastasizes readily, producing generalized carcinomatosis and death, usually within 4—5 weeks. The tumor behaves biologically in a fairly uniform manner, and spontaneous regressions in our experience are unusual. The technic of transplantation has been previously described.

The antigen used to produce the hyperergic state was horse serum mixed with an adjuvant. This was prepared by mixing 92.5 cc. of Fabla with 92.925 cc. of horse serum, until thoroughly emulsified, and adding 9 cc. of Atreol #9 to this mixture. Two subcutaneous injections of 1 cc. of this mixture were given at 17-day intervals.

Four groups of rabbits, each group consisting of twelve animals, were sensitized to the horse serum by the technic described above. Six unsensitized normal rabbits were used as controls with each group. The time interval between the production of sensitization and the tumor transplantation was varied with each group. Tumor transplantation was done at the following time intervals in relation to the establishment of sensitization:

1. Ten days before the first injection of antigen.
2. Coincident with the first injection of antigen.
3. Four weeks after the first injection of antigen.
4. Five weeks after the first injection of antigen.

With each group, six normergic rabbits were given transplants of the same tumor, to compare the rate of growth and spread and the general biologic behavior of the tumor in the sensitized rabbit with those in the normergic animal.

Precipitin titers were done by the following technic:

1. 0.1 cc. of serum was placed in each microtube.
2. This was overlaid with 1 cc. of various horse serum titers (1:50,000 to 1:300,000).
3. Readings were taken at 15 minutes, 30 minutes, and 1 hour. Horse serum and normal saline were used as controls.

RESULTS

The immunologic responses were striking. Intracutaneous inoculation with 0.1 cc. of horse serum in the sensitized animals produced severe reactions, varying from marked hyperemia to extensive necrosis of the skin, with ulceration. All rabbits showed precipitin titers in the range of 1:300,000. Samples of blood taken at various periods between the time of transplantation and the deaths of the animals showed these antibody levels to be maintained throughout the experiments. Histologic studies of tissues removed at autopsy showed changes indicative of hypersensitivity, characterized by focal cellular infiltration in relation to small arteries with or without involvement of the vessel wall itself; leukocytic infiltration in the myocardium; and, in the early stages, edematous swelling of collagen. In the later stages

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957
there was considerable deposition of scar tissue, particularly in relation to vascular channels.

However, no significant changes could be demonstrated either in the biologic behavior of the tumor or in its histologic structure. Spontaneous regression of tumor was observed in a small proportion of the sensitized rabbits, but the incidence of such regression was no greater than is observed in the natural growth of the tumor. Preliminary experiments had indicated that the incidence of regression of the tumor was greater in the sensitized rabbits than in the controls, but final analysis of all these data upon completion of the study did not corroborate this. Extensive necrosis was observed in the tumors of many of the experimental animals, which at first suggested a possible influence of the sensitization of the tumor growth; however, careful histologic studies revealed changes, similar both quantitatively and qualitatively, in the control animals.

DISCUSSION

These experiments did not reveal any significant variation in tumor growth among the animals sensitized to horse serum as compared with that in the normal animal. Undoubtedly, the rabbits were in a hyperergic state. This was demonstrated by the severe skin reactions and by serologic and histologic studies, but there is little evidence to indicate any effect of this sensitization on the biologic behavior of the tumor.

Whether or not sensitization to the tumor protein can be effected is still debatable. Spencer (1) has stated that “Dead tissue or tissue products of mammalian tumors do not immunize—living cells seem to be necessary at the present time.” Antibodies have been demonstrated in tumor-immune animals but not in titers comparable to those which are produced by the body against bacterial invasion.

SUMMARY

The growth of the Brown-Pearce carcinoma in hyperergic rabbits, sensitized to horse serum, was studied. There was no significant alteration in the biologic behavior of the tumor in the hyperergic animal as compared with that in the normergic animal.

REFERENCES

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Max Appel and Otto Saphir


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