On a Law of Growth of Jensen's Rat Sarcoma

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ON A LAW OF GROWTH OF JENSEN'S RAT SARCOMA

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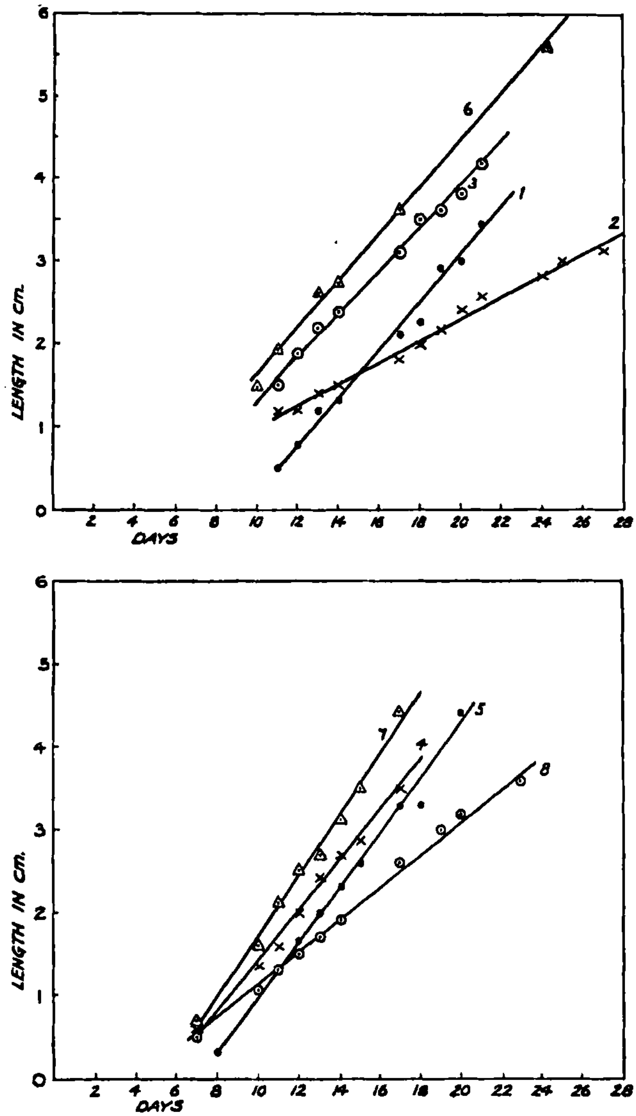
During the course of experimental work on the effects of X-radiations on the growth of Jensen's rat sarcoma, it became clear that the mere disappearance or continued growth of the tumours after irradiation afforded a very inadequate criterion of the effect of the radiations. The rate of growth of the tumour was, therefore, investigated, daily observations of the linear dimensions of grafted tumours being made in a series of rats. Usually the length and breadth of the tumour were measured, but since the ratio of these measurements remained approximately constant throughout growth, we may confine our attention to one set of results, say for length only. The results of such measurements carried out for quite a different purpose by my colleague Mr. Harold Burrows, F.R.C.S., on his experimental animals, are given in Figs. 1 and 2. These represent measurements on "control" sarcomata, *i.e.* untreated rats. Similar results have been obtained with many such tumours. Examples of the actual tumour silhouettes are given in Fig. 4, the numbers above the tumours representing the number of days since implantation.

The rather surprising fact emerges that the increase in long diameter of the implanted tumour follows a linear law; that is, if l equals the length of the tumour in centimeters after t days, then over a fair region of time $l = k[t - t_0]$ where t_0 varies somewhat but is usually of the order of six to eight days, while k is a constant whose value is different for different tumours, but usually of the order of 0.3 cm./day; t_0 represents (presumably) the time taken for the implant to obtain a blood supply and commence growth.

It is notoriously dangerous to obtain straight line relationships, but it has been found impossible to represent as accurately in any other way, more particularly by means of the exponential curve which might have been expected, the variation in size of the tumour.

There is, moreover, a simple explanation of the approximate linearity in terms of the structure of the sarcoma. On cutting open the tumour it is often apparent that not the whole of the mass



FIGS. 1 AND 2

is in a state of active growth, but only a thin capsule (sometimes not more than 1 mm. thick) enclosing the necrotic centre of the tumour.

We may investigate the effect of distribution of growing substance as below:

(*a*) Suppose the whole of the tumour in a state of active division and for simplicity suppose the tumour spherical. Then the rate of increase in volume, [V], is evidently proportional to V, since we might imagine to a rough approximation that a constant fraction λ of the component cells divided per second.

Then $dV/dt = \lambda V$ or $\log_e V/V_0 = \lambda[t - t_0]$, where V_0 is the initial volume at a time t_0. The increase of linear dimension (say r the radius of the sphere) is given by $\log_e r/r_0 = \lambda/3[t - t_0]$. Thus we obtain a logarithmic law of increase. $1/\lambda$ may also be regarded as the "mean life" of the cell.

(*b*) Suppose, however, that only a very thin shell of thickness α, is in a state of active division. The change in volume in time $dt = \lambda dt[V_A]$ where V_A = active volume. Thence $dV = \lambda dt[r^3 - (r - \alpha)^3] \cdot \frac{4\pi}{3} \cdots$ (1) But $V = \frac{4\pi r^3}{3}$ and $dV = 4\pi r^2 dr \cdots$ (2) Whence equating these expressions for dV

$$\lambda dt = \frac{3r^2 dr}{3\alpha r^2 - 3\alpha^2 r + \alpha^3}.$$

If α is very small and constant, this reduces to $\alpha\lambda dt = dr$, and we have $\lambda[t - t_0] = \frac{1}{\alpha}[r - r_0]$, *i.e.* the linear law of increase of r.

If $\alpha = r$, *i.e.* the whole is growing, then as above $\lambda dt = \frac{3dr}{r}$, and we have the logarithmic law.

(*c*) The more general case where α is constant and has any value may be solved for spherical masses as below:

We have, generally

$$\lambda dt = \frac{3r^2 dr}{r^3 - (r - \alpha)^3} = \frac{1}{\alpha} \cdot \frac{r^2 dr}{r^2 - \alpha r + \alpha^2/3}.$$

Write

$$\frac{r^2}{r^2 - \alpha r + \alpha^2/3} = F_1(r),$$

then

$$F_1(r) = 1 + \frac{\alpha r - \alpha^2/3}{r^2 - \alpha r + \alpha^2/3} = 1 + F_2(r).$$

To integrate $F_2(r)$, write

$$r^2 - \alpha r + \alpha^2/3 = [r - \alpha/2]^2 + \alpha^2/12,$$

then

$$\int F_2(r) \cdot dr = \int \frac{[\alpha r - \alpha^2/3]dr}{r^2 - \alpha r + \alpha^2/3} = \int \frac{\alpha/2[2r - \alpha] + \alpha^2/6}{[r - \alpha/2]^2 + \alpha^2/12} \cdot dr$$

$$= \alpha/2[\log_e (r^2 - \alpha r + \alpha^2/3)] + \alpha^2/6 \left[\frac{\sqrt{12}}{\alpha} \tan^{-1} \frac{\sqrt{12}(r - \alpha/2)}{\alpha}\right],$$

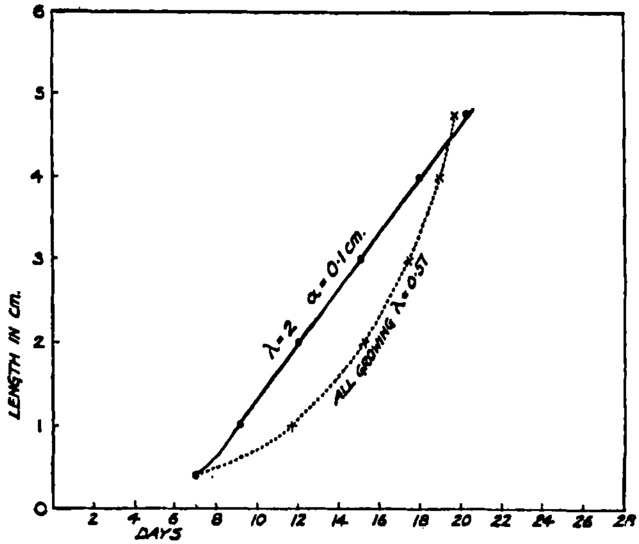


FIG. 3

whence finally

Eqn. [A] $$\lambda[t - t_0] = \frac{1}{\alpha}[r - r_0] + \frac{1}{2}\log_e \frac{r^2 - \alpha r + \alpha^2/3}{r_0^2 - \alpha r_0 + \alpha^2/3} + \frac{1}{\sqrt{3}}\left[\tan^{-1}\frac{[r - \alpha/2]\sqrt{12}}{\alpha} - \tan^{-1}\frac{\sqrt{12}(r_0 - \alpha/2)}{\alpha}\right].$$

This expression may be simplified a little if $\alpha = r_0$, *i.e.* the radius of the original implant. In this case

$$r_0^2 - \alpha r_0 + \alpha^2/3 = \alpha^2/3 \quad \text{and} \quad \tan^{-1}\frac{\sqrt{12}(r_0 - \alpha/2)}{\alpha} = 1.047,$$

whence

Eqn. [B] $$\lambda[t - t_0] = \frac{1}{\alpha}[r - r_0] + \frac{1}{2}\log_e \frac{r^2 - \alpha r + \alpha^2/3}{\alpha^2/3} + \frac{1}{\sqrt{3}}\left[\tan^{-1}\frac{\sqrt{12}(r - \alpha/2)}{\alpha} - 1.047\right].$$

The solutions under conditions (*a*) and (*b*) may be deduced from this equation.

Using the general equation A, the growth of a tumour for which $\alpha = 0.1$ cm. and $r_0 = 0.2$ cm. has been calculated. A value of $\lambda = 2.0 \cdot \text{day}^{-1}$ has been adopted, and it will be seen (Fig. 3) that a linear relationship for all values of the time is obtained, except, as would be expected, for very small tumours where α is comparable with r. For comparison, the exponential curve is also plotted, which might be expected to represent the growth of the whole mass were all of it in a state of division; the value of λ has been adjusted to give approximately the same total growth in the same total time in the two cases.

It is probable that generally, if a tumour retains its shape, *i.e.* is "similar" throughout its life, and only the surface is in active division, *i.e.* α small, the law of increase of linear dimensions of the tumour will be approximately linear whatever its shape, if approximately spherical. Immediately α is dependent on r, more especially if α is proportional to r, the law changes in form, though one naturally merges into the other. We may note that if a

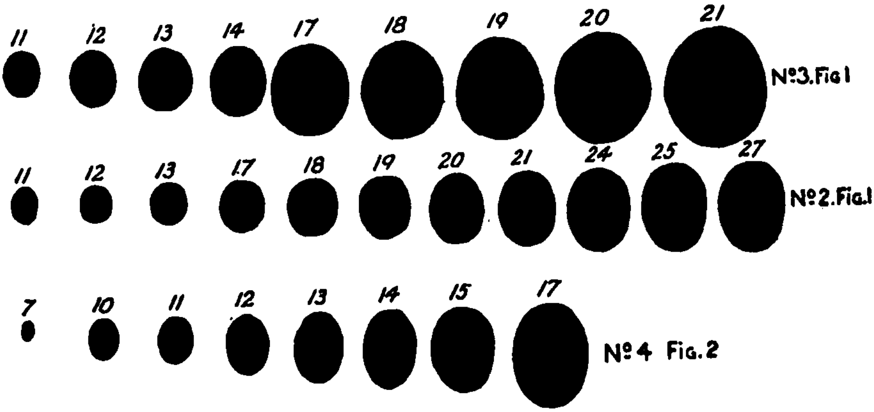


FIG. 4

constant number of cells divide per second we have a "law" represented approximately by $r = k't^{1/3}$ with a curvature in the opposite sense to the exponential one.

A linear relationship also arises for the case of a circular disc whose edge only is proliferating.

It will be observed that if α is known, λ may be calculated very easily for the linear curves. For $\alpha = 1$ mm., $1/\lambda$ appears to be approximately 12 hours for the case examined, *i.e.* 12 hours is the average time between successive cell divisions.

Finally it is not supposed that the circumstances discussed above are the only ones capable of explaining the linearity of the growth, or that all rat sarcomata will behave in exactly the same way, but it seemed worthy of record that a simple geometrical circumstance can produce the observed effect. It must, moreover, be mentioned that the surprising regularity of the results obtained with different animals probably arises from the fact that the conditions had been carefully standardized, the same strain of rats and the same sized implants from the same tumour material having been used throughout, all manipulations having been performed by the same person (Mr. H. Burrows). The measurements of the tumours had been completed before the idea of any mathematical treatment had arisen.

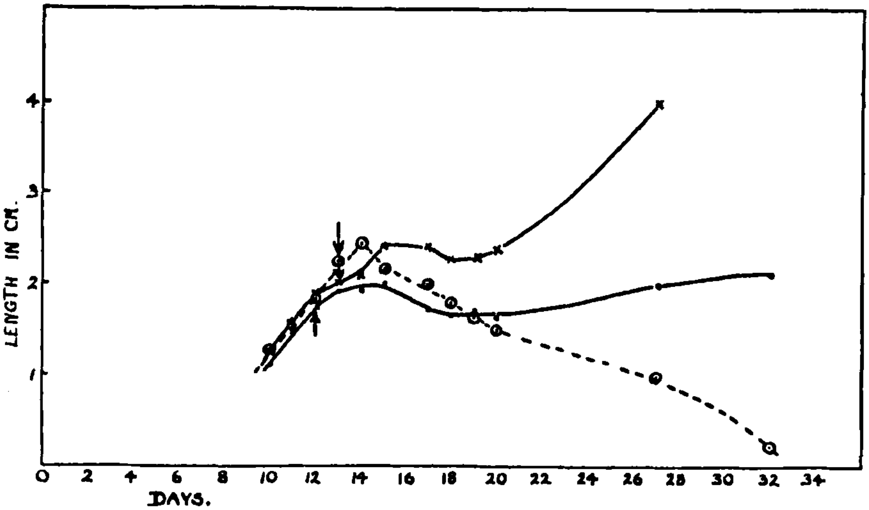


FIG. 5

The effects of X-radiation may be seen from Fig. 5. The arrows denote the giving of 3000r to the rat sarcoma, and curves are given for three tumours, one of which was "cured," one just survived, and the third continued to grow rapidly after an arrested growth. The "family relationship" of the curves is apparent. γ rays have exactly similar effects. These experiments are being continued since the rate of growth offers a quantitative biological phenomenon of great interest.

SUMMARY

It is pointed out that a number of Jensen's rat sarcomata increase in linear dimensions linearly with the time, and not exponentially as might at first be expected.

The linear law can result from the fact that only cells near the surface of the tumour are in active division.

The mathematical theory is developed.

The results of X-radiation on the tumours are exemplified.

I wish to record once more my thanks to my colleague, Mr. Burrows, for so kindly allowing me to use his measurements of rat tumours, and to Miss Woodroffe, who carried out the irradiations.