THE MATHEMATICAL MODELING
OF
TUMOR GROWTH AND THE PROCESS OF IRRADIATION

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INTRODUCTION

Mathemathical modelling in the field of medicine has played an incisive role. Not only are its priciples used extensively in biology, biochemestry, physiology and physics, but today more than ever the techniques of applied mathematics are being used in the field of cancer research. Finding an accurate model to assess the anticipated growth rate of malignant tumors has proved invaluable. Since the early 1930's, researches have worked diligently to understand the various attributes associated with potential models of tumor growth. The Gompertz model has been found to be quite an accurate predictor of solid tumor growth, ascites tumor growth as well as distinct examples of each. Although a full understanding of the "way" in which tumors grow has yet to be resolved. It seems that the Gompertz model proposes alternative lines of reasoning which shall be discussed in due course. By way of comparable mathematical techniques, the treatment of tumors can only be properly addressed once a workable model is in place. In practice, various issues must be handled; the problem is quite complex. There are some difficulties, however It is in the first place, ungauranteed that ethically acceptable methods of characterizing particular human tumors will ever be found. With this understanding, we recognize that there might never be any alternative other than empiricism to perfecting the development of treatment schedules. The better the model the better the results.

Accordingly, the goal of this paper is to clearly outline the development of a model to best predict the rate of solid tumor growth, (there will be mention of

ascite tumors however, emphasis is on the solid tumor) . The discussion will then turn to examining the justifications governing current trends in the treatment of tumors by irradiation.

STATEMENT OF THE PRIMARY PROBLEMS

The therapists' goal is to administer the best possible treatment to each of her patients. This varies with the tumors location in the body, the type of malignancy, and understanding its growth pattern and form of the propagation of tumor cells (D.A. Abercrombie (1978), J.R. Usher and D.A. Abercrombie (1981)). Hence, the questions that will be addressed are:

(i) How do tumors grow?

(ii) What effect does irradiation have on tumour cells?

PRELIMINARY BACKGROUND MATERIAL

WHAT ARE TUMORS ?

By definition, a tumor is a circumscribed, non-inflammatory growth arising from existing tissue but growing independently of the normal rate or structural development of such tissue and serving no physiological function (The American Heritage Dictionary), yet inhibits natural physiological functions from taking place . Both normal and tumour cells are derived by mitosis. This is the process of cell division: each chromosome splits into two, one of the resulting duplicates passing to each of the daughter cells. In the case of normal cells they develop into different classes each with distinct functions.
This process is referred to as 'differentiation'.

Most tumors exhibit the following characteristics:

(a) growth is relatively autonomous, free from the body's control mechanisms which attempt to maintain equilibrium between the body and

its surroundings;

(b) tumor cells propagate outwards replacing normal tissue;

(c) there is always the chance that the presence of one tumor may induce the formation of a secondary tumor at a remote site (metastasize). In fact, more patients presently die of metastatic disease than of their primary neoplasm (Weldon and Kirk 1976).

The prognosis for those who develop therapy-related second malignancies is very poor and that treatment is often unsuccessful. Consequently, clinicians are examining ways to effectively treat the primary cancer while reducing the risk of a second malignancy. This however, has proven to be a complex task. Given that patients are offered combined-modality treatment, it is difficult to determine which mode of therapy, chemotherapy, radiology and/or surgery, contributes most to the long-term complications. (M.B. Uhlenhopp 1992).

DEVELOPING A MODEL FOR TUMOR GROWTH

TUMOR GROWTH

For a long time it had been commonly believed that tumor growth under ideal conditions is a simple exponential process terminated by the exhaustion of the nutritional support provided by the host. However, a survey of the literature shows that exponential growth of tumors has been observed only rarely and then only for relatively brief periods. (See WRITE-up 1)

ASSUMPTIONS

(i) Assumes a constant rate of relative growth.

(ii) Growth is unrestricted-unbounded.

When we consider those tumors whose growth has been followed over a sufficiently

extensive range (100 to 1000-fold range of growth or more), we find that nearly all such tumors grow more and more slowly as the tumor gets larger, with no appreciable period of growth at a constant specific growth rate as would be expected for simple exponential growth. This continuous deceleration of growth has the consequence in many cases that the diameter, in the case of the solid tumor, or the cube root of total cell number, in the case of an ascites tumor, when plotted against time gives a close approximation to a straight line (Mayneord (1932), Platt and Blackford (1954)). (See Figure 1 and 2, Sheet I) According to the model we wish to propose, tumor cells proliferate by a modified exponential process in which successive doublings occur at increasingly longer intervals. It has been shown that the doubling times increase more rapidly than they would in a simple exponential process (A.K.Laird 1964) (See Fig 1 Sheet I). In fact few tumours grow in purely exponential fashion.

MODIFICATIONS

Let us allow for the relative growth rate to change proportional with respect to time. This is recognized as Gompertzian growth. (See write-up 2)

Gompertzian growth appears to be more common (Bischel, 1971).However even Gompertzian growth is not necessarily charcateristic of all tumors need not be followed. (Fig.2 Sheet I) In this display of various tumors fit to the Gompertzian model having the parameters

The mouse and rabbit tumours' actual upper bound is quite well estimated using Gompertz' model. However as you will see it is not so well matched up with the rats' upper limit. This is examined in the graphs of Sheet III and Sheet IV for the exceptional cases.

We begin our discussion concerned with explaining this deviation from simple exponential growth. Examining the below differential equation will act as a guide

in our analysis:

(a) $\frac{dS}{dt} = (\beta e^{-\alpha t})S(t)$

or alternatively,

(b) $\frac{dS}{dt} = \beta(e^{-\alpha t}S(t))$

Interpretations :

(a) Recognized as depicting the hazard due to aging. Clearly, expressed in this manner, dS/dt represents how, as time goes on, the reproducing cells mature, or age, and thus divide more slowly. Growth rate declines as cell mass grows.

One can think of such proliferation as occurring by a rapid increase in the mean duration of successive cell generations, by a rapidly increasing loss of cells from the generative population, or by some combination of these processes that would result in a rapid deceleration of the growth of the tumor according to the function described.

(b) An alternative interpretation is found in this second method of bracketing. It suggests that the mean generation time of the dividing cells remains constant, and the retardation of growth is due to a loss in reproductive cells in the tumor. (Braun 1978)

The theory holds to the justification that in many tumours the supply of blood, and thus the supply of oxygen and nutrients is almost completely confined to the surface of the tumor and a short distance beneath it. As the tumor grows, the supply of oxygen to the central core by diffusion becomes more and more difficult resulting in the formation of a necrotic core; simply a mass of dysfunctional tissue in the centre of the tumor. However, it has been suggested (A.K. Laird 1964) that the Gompertzian retardation of growth is not a fortuitous result of

the failure of the dying host to afford nutritional support to tumor growth, but is a characteristic property of the growth of tumors in the animal host.

Mayneord had shown that cube root growth could be relatively explained in mathematical terms if the active growth of a solid tumor were limited to a thin layer of cells at the surface of the tumor. However, in practice most solid tumors do not grow only at the surface, and in the case of ascites tumors it has been possible to label the DNA of nearly 100 per cent of the tumor cells (Baserga, Kisieleski, and Halvorsen, 1960), indicating that almost all of these cells are viable and proliferating. Hence, although cube root growth has been empirically established for many tumor cells, it is difficult to relate it mathematically to proliferation of tumor cells.

There are theoretical reasons for believing some neoplasms (e.g. acute luekaemia) may follow a stochastic growth law which cannot be easily reconciled with any simple deterministic growth curve, such as the Gompertz curve, at all (Wheldon 1975). However, for most solid tumors Gompertz growth is employed as it is seemingly as good a general predictor to this point as we can get. (See approximations of various types of tumor growth by the Gompertz curve on Tables following WRITE-up 2. As well a data is fit by these two curves and the two graphs are superimposed).

FURTHER MODIFICATIONS

As it has already been stated the Gompertz curve is quite good at predicting the size of solid tumors at any given time. Looking back at some of our examples, some show strong retardation within the life of the host, while others, although conforming to the Gompertzian model deviate relatively little from the exponential growth during the period of observation. It might just be that either of the interpretations (a) or (b) could satisfy various classifications of

tumors. Possibly an extension of this model of analysis should be taken to the various types of tumor growth in various parts of the body in order to assess which of (a) or (b) seem to hold true. If anything it will bring in new information. It will not however, be done here.

DEVELOPING A MODEL TO EXPLAIN THE IRRADIATION OF TUMOR CELLS

WHAT DOES IRRADIATION DO TO TUMOR CELLS ?

In treating a tumor by irradiation the tumor is bombarded by ionizing radiation with the specific purpose of inflicting maximum damage on the tumor while keeping damage to surrounding and enclosed normal tissue below that level above which the normal tissue cannot recover. It has been found that normal tissue has a better ability than tumor cells to recover following a fractionated (i.e. split) dose (N.M. Bleehan 1972).

Now if tumor growth curves are to be utilized in estimating the effectiveness of a therapeutic regimen, then some relationship between cells surviving therapy and growth must be found. Such a relationship can be formulated based upon the following assumptions:

ASSUMPTIONS

(a) A Gompertz function can be found which will be valid over the entire growth range (measurable and unmeasurable) of the tumor.

(b) Cells affected by treatment are killed instantaneously, or at least within an interval small compared to the period of regrowth.

(c) Cells surviving treatment begin to repopulate immediately, producing tumor growth in accordance with the same Gompertz function found for the untreated tumor growth. (H.H. Lloyd 1975)

(d) The fewer the number of viable cells remaining after therapy, the longer the duration required for the tumor to return to the size at treatment.

(e) The greater the dose, the smaller is the proportion of cells which survive the attack, cancerous and normal included.

In 1956, Puck and Marcus described the quantitative relationship between the surviving fraction of Hela S3 tumor cells and an X-ray dose. They were the first to observe such a relationship for mammalian cells. This survival curve is a shown in the graph of the log of the surviving fraction versus the dose (See sheet V):

Notice:

(a) survival curves are asymptotic to a straight line for large dosages; the point where this asymptotic line cuts the log (surviving function) axis is called the extrapolation number which is real and varies for different cell classifications and types of radiation (X-rays or gamm rays)

(b) they exhibit a 'shoulder' at relatively small dosages.

DERIVING A MATHEMATICAL MODEL TO 'EXPLAIN' THE SHAPE OF THE SURVIVAL CURVE

Probabilistic techniques shall be employed for reasons that are soon to be realized. Firstly, there should be a clear understanding of how the results presented by the survival curve can be used:

1. The shoulder on the survival curve illustrates that there is an accumulation of damage before the cell is killed. The second fifty rads kills a greater proportion of cells than the first.
2. X-rays or gamma rays should be understood as being made up of particles

of high energy with which we bombard the cells. A certain number of these particles (the extrapolation number) can succeed in killing a cell.

This over simplification of the real problem must not go without stating its crude assumptions that will lead to the development of the classical multi-target model widely used by radiobiologists.

ADDED ASSUMPTIONS

(A) The extrapolation number n of any particular tumor cell represents the number of hits each cell requires to die; i.e. each of the n targets must be hit at least once;

(B) The number of hits received by each of the targets is a Poisson variate with mean proportional to the dose of the radiation;

(C) Each target receives hits independently of the others.

Definition: If the probability density function of the interarrival times is exponential, calling units arrive according to the POISSON process.

DISCUSSION OF WRITE-UP 3

When n=1,

$$\ln S = \frac{-D}{Do}$$

and the associated survival curve has no shoulder. Cells with such a survival curve are said to undergo exponential survival ie. unlike when there is a shoulder as explained above.

When n > 1, the survival curve has no shoulder which becomes more distinct with increasing n.

Puck and Marcus found that the equation for S fit their data well when n=2, and Do = 96rad. However this does not necessarily imply that Hela S3 cells have

only two targets. The model has not yet been fully accepted, there are still many problems with accepting such assumptions as possible in the 'real world'.

CRITICISMS OF THE MODEL AND POSSIBLE MODIFICATIONS

1. The survival function we have introduced is continuous and so for a given set of data the chance of getting a non-integral extrapolation number is quite likely. Maybe n can be taken as some type of 'average'.
2. For n > 1 the survival curve associated with $S=1-[1-EXP[-D/Do]]^n$ would become 0 when D=0; an interpretation of this would be that there would not be a surviving fraction, although no dose of radiation was administered. This model cannot be applied when no dose is administered. Therefore the model holds only for D > 0 only.
3. The assumption that each cell receives at least one hit is somewhat arbitrary. Anticipating the path of the particles X-rays and gamma rays is known to be quite complex at that microscopic a level. Now this is where the answer to how tumors grow might be useful. An understanding that the cells on the surface of the tumor are getting weeker and weeker might intice us to concentrate high doses only at the surface to destroy those cells only. Again, however, we are dealing with a medium that is a little more difficult to control.
4. The model does not take into account the repair processes which are known to be taking place.

CONCLUSIONS

The importance of understanding the way in which tumors grow has proved itself through the course of this discussion. We had to make a growth assumption inorder to begin the development of a model to describe the irradiation of tumor. Using what Gompertzian growth tells us about a tumor following such a growth curve is that as it is slow-growing when large, and fast-growing when small, in order to achieve optimal results in radiation therapy it would follow that radiation fractions, spliting up the dosage should be spaced well apart at the beginning of the treatment but should come closer together as treatment proceeds. Provided the Gompertzian parameters can be estimated, non-uniform optimal schedules can be designed by regarding the tumor as exponentially growing at any instant but with different doubling times over different intervals (Lloyd 1975).

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(Write-Up 1) Exponential Relation

Bacteria cells are one example of "free living" cells

By this example we might be persuaded to think of the size of dividing cells $S(t)$ to be proportional to the size of the cells at time t (time being calculated from when data is first observed)

Then $\frac{dS}{dt} = \lambda S$ for some constant λ, $S > 0$
$t > 0$ (days)

The solution is: $\int \frac{1}{S}\, dS = \lambda \, dt$ $\quad S > 0$

$\ln S = \lambda t + C$ $\quad S > 0$

$S(t) = e^{\lambda t + C}$ $\quad S > 0$

$S(t) = e^C e^{\lambda t}$; $S(0) = e^C$ so that

$$\boxed{S(t) = S(0) e^{\lambda t} \qquad \lambda > 0,\ S > 0,\ t > 0}$$

As $t \to \infty$

$S_\infty = S(0) e^{\lambda t} \to \infty$ unbounded

Examining new data collected. We find that this model is inadequate in representing tumour growth

The following conclusion drawn by this model are not supported by what is known of tumours

Consequences: i) Free living dividing cells grow exponentially with time

ii) The size of cells keeps doubling every time interval of length $\frac{\ln 2}{\lambda}$. ie. $S(t) = 2S(0)$ iff $S(0) e^{\lambda t} = 2S(0)$

$e^{\lambda t} = 2$

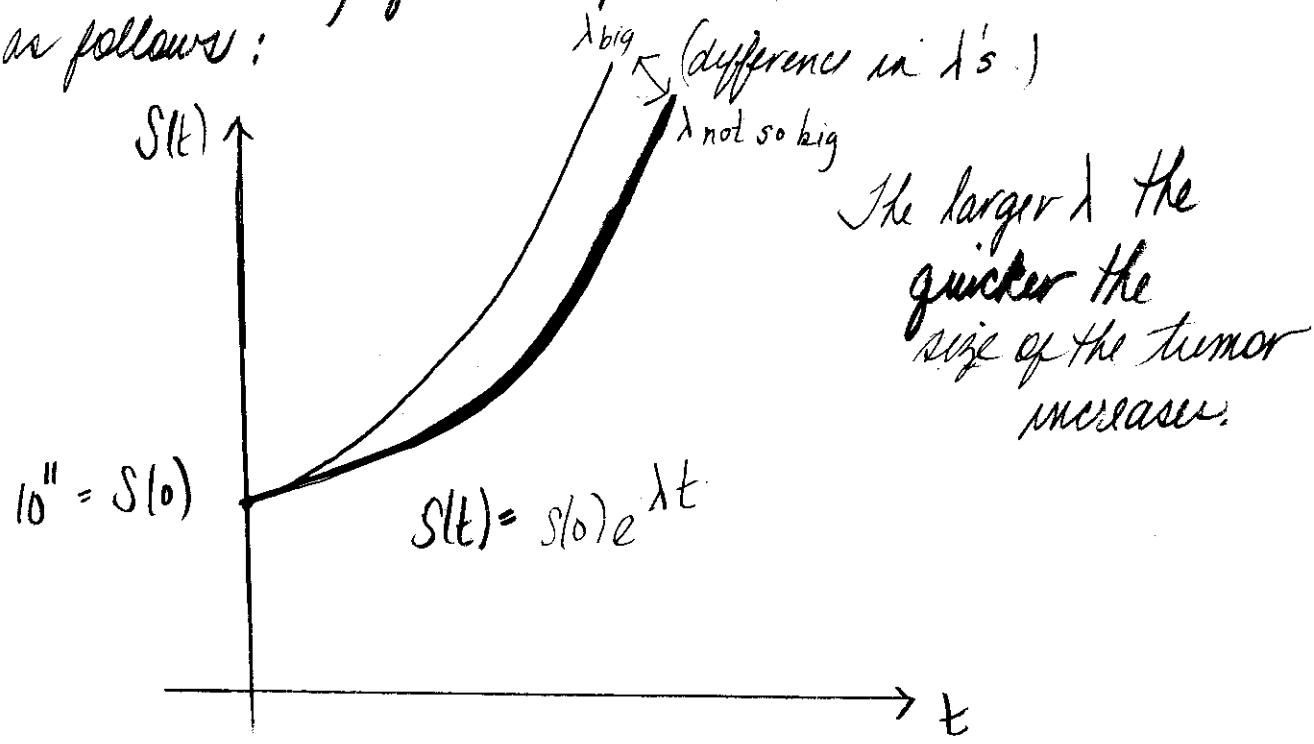
$\lambda t = \ln 2$

$t = \frac{\ln 2}{\lambda}$

However, in contrast
(i) Solid tumors do not grow exponentially with time;
(ii) the doubling time of the total tumor volume continuously increases. We know the doubling time is increasing by an exponential process.
(iii) tumours are bounded – the host does die.

Considering their relatively simple form, the predictions of any of the Gompertz equations agree remarkably well with the data for tumor growth (See Aroesty et Al., 1973, or Newton, 1980,)

A drawing of this exponential curve would be as follows:



The larger λ the **quicker** the size of the tumor increases.

Where λ is the relative growth rate. It does make sense that the larger the λ the quicker the size of the tumor increases

note: $\lambda = \frac{\ln 2}{\tau}$ where τ is the doubling time of the tumour.

This is where we first can notice a problem with λ since τ the doubling time does initial appear constant but soon begins to increase as time wears on, more rapidly than would this simple exponential process (A.K. LAIRD. 1964 pg 493)

λ: the relative rate of growth of the tumor.

β: initial growth rate

α: the positive constant $\alpha = -\frac{1}{\lambda}\frac{d\lambda}{dt}$ is the relative rate of change/growth of λ.

$$\therefore \frac{d}{dt}S(t) = \beta e^{-\alpha t} S(t)$$

Solving to obtain (*)

$$\frac{1}{S}dS = \beta e^{-\alpha t}dt \iff \ln|S| = -\frac{\beta}{\alpha}e^{-\alpha t} + C \qquad S>0, \alpha>0, t>0, \beta>0$$

$$\iff e^{-\frac{\beta}{\alpha}e^{-\alpha t}+C} = S(t) \iff S(0) = e^{-\frac{\beta}{\alpha}+C}$$

$$S(t) = e^{\left(-\frac{\beta}{\alpha}+C\right)} e^{\left(-\frac{\beta}{\alpha}e^{-\alpha t} + C + \frac{\beta}{\alpha} - C\right)}$$

$$S(t) = S(0)\, e^{\frac{\beta}{\alpha}(1-e^{-\alpha t})}$$

(Consequences of (2):

(i) the tumor grows more and more slowly as time goes on.

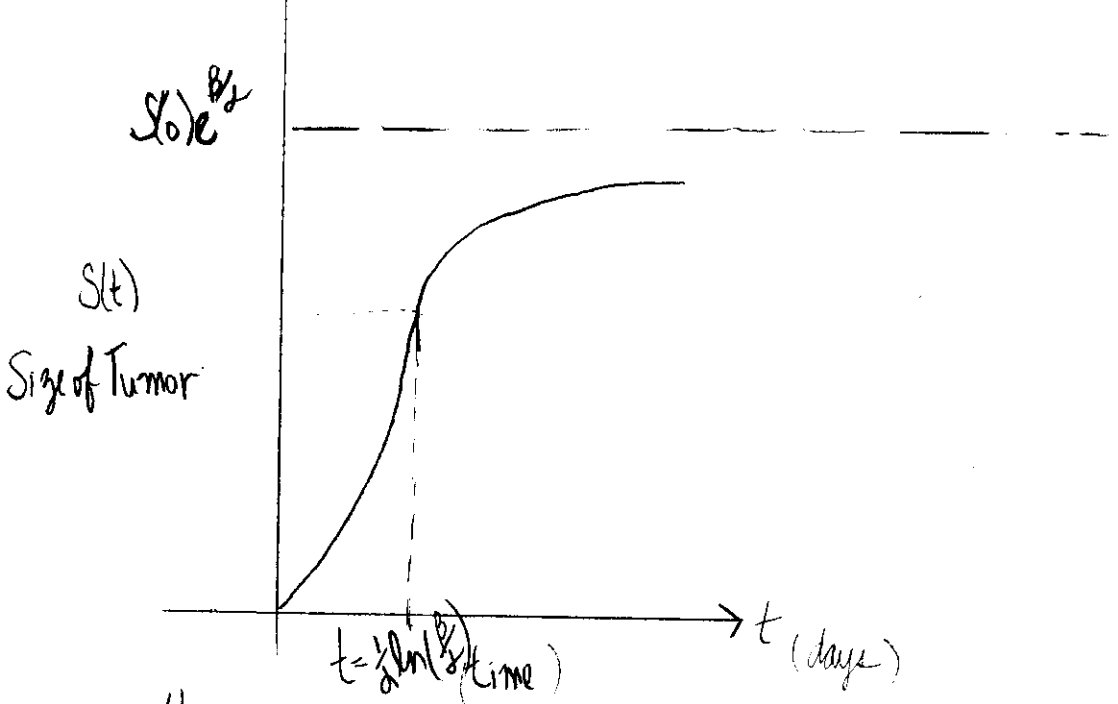
(ii) boundedness $S_\infty = S(0)e^{\beta/\alpha}$ the quantity being the "theoretical maximum" size of the tumor, is usually larger than the largest observed tumor size and represents the maximum size the tumor is to attain (Lloyd H. 1975)

Let's examine the point of inflection:

$$\frac{d^2S}{dt^2} = -\beta e^{-\alpha t}S(t) + \beta e^{-\alpha t}\left(\beta e^{-\alpha t}S(t)\right)$$

then the point of inflection occurs where $\frac{d^2S}{dt^2} = 0$ or is undefined

$$\beta e^{-\alpha t}S(t) = \beta e^{-\alpha t}\beta e^{-\alpha t}S(t) \iff \alpha = \beta e^{-\alpha t} \iff t = \frac{1}{2}\ln\left(\frac{\beta}{\alpha}\right)$$



$$S(t) = S(0)e^{\beta/\alpha}(1-e^{-\alpha t})$$

i) As $t \to \infty$ $S \to S(0)e^{\beta/\alpha}$ ie. limiting value for tumor size $\ln S_{(0)} = \beta/\alpha$

ii) As $\alpha \to \infty$ $S \to S(0)$ ie for a large neg relative rate of growth of λ, S(t) remains stable
$\alpha \to 0$ (no rel. rate of growth)

iii) As $\beta \to \infty$ $S \to S(0)e^{\beta/\alpha}(1-e^{-\alpha t}) \to \infty$
and $t \to \infty$ $S \to S(0)e^{\beta/\alpha} \to \infty$ ie. for a large initial relative growth rate, the tumor grows without bound.

Interpretations:

i) This has been presented already as being the maximum attainable size. See examples of Gompertz approximated maximal values on the following pages. Notice that the patient usually dies as a result of the cancer before his/her tumor has reach the upper bound.

ii) If the relative rate of growth has a greatly negative value – this implies that λ has decreased extraordinarily – the result would of course mean the growth of the tumor has ultimately ceased. If no relative growth rate the tumor remains stable (benign).

iii) If the tumor is not discovered until far into its propagation then it grows without bound. This is a little more difficult to interpret at its extreme.

Doubling time

Where $S(t) = 2S(0)$ solve for t.

$$S(0)e^{\beta/\alpha(1-e^{\alpha t})} = 2S(0)$$

then

iff $$e^{\beta/\alpha(1-e^{-\alpha t})} = 2$$

iff $$\frac{\beta}{\alpha}(1-e^{-\alpha t}) = \ln 2$$

iff $$e^{-\alpha t} = 1 - \frac{\alpha}{\beta}\ln 2 \quad t = -\frac{1}{\alpha}\left(\ln\left[1 - \frac{\alpha}{\beta}\ln 2\right]\right)$$ where $\ln S_\infty = \frac{\beta}{\alpha}$

We write $$L(S) = -\frac{1}{\alpha}\ln\left(1 - \frac{\ln 2}{\ln(S_\infty/S)}\right), \quad S < \tfrac{1}{2}S_\infty$$

The doubling time of a hypothetical single cell tumor may be found by setting S to unity. Therefore,

$$L(1) = \frac{-1}{\alpha}\ln\left(1 - \frac{\ln 2}{\ln S_\infty}\right)$$

Since $\ln 2/\ln S_\infty$ is small compared to unity the above equation reduces approximately to

$$L(1) = \frac{\ln 2}{\alpha \ln S_\infty} = \frac{\ln 2}{k}$$

It is now seen that the intrinsic growth rate of $k = \alpha \ln S_\infty$ can be identified with the rate of growth of a hypothetical single cell tumor. Therefore $L(1)$ might be expected to correspond to the cell cycle times determined by the method of labelled mitoses.

TABLE 1.—Comparison of hypothetical single-cell tumor doubling times predicted by extrapolation* of Gompertz growth curves and measured cell-cycle times

Tumor	Doubling time (days)	Cell-cycle time† (days)
Sarcoma 180	0.12	0.54‡
DMBA-induced	0.14	0.92‡
Amelanotic melanoma	0.15	—
Adenocarcinoma 755	0.16	0.50‡
AKR lymphoma (sc, 4th generation)	0.17	1.1§
Walker 256 carcinosarcoma	0.18	—
Ehrlich carcinoma	0.24	0.80‡
B16 melanoma	0.26	0.60§
Plasmacytoma No. 1	0.27	0.58‡
Lewis lung	0.35	0.59§
L1210 leukemia (ip)	0.40	0.53‡
Melanotic melanoma No. 1	0.51	0.73‡
C3H mammary	0.69	0.73¶

*Assuming 1 g of tumor is equivalent to 10^9 cells.

†Only the smallest observed value is listed. In general, the cell-cycle time increases with tumor size.

‡*See* ref 15.

§Simpson-Herren L. Unpublished data.

¶Doubling time is computed for the transplanted C3H mammary tumor (15), while the cell-cycle time is for Mendelsohn's (fast line) transplanted C3H mammary tumor (23).

It appears that in general the quantitative agreement is not good although the discrepancy is not too large

It seems that the Gompertz might be underestimating tumor size.

Remember what is being done here. We have extrapolated a model far beyond the range in which the parameters of that model were determined.

Extrapolation of the Gompertz curve will probably be accurate to a point where the "instantaneous" doubling time is approximately equal to the minimum observed cell-cycle time, but below this point the extrapolation will predict growth rates that are too high and thus tumor sizes that are too small.

For those cases where estimation (Lloyd 1975)
is necessary because direct or indirect measurements are not possible, the extrapolation of the Gompertz fitted growth curve may provide additional information about the growth of very small tumors.

Sheet 1

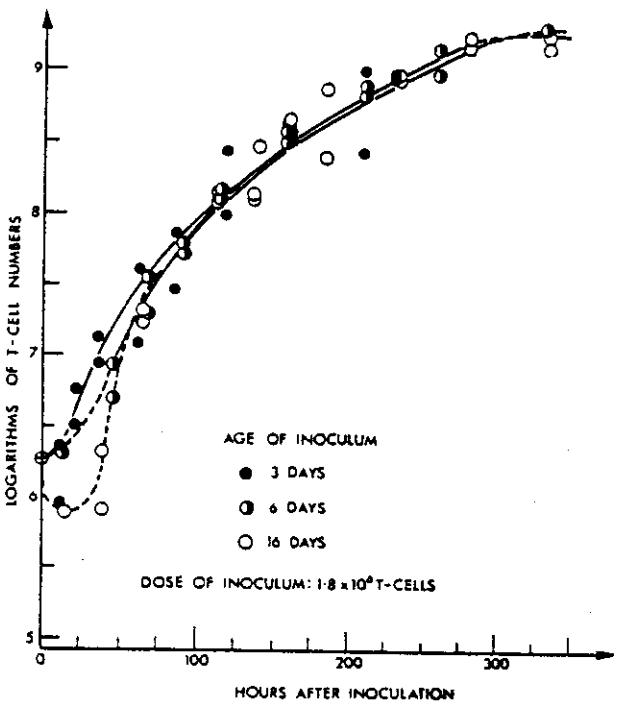


FIG. 1.—Growth of the Ehrlich ascites tumor. Log number of tumor cells plotted against time. Dose of inoculum kept constant while physiological age of inoculum varied. Dotted lines are freehand drawings; black curves represent authors' equation fitted to the data. Redrawn after Klein and Révész (1953).

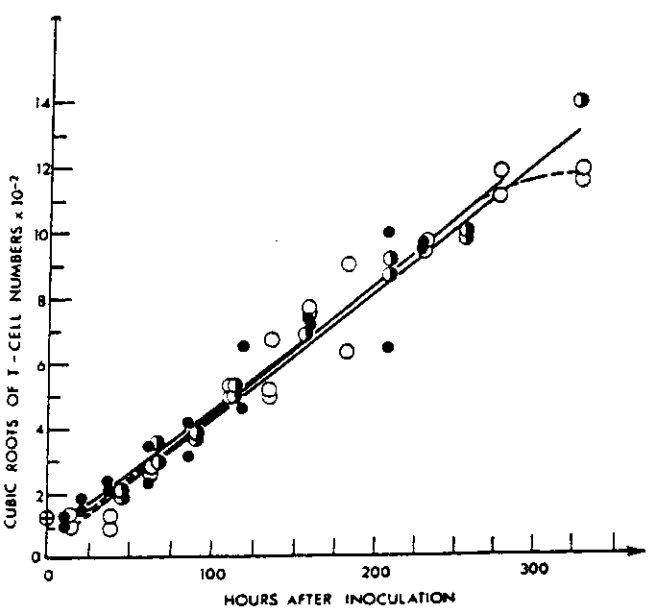


FIG. 2.—Same data as in Fig. 1, replotted so that the ordinate now represents the cube roots of tumor cell number ($\times 10^{-2}$) instead of the logarithms. The black lines are calculated regression lines, and the dotted lines are freehand drawings. Redrawn after Klein and Révész (1953).

Sheet II The time in days that would be required to double the size already attained at the instant previous rate of growth present at this point. The ratio in doubling times will necessarily reflect the degree of correlation between the tumour size and growth rate. (A.K. LAIRD 1964)

Fig 1

Rates of Growth of Various Tumors at a Size Corresponding to 0·137 Times the Asymptote

Tumor	Time from T_0 (days)	Cells already present ($\times 10^{-6}$)	Rate of growth cells/day $\times 10^{-6}$	Doubling time (days)*
Mouse—				
MC_1M	3·98	63	44·1	1·4
Ehrlich	6·83	350	150	2·3
Osteosarcomas	51·20	367	16·6	22·0
Krebs	4·53	134	109	1·2
EI_1-low dose	3·74	183	166	1·1
EI_1-high dose	2·40	171	187	0·9
DBA lymphoma	3·07	144	164	0·9
$6C_3HED$-high	1·72	182	105	1·7
$6C_3HED$-low	3·60	307	169	1·8
E0771	26·20	6,665	840	7·9
Rat—				
Walker 256:				
W26b1	74·2	580,000	25,000	23
W12a7	104·0	561×10^6	$22{\cdot}9 \times 10^6$	25
W10a6	39·4	$33{\cdot}9 \times 10^6$	$2{\cdot}64 \times 10^6$	13
W10b4	1018·0	945×10^{18}	$5{\cdot}70 \times 10^{18}$	166
R39 Sarcoma:				
R3a7	13·2	$1{\cdot}6 \times 10^6$	388,000	4·1
R4C4	16·0	$3{\cdot}8 \times 10^6$	585,000	6·5
a7R3	28·4	$2{\cdot}1 \times 10^6$	261,000	8·0
Flexner-Jobling	29·0	1644	159	10·2
Rabbit—				
Brown-Pearce:				
B18a5	7·8	986,000	332,000	3·0

* This is an "instantaneous" doubling time; that is, it is the time that would be required to double the number of cells already present when the tumor has reached a size equal to 0·137 times the asymptote, if growth continued at the rate occurring at that instant. Since the doubling time is constantly increasing, by an exponential process (Laird, 1964), the time required to double the tumor size would itself be lengthening appreciably during the doubling process.

Fig 2 Gompertzian Analysis of Tumor Growth

Tumor	Reference	β	α	S_0	Theoretical Upper limit	Approximate Size at death
Mouse:						
Krebs	(1)	$5{\cdot}25 \pm 2{\cdot}00$	$0{\cdot}411 \pm 0{\cdot}056$	$2{\cdot}7 \times 10^3$ cells	1310×10^6 cells	800×10^6 cells
Ehrlich	(2)	$0{\cdot}078 \pm 0{\cdot}011$	$0{\cdot}009 \pm 0{\cdot}0008$	426×10^3 cells	2500×10^6 cells	1593×10^6 cells
MC_1M, low dose	(2)	$0{\cdot}119 \pm 0{\cdot}004$	$0{\cdot}0147 \pm 0{\cdot}0015$	139×10^3 cells	427×10^6 cells	467×10^6 cells
$6C_3HED$, high dose	(3)	$0{\cdot}0397 \pm 0{\cdot}003$	$0{\cdot}012 \pm 0{\cdot}0015$	50×10^6 cells	1340×10^6 cells	890×10^6 cells
$6C_3HED$, low dose	(3)	$0{\cdot}0626 \pm 0{\cdot}0062$	$0{\cdot}0116 \pm 0{\cdot}0021$	10×10^6 cells	2190×10^6 cells	776×10^6 cells
DBA lymphoma	(3)	$0{\cdot}276 \pm 0{\cdot}023$	$0{\cdot}0238 \pm 0{\cdot}0021$	10×10^3 cells	1070×10^6 cells	$(1000 \times 10^6$ cells)*
EI_1, low dose	(3)	$0{\cdot}207 \pm 0{\cdot}096$	$0{\cdot}019 \pm 0{\cdot}003$	24×10^3 cells	1290×10^6 cells	1260×10^6 cells
EI_1, high dose	(3)	$0{\cdot}172 \pm 0{\cdot}097$	$0{\cdot}023 \pm 0{\cdot}004$	695×10^3 cells	1240×10^6 cells	1290×10^6 cells
E0771	(4)	$0{\cdot}666 \pm 0{\cdot}304$	$0{\cdot}063 \pm 0{\cdot}022$	3 mm³	109 cm³	31 cm³
Osteosarcomas	(5)	$1{\cdot}02 \pm 0{\cdot}115$	$0{\cdot}159 \pm 0{\cdot}026$	0·01 cm³	6·03 cm³	4·3 cm³
Rat:						
Walker, W26b1	(6)	$0{\cdot}220 \pm 0{\cdot}0227$	$0{\cdot}0218 \pm 0{\cdot}0061$	0·4 g	9600 g	175 g
Walker, W12a7	(7)	$0{\cdot}342 \pm 0{\cdot}040$	$0{\cdot}0205 \pm 0{\cdot}0058$	4·2 mm³	72,800 cm³	212 cm³
Walker, W10a6	(7)	$0{\cdot}362 \pm 0{\cdot}017$	$0{\cdot}039 \pm 0{\cdot}0037$	418 mm³	1780 cm³	490 cm³
Walker, W10b4	(7)	$0{\cdot}132 \pm 0{\cdot}012$	$0{\cdot}003 \pm 0{\cdot}0026$	16·7 mm³	—	196 cm³
R39 Sarcoma, R3a7	(8)	$1{\cdot}28 \pm 0{\cdot}250$	$0{\cdot}124 \pm 0{\cdot}011$	8·36 mm³	241 cm³	188 cm³
R39 Sarcoma, R4c4	(8)	$0{\cdot}540 \pm 0{\cdot}120$	$0{\cdot}078 \pm 0{\cdot}012$	475 mm³	496 cm³	276 cm³
R39 Sarcoma, a7R3	(8)	$0{\cdot}737 \pm 0{\cdot}162$	$0{\cdot}063 \pm 0{\cdot}0068$	2·1 mm³	270 cm³	202 cm³
Flexner-Jobling	(9)	$0{\cdot}394 \pm 0{\cdot}066$	$0{\cdot}049 \pm 0{\cdot}0063$	0·015 g	48·4 g	18·3 g
Rabbit:						
Brown-Pearce	(8)	$1{\cdot}262 \pm 0{\cdot}270$	$0{\cdot}169 \pm 0{\cdot}0168$	18 mm³	31·4 cm³	29·8 cm³

Literature references: (1) Patt and Blackford, 1954; (2) Klein and Révész, 1953; (3) Révész and Klein, 1954; (4) Ting, 1952; (5) Finkel, Bergstrand, and Biskis, 1961; (6) Schrek, 1936*a*; (7) Schrek, 1935; (8) Schrek, 1936*b*; (9) Sugiura and Benedict, 1920.

* This is the value for the last two experimental points on the curve; terminal scatter of the data included two previous points that were higher, 1290 and 1620 $\times 10^6$ cells.

Sheet IV

time continues. In Fig. 1, in addition to the computed Gompertz curve, we have shown the exponential curve that corresponds to the initial exponential growth of the El_4 tumor at the time of the first data point; this is the curve tumor growth would have followed if no retardation had occurred.

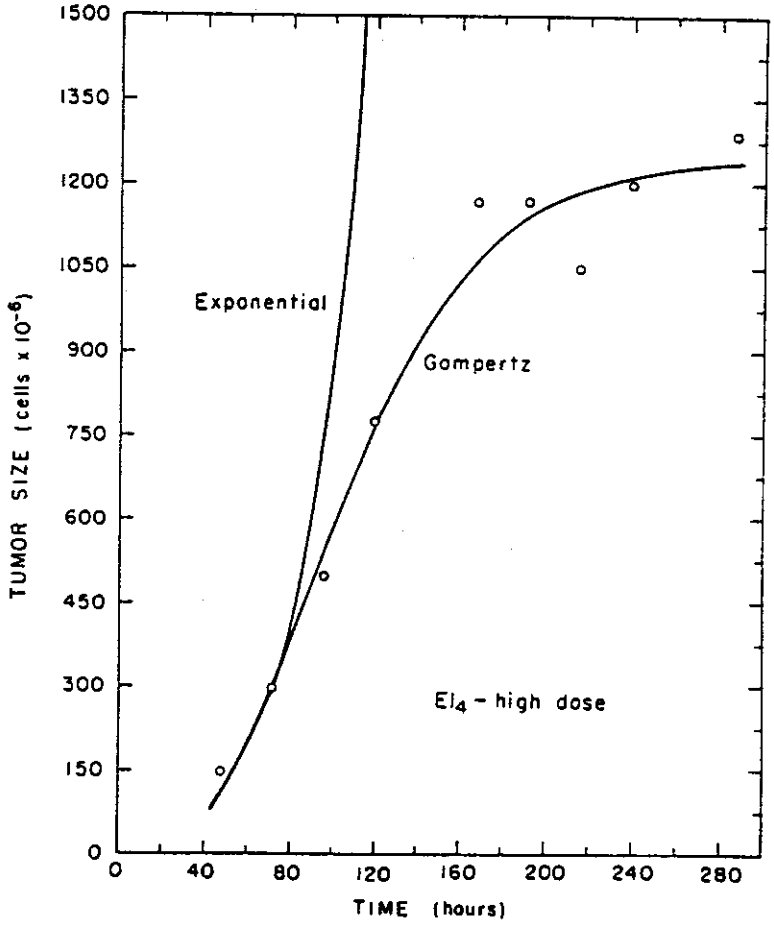


FIG. 1.—A plot of the growth data of the El_4 tumor at high dose. The theoretical Gompertz curve that best fits the data is shown; the data cover a wide range of the curve, and approach the asymptote. A simple exponential curve is also shown, constructed on the basis that the doubling time observed at the time of the first data point remains constant throughout growth of the tumor; the great deviation from simple exponential growth is obvious.

The growth data for many other tumors show proportionally less retardation during the period of observation; in these cases the Gompertz function will fit the data best in a region of the curve further to the left than is the case for the El_4 tumor shown in Fig. 1. The growth of the $6C_3HED$, high dose, is illustrated in Fig. 2; the best fit of the Gompertz curve for this tumor occurs in the region either side of the inflection point, where the curve is relatively straight.

(AK LAIRD 1964)

Sheet IV

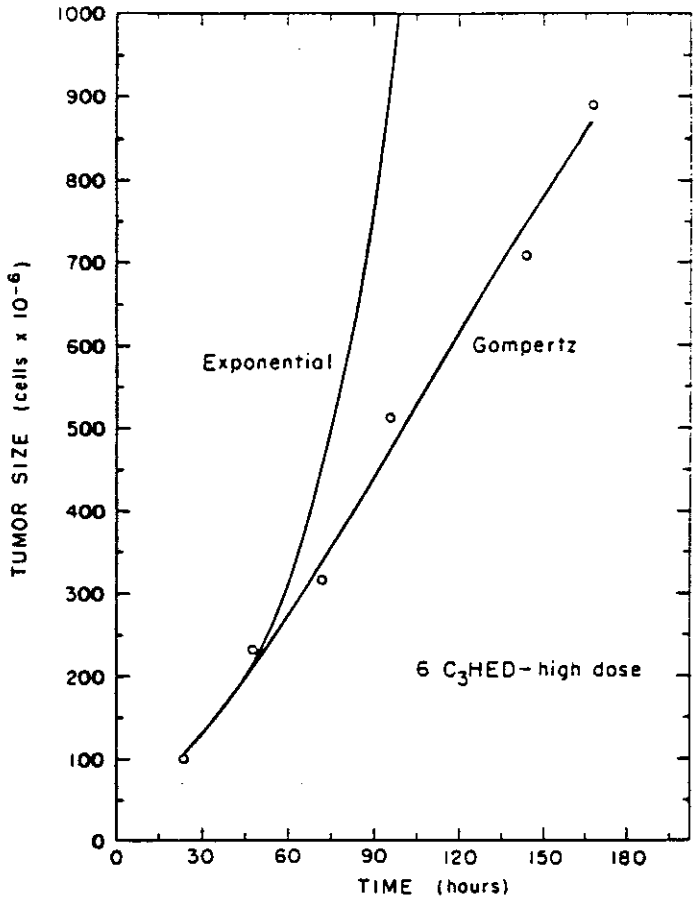


FIG. 2.—The growth data of the $6C_3HED$ tumor at high dose. The growth of this tumor lies a short distance on either side of the inflection point, and because of its position in the middle of the sigmoid curve, it approximates a straight line. In this region, the growth curve deviates appreciably from a simple exponential curve.

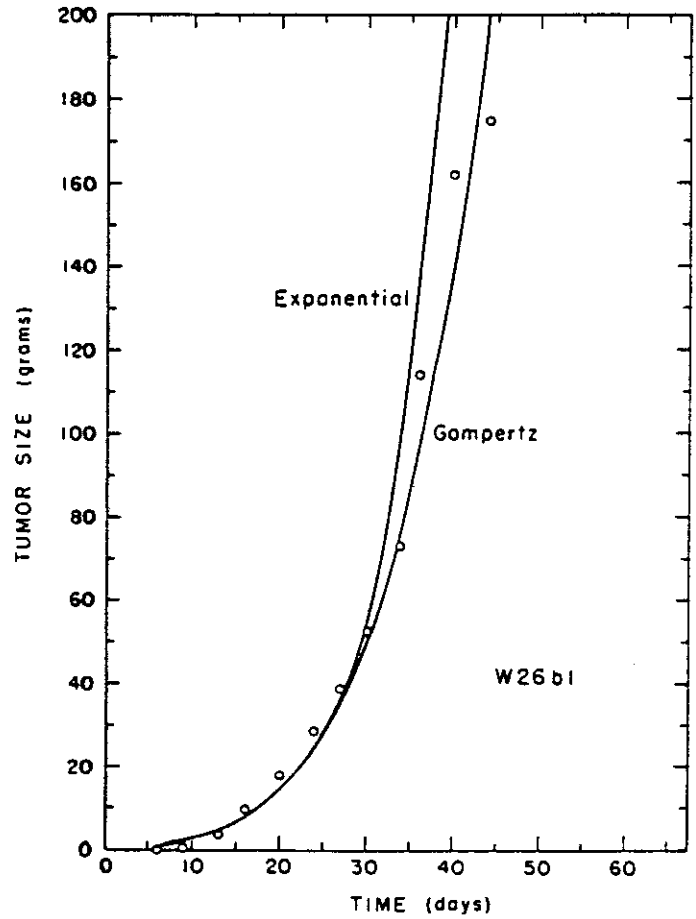


FIG. 3.—One of the Walker tumors, the W26b1. Deviation from simple exponential growth is small, but statistically significant.

(A.K. LAIRD 1964)

(Write-Up 3)

$$P(\text{a given target receives } h \text{ hits}) = \frac{e^{-kD}(kD)^h}{h!} \quad h = 0, \ldots$$

D - dose
k - constant of proportionality

$$P(\text{a given target receives 0 hits}) = e^{-kD}$$

$$P(\text{a given target receives at least 1 hit}) = 1 - e^{-kD}$$

As each target receives hits independently of all of the others

P(the 1st target receives at least 1 hit and the 2nd and ... and n^{th})

$= P(1^{st} \text{ gets 1 hit}) \cdot P(2^{nd}) \cdots P(n^{th})$

$= [1 - e^{-kD}]^n$ = Probability a given cell dies.

$$P(\text{a given cell survives}) = 1 - [1 - e^{-kD}]^n = 1 - [1 - e^{-\frac{D}{D_0}}]^n$$

for $k = 1/D_0$; D_0 the dose required to produce an average of one hit per target

Then the expected proportion of survivors following a dose D is denoted as

$$S = 1 - [1 - \exp(-\tfrac{D}{D_0})]^n = 1 - (1 - ne^{-D/D_0} + \frac{n(n-1)}{2} e^{-D/D_0} + \cdots)$$

Now consider the behaviour of the associated survival curve.

$$\frac{D}{D_0} \to \infty \qquad S = ne^{-D/D_0} \Rightarrow n$$

$$\ln S = \ln n - \frac{D}{D_0} \ln e = \ln n - \frac{D}{D_0}$$

[like: $y = b + mx$, $x = D$, $y = \ln S$, $b = \ln n$, $m = -1/D_0$]

Thus a semi-log plot of fraction surviving (S) versus D approaches a straight line with slope $-1/D_0$ and with zero dose intercept $S = n$

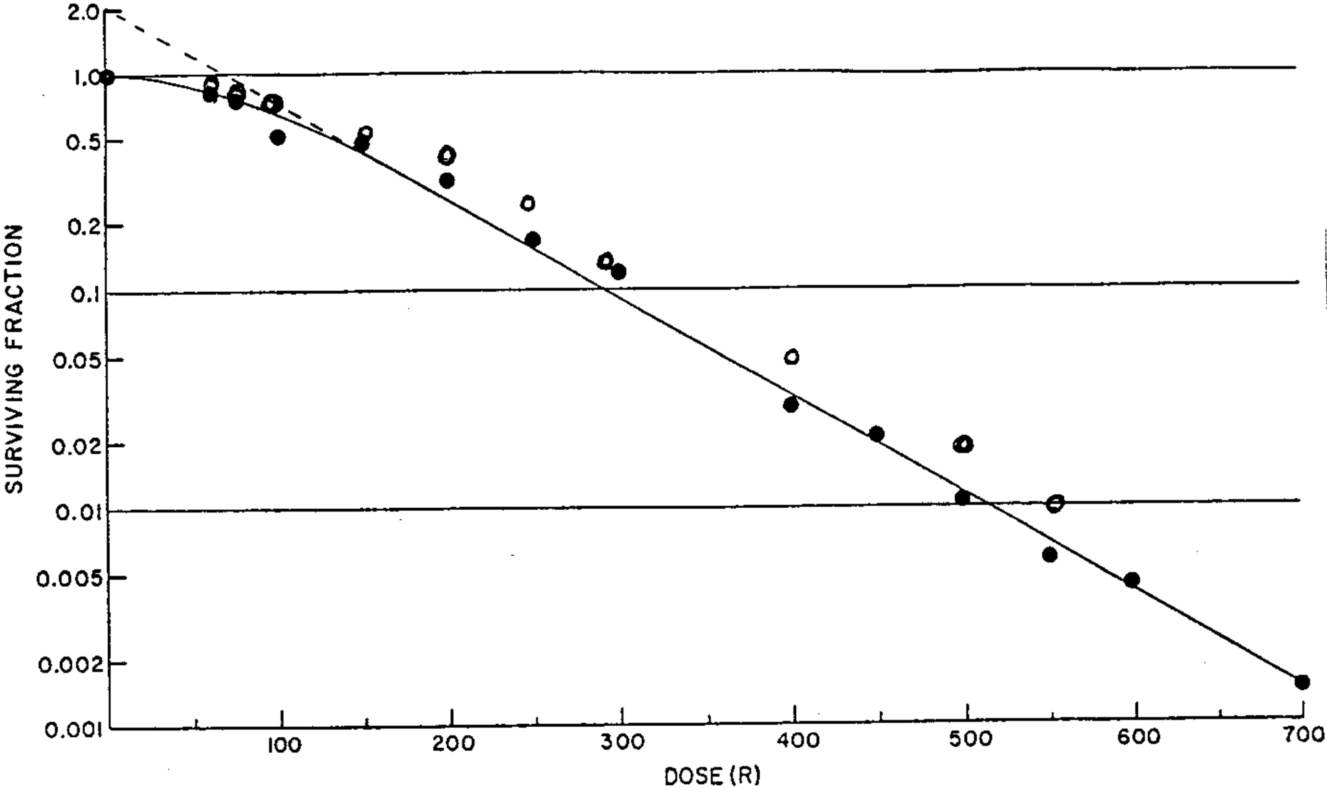
(this is why we refer to n as the extrapolation number)

PROBEM

or in other words

However n, in this case would not be an integer

Surviving fraction would be an integer which makes no sense



(closed circles) $n = 2$ $k = \frac{1}{a_0} = \frac{1}{50}$ / [illegible]

(open circles) $n = 3$ $k = 1/a_0 = 1/60$

	Dose (R)	$S = (1-(1-e^{-D/a_0})^2)$		$S = (1-(1-e^{-D/a_0})^3)$	
[illegible]	25	.9474	≃ .95	.987936353	≃ .99
provided $n = 1$ always	50	.85985	≃ .86	.92[illegible]	≃ .93
	75	.756[illegible]	[illegible]	.840632736	≃ .84
There [illegible]	100	[illegible]	[illegible]	.7290[illegible]	≃ .73
[illegible]	150	[illegible]	8	.506[illegible]	≃ .51
ss of a [illegible]	[illegible]	[illegible]		.33[illegible]	≃ .33
[illegible]	[illegible]	[illegible]59		[illegible]	≃ .21
	[illegible]	.0[illegible]		[illegible]	≃ .13
	[illegible]	[illegible]		.076[illegible]	≃ .08
	[illegible]	[illegible]		[illegible]	≃ [illegible]
	450	.0[illegible]		[illegible]	≃ [illegible]
	500	[illegible]		[illegible]	≃ [illegible]
	550	.00[illegible]98007		[illegible]	≃ .02
reduced i.e. survival [illegible]	600	.00[illegible]		[illegible]005990157	≃ .0[illegible]

(Write-up 2) Gompertzian Relation

For tumor growth the Gompertz function can be written as:

$$S(t) = S(0)e^{(1-e^{-\alpha t})\frac{\beta}{\alpha}} \qquad \beta > 0, \alpha > 0 \qquad (*)$$

Defining Parameters:

$S(t)$: S is the tumor size at time t; tumor size can be expressed as weight, volume, or cell number.

$S(0)$: the initial tumor size - when speaking of size in terms of number of cells, tumours are first detectable when $S = 10^9$, we then refer to this as our initial size

t: time from when the tumour was first detected $- t \geq 0$. (usually days)

In order to understand the other parameters we need to do the following:
The above equation is the exact solution to the following pair of differential equations:

$$(i) \quad \frac{dS(t)}{dt} = \lambda S(t) \quad \text{and} \quad (ii) \quad \frac{d\lambda}{dt} = -\alpha\lambda$$

(i) The rate of growth of the tumour is proportional to its size at that moment, where the function of proportionality is $\lambda(t)$.

(ii) represents how any Gompertz curve can be considered to begin as a simple exponential process which is then retarded exponentially as time goes on

Solving (ii) first $\frac{d\lambda}{dt} = -\alpha\lambda$

$$\Leftrightarrow \int \frac{1}{\lambda} d\lambda = -\alpha \int dt$$

$$\ln|\lambda| = -\alpha t + C$$

$$e^{-\alpha t + C} = \lambda$$

let $t = 0$ then $\lambda(0) = e^C$

$$\beta = e^C$$

$$\therefore \lambda = \beta e^{-\alpha t}$$

restrictions

$\lambda \neq 0$

$\lambda > 0$

$\lambda > 0$

let β = initial relative growth rate