A COMPARISON OF THE GROWTH CURVES OF MALIGNANT AND NORMAL (EMBRYONIC AND POSTEMBRYONIC) TISSUES OF THE RAT *

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The histological and biochemical similarities between embryonic and tumor tissues have led some investigators to compare mathematically embryonic and tumor growth. Bashford,[1] working with mice, showed that the growth rate of the embryo is approximately equal to or higher than the growth rates of 53 different types of transmissible tumors. Sugiura and Benedict [2] state that the growth of the Flexner-Jobling carcinoma and the fetal growth of the rat can be represented graphically, with the weight as ordinates and time as abscissas, by almost identical parabolic curves. Carrel and Ebeling,[3] and Fischer, Laser and Meyer,[4] using tissue culture methods, could not observe any differences in the growth curves or the growth rates of tumor and embryonic cells.

The recently developed method [5] for the graphical representation of tumor growth affords another approach to the comparative study of embryonic and tumor growth. A study was therefore undertaken to determine whether or not the previous findings could be substantiated and extended by the new graphical method. The present paper compares the growth of 3 rat tumors (Walker tumor 256, Flexner-Jobling carcinoma, and R39 sarcoma) with the embryonic and postembryonic growth of the rat.

GROWTH OF RAT TUMORS

The mean diameter has been defined [5] as the cube root of the product of the three dimensions of a tumor. Growth curves of the Walker and the Flexner-Jobling rat tumors with the mean diameter as ordinates and time as abscissas have been shown to be linear. The slope of the linear growth curve represents the growth rate of the tumor and the intercept of the curve on the abscissa represents the latent period of the tumor.

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The average growth rate of 254 Walker tumors No. 256 was found to be 1.215 mm. per day, while the average growth rate of 95 Flexner-Jobling carcinomas was 0.649 mm. per day. Recent work [6] on the R39 sarcoma has shown that the average growth rate of 184 tumors was 1.777 mm. per day.

In order to compare these data on tumor growth expressed in units of mean diameter with those obtained by others on the embryonic and postembryonic growth of rats expressed in units of weight, it is necessary to use the cube root of the weight instead of the mean diameter as a measure of the size of the tumor. It was previously shown [5] that the weight of a tumor can be calculated by means of the formula

$$W = S\ (0.5236\ d^3)$$

where W = the weight of the tumor in grams, S = the specific gravity, and d = the mean diameter in centimeters. Therefore

$$\sqrt[3]{W} = \sqrt[3]{S} \times \sqrt[3]{0.5236} \times d$$

This formula enables one to find the cube root of the weight of a tumor when the mean diameter and the specific gravity of the tumor are known.

It is also necessary to use a growth constant to correspond with the new measure of the size of tumors. This constant can be determined by the formula

$$k_{\sqrt[3]{W}} = \sqrt[3]{S} \times \sqrt[3]{0.5236} \times k_d$$

where k_d = the growth constant expressed in centimeters per day and $k_{\sqrt[3]{W}}$ = the growth constant expressed in grams $^{1/3}$ per day.

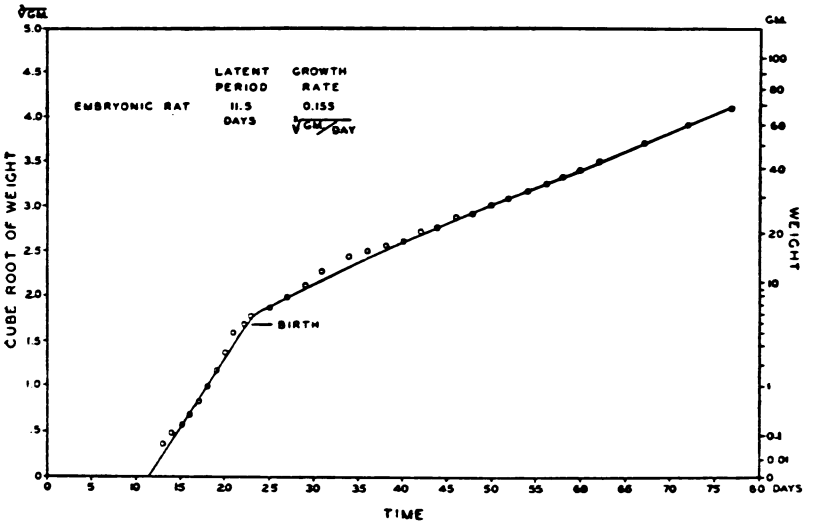
The specific gravity of the tumors has been found to be 1.038 for the Walker tumor,[5] 1.036 for the R39 sarcoma,[6] and 1.044 for the Flexner-Jobling carcinoma.[7] With these data on the specific gravity and the average growth rate (k_d), it was found that the new growth constants ($k_{\sqrt[3]{W}}$) are 0.151 grams $^{1/3}$ per day for the R39 sarcoma, 0.099 for the Walker tumor, and 0.053 for the Flexner-Jobling carcinoma.

Embryonic and Postembryonic Growth of the Rat

Stotsenburg's data [8] on the embryonic growth of the rat and Donaldson's data [9] on the postembryonic growth were used to con-

struct the growth curve in Text-Fig. 1 with the cube root of the weight as ordinates and time as abscissas.

The text-figure shows that the embryonic growth curve, like tumor growth curves, is linear. Schmalhausen [10] also observed a linear relation between the cube root of the weight of the rat embryo and time. The embryo has a latent period of 11.5 days and a growth rate of 0.155 grams $^{1/3}$ per day. This embryonic growth rate is approximately equal to the average growth rate of R39



TEXT-FIG. 1. Growth curve representing the embryonic and postembryonic growth of the rat.

sarcoma (0.151 grams $^{1/3}$ per day) and is somewhat higher than the average growth rates of the Walker tumor (0.099) and the Flexner-Jobling carcinoma (0.053). It seems then that the growth rates of rat embryonic and the rat malignant tissues are in the same order of magnitude.

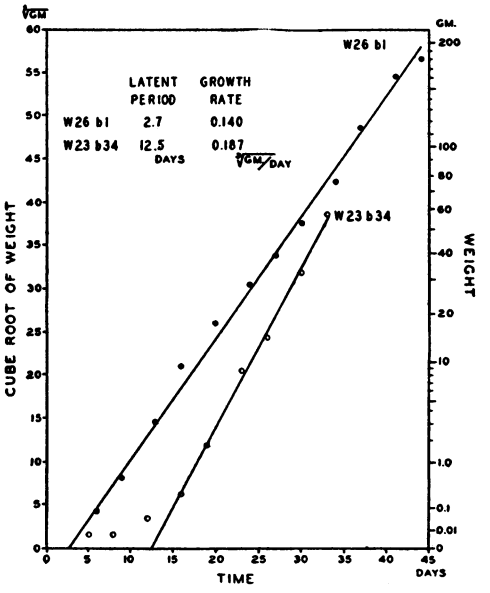
The text-figure also shows that the rat grows at a constant rate for about 11 days, attaining a weight of 5.5 gm., and then the growth rate begins to decrease. This inhibition to growth is presumably an expression of the increasing differentiation of the tissues of the rat. No inhibition, on the contrary, can be observed in the growth curves of the Walker tumor (Text-Fig. 2).

Tumor W26b1, for example, grew at a constant rate (0.140) for 40 days and was found to weigh, on postmortem examination, 175 gm.

On the other hand, the rat itself attains a weight of only 29 gm. after 40 days of growth. It follows then that the tumor has approximately the same growth rate as the embryonic rat but has a much higher growth rate than the postembryonic rat.

Discussion

The work presented shows that the growth of embryonic and malignant tissues can be represented by linear curves, and that the



Text-Fig. 2. Growth curves of 2 Walker tumors.

growth rates of rat embryonic and rat malignant tissues are in the same order of magnitude. From this it would appear that the malignant cell does not possess an excessive growth capacity.

Bashford [1] compared the growth capacities of mouse tumors and the mouse embryo. He defined the growth rate as 1000 times the reciprocal of the number of days required to develop 1 gm. of tissue. Bashford found that the mouse embryo grows faster than transplantable mouse tumors but that the growth rates of some of the tumors approximates the growth rate of the embryo mouse. Bashford concluded that the proliferative energy of tumors does not exceed that of embryonic tissue. The present investigation, using a

different species and a different method of determining growth rate, is in complete agreement with Bashford's conclusion.

The growth capacities of normal and malignant cells have also been studied in tissue culture. Carrel and Ebeling[3] found that the malignant fibroblasts of Crocker sarcoma No. 10 and Jensen rat sarcoma have the same growth rate as normal rat fibroblasts. Fischer, Laser and Meyer[4] summarize their results on Ehrlich's mouse carcinoma with the statement: "It is astonishing to find that tumor cells in culture not only do not grow more rapidly, but in many cases grow more slowly than the corresponding normal cell." These *in vitro* studies agree with Bashford's and the present *in vivo* findings that the malignant cell does not possess a growth capacity in excess of that of normal embryonic tissue.

Embryonic tissue has, in addition to its growth capacity, a tendency to differentiate. This differentiation would be expected to inhibit the growth of the normal tissue, producing a decrease in the growth rate. It should be noted that the inhibitory factor caused a marked decrease in the growth rate of the rat when the weight of the rat was 5.5 gm.

Malignant tissue like the Walker tumor exhibits no inhibition to growth, although the Walker tumor may attain a weight of 175 gm. before ulcerating or causing the death of the host. It seems that the Walker tumor has a lesser tendency to differentiate than normal tissues.

The capacity of normal tissues to differentiate has been studied *in vitro*. Fischer and Parker[11] succeeded in stimulating embryonic cells to differentiate in tissue culture by the use of certain media. It would be of interest to know to what extent malignant cells could differentiate under identical conditions.

This study suggests that the tumor cell in acquiring its malignancy regains its primitive growth capacity and loses more or less completely its tendency to differentiate.

Conclusions

The growth of the Walker tumor and the rat embryo can be represented by linear curves. The growth rates of rat tumors, *in vivo* and *in vitro*, are in the same order of magnitude as the growth rate of rat embryonic tissue.

After the embryonic stage the growth rate of normal tissues is markedly diminished. This decrease in growth rate is presumably due to the differentiation of the tissues. In contrast, there is no appreciable inhibition in the growth rate of malignant tumors like the Walker tumor.

Transmissible rat tumors are characterized not by an abnormal proliferative capacity but by a lesser tendency to differentiate.

REFERENCES

1. Bashford, E. F. The behaviour of tumour-cells during propagation. *Imp. Cancer Research Fund, Scient. Rep.*, 1911, 4, 131–214 (see pages 197–200).
2. Sugiura, Kanematsu, and Benedict, Stanley R. The influence of certain diets upon tumor susceptibility and growth in albino rats. *J. Cancer Research*, 1920, 5, 373–401.
3. Carrel, Alexis, and Ebeling, Albert H. The fundamental properties of the fibroblast and the macrophage. III. The malignant fibroblast of Sarcoma 10 of the Crocker Foundation. *J. Exper. Med.*, 1928, 48, 105–123.

   Carrel, Alexis, and Ebeling, Albert H. The fundamental properties of the fibroblast and the macrophage. IV. The malignant fibroblast of Jensen sarcoma. *J. Exper. Med.*, 1928, 48, 285–298.
4. Fischer, Albert, Laser, Hans, and Meyer, Hertha. Ein 3 Jahre alter Carcinomstamm in vitro. Einige Betrachtungen nach den bisherigen Arbeitsergebnissen. *Ztschr. f. Krebsforsch.*, 1930, 32, 99–106. Translation cited *Am. J. Cancer*, 1930, 15, 337.
5. Schrek, Robert. A quantitative study of the growth of the Walker rat tumor and the Flexner-Jobling rat carcinoma. *Am. J. Cancer*, 1935, 24, 807–822.
6. Schrek, Robert. A quantitative study of the growth of the R39 rat sarcoma and the Brown-Pearce rabbit carcinoma. (To be published.)
7. Okada, Osamu. On the mensuration of the transplantable animal malignant tumors. *Tr. Jap. Path. Soc.*, 1930, 20, 753.
8. Stotsenburg, J. M. The growth of the fetus of the albino rat from the thirteenth to the twenty-second day of gestation. *Anat. Record*, 1915, 9, 667–682.
9. Donaldson, Henry H. The Rat. Data and Reference Tables for the Albino Rat (*Mus norvegicus albinus*) and the Norway Rat (*Mus norvegicus*). Wistar Institute of Anatomy and Biology, Memoirs, No. 6, Philadelphia, 1924, Ed. 2, 276.
10. Schmalhausen, J. Beiträge zur quantitativen Analyse der Formbildung. I. Über die Gesetzmässigkeiten des embryonalen Wachstums. *Arch. f. Entwcklngsmechn. d. Organ.*, 1927, 109, 455–512.
11. Fischer, Albert, and Parker, R. C. Proliferation und Differenzierung. *Arch. f. exper. Zellforsch.*, 1929, 8, 297–324.