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Models for the Growth of a Solid Tumor by Diffusion

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A simple mathematical model of tumor growth by diffusion is constructed in order to examine and evaluate different hypotheses concerning the evolution of a solid carcinoma. A primary objective is to infer the chemical source of growth inhibition from the most easily obtained data, namely, the outer radius of the nodule as a function of time and a histological examination of the final dormant state. In section 6 some of the conclusions of this study relating to a prototype experiment and described with as little mathematics as possible.

1. Introduction

Although the growth of solid tumors in animals always involves some vascularization, the earliest stages of development are apparently regulated by the direct diffusion of nutrients and wastes from and to surrounding tissue. Experiments on the in vitro growth of nodular carcinomas [4], [8], [10], or those involving techniques for the in vivo isolation of tumors [5], [6], [11] show that growth of a solid malignancy by diffusion alone leads asymptotically to a dormant but viable steady state.

When the tumor is very small, every cell receives adequate nourishment by simple diffusion and the growth rate of the population is exponential. However, the consumption of a nutrient means that its concentration must decrease towards the center of the nodule. Eventually the concentration there of a vital nutrient falls below the critical level to sustain cell life and a central necrotic core develops. The growth rate of the tumor then diminishes markedly because it becomes increasingly difficult to obtain nourishment and to dispose of wastes solely by diffusion. The typical steady state configuration, Figure 1, is a sphere, a few millimeters in diameter, which histological examination shows to consist of three distinct concentric annular shells. In the thin outermost shell, a layer several cells thick, cells are observed to grow and divide as they do in the initial exponential phase. In the adjoining shell, cells are alive and viable but exhibit almost no mitosis and proliferation. The innermost central core consists of necrotic debris in various stages of disintegration.

The actual distances and times scales that characterize the evolution of a solid tumor strongly depend on the conditions of the experiment, i.e., cell strain, nutrient levels, etc. The few tumor cells of the original colony increase in number to a final

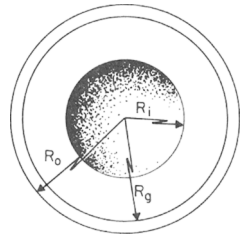

Figure 1. Cross-section of a nodular carcinoma showing the central necrotic core, $r \leq R_i$, the layer of viable non-proliferating cells, $R_i \leq r \leq R_g$, and the outer shell where all mitosis occurs, $R_g \leq r \leq R_0$.

aggregate of about a million or so, in a growth period that can be several days, or several months. The spherical nodule expands from the microscopic to the size of a "pin head" whose radius is the order of a millimeter (1,000 μ in normal units).

This range of scales makes it very desirable to formulate any theory in dimensionless terms for then the data of different experiments can be incorporated within one framework simply as specific parameter settings. These dimensionless parameters, which are groupings of the rate constants of the various diffusive and metabolic processes, are for the most part readily found from observation. This is an important point because the rate constants themselves are either unknown or very difficult to determine.

Diffusion in tissues and tissue cultures has been widely studied and the early paper by Hill [7] is a common antecedent to both the mathematical and biological literature. Analogous problems that concern diffusion and moving boundaries are quite common in science and engineering, especially in the subjects of filtration, absorption, heat conduction, ablation (melting and freezing), change of state, gas–liquid reactions and chemical kinetics (see [2] and [3]).

The increased resistance of oxygenated cancer cells to x-ray therapy has been a major reason for the study of nodular carcinomas. Most of the existing theory and much experimental data have been developed in this context and the papers of Thomlinson and Gray [11], Burton [1], Sutherland et al. [8], [10] are especially noteworthy.

A new approach to the control of cancer based on the relationship of tumor growth and vascularization has been proposed and examined by J. Folkman [4], [5], [6]. Briefly this research shows that cancer cells produce a distinct chemical factor, called TAF or Tumor Angiogenesis Factor, which stimulates the rapid formation of new capillaries. As the tumor, in vivo, approaches its diffusion limited size the local T.A.F. concentration increases and induces neighboring blood vessels to grow towards and into the colony. The malignancy becomes vascularized and perfusion then supplants simple diffusion as the dominant mechanism for the supply of nutrients and the removal of wastes. Once the tumor connects with the circulatory system all constraints imposed on it by diffusion are eliminated and subsequent growth is almost explosive. Folkman's primary objective is to prevent this metastasis by blocking the chemical message for vascularization that is sent from the tumor to the surrounding tissue. If this can be accomplished, it may be possible to maintain a tumor indefinitely in its dormant, prevascularized state. Moreover, a blood test for T.A.F. would provide a very early indication of cancer, long before it can be discovered by present techniques. As a result of this work, the future treatment of many types of cancer may focus

on the early detection of a solid malignancy and chemo-therapy to confine it to a dormant and harmless state.

The isolation and analysis of T.A.F., and the discovery of a counter-agent or anti-angiogenesis compound, are clearly chemical and biological problems that are outside the immediate sphere of mathematics. Although relegated to a secondary role, mathematical models can still provide some information and understanding that is not now accessible or readily obtained. Problem areas susceptible to theoretical analysis are the structure of the tumor at any time and the major processes that affect its growth.

In this paper, a very simple model of growth by diffusion is constructed with the goal of evaluating several hypotheses about the evolution of a solid carcinoma. In particular, the following question is considered: What can be learned about the major internal mechanisms of the developing tumor from the most easily obtained data—the outer radius of the nodule as a function of time and a histological examination of its steady state?

2. Assumptions

Simple mathematical models of solid tumors nourished and sustained solely by diffusion have been discussed by Thomlinson and Gray [11] and Burton [1]. The basic assumptions of these studies, which are also adopted here, are as follows:

(i) The solid tumor is a sphere and complete spherical symmetry prevails at all times. Time, t, and radial distance, r, are the only independent variables.

(ii) Cancer cells die when the concentration of a crucial nutrient, denoted by $\sigma(r, t)$, falls below a critical level σ_l. The most indispensable nutrient is thought to be oxygen, whose concentration is usually given as a partial pressure. Glucose may be as, or more essential in certain cases.

(iii) The vital nutrient, say oxygen, is consumed by living cells only; the consumption rate may depend on nutrient concentration and cell proliferation as well as other factors.

In order to describe the observed characteristics of tumor growth and the dormant steady state, several new hypotheses and approximations must be added to the preceding list:

(a) There is an adhesion or surface tension among living cancer cells [10], which in a spherical geometry produces an inward pressure that maintains a compact solid mass.

(b) Necrotic cellular debris continually disintegrates into simpler chemical compounds that are freely permeable through cell membranes. The mass, or equivalently, the cell volume lost this way in necrosis is replaced by cells pushed inward by the forces of adhesion and surface tension.

These assumptions constitute an explanation of why cell proliferation can and indeed must continue even when the tumor is in a quiescent steady state. In equilibrium, cells produced in the growth layer flow inward exactly compensating the loss of cell volume in the necrotic center. Moreover, a tumor grows when the rate of cell production exceeds the mass and volume loss due to necrotic disintegration. In the reverse situation, the nodule contracts.

Supposition (a) above gives a dynamical basis for cell migration whereas (b) essentially states the conservation of mass which must apply to such movements. Both will be made more precise shortly.

Although experiments show an inner layer of living, viable cells with a low mitotic index (i.e., mitosis is almost negligible), there is no conclusive evidence on the nature or source of this inhibition. In this regard, a theoretical model can provide some useful insight and for this purpose another basic assumption is introduced.

(c) A chemical is produced somewhere within the tumor which inhibits the mitosis of cancer cells without causing their death. Its concentration, in units per cc, will be denoted by $\beta(r, t)$; the critical level is β_1.

The source of this inhibitor may be the metabolic wastes from live cells, the necrotic debris or simply an inadequate supply of nutrient. Each possibility will be considered separately to determine its peculiar, and hopefully recognizable effects on tumor growth. The comparison of these results with the observed growth rate of a carcinoma and the histological examination of its steady state may be sufficient to rule out one possibility, or to focus attention on another.

(d) The carcinoma is in a state of diffusive equilibrium at all times.

The diffusion of oxygen or most metabolites over the microscopic distances that characterize the tumor's size and structure, is achieved in a time interval that is very small compared with the total period of growth. For example, it takes about 10 seconds (1,000 seconds) for oxygen to diffuse across a distance of 100 μ (1,000 μ). Both time intervals are certainly very short compared to a growth period measured in days and they may even be regarded as small relative to the twelve to eighteen hour period for mitosis (in epithelial cells of a Chinese hamster). The approximation of instantaneous diffusive equilibrium is based on these disparate time periods. Its general validity enables important simplifications to be made and actually renders the theory tractable.

3. Conservation of mass

The correct statement of the conservation of mass for an active, multi-component chemical system that is a living cell would be far too complicated for use here, even if it could be given explicity. As befits the present state of knowledge, a simpler approach is adopted the motivation for which is drawn from the flow of an incompressible fluid. The loose analogy is to view the tumor as a "fluid" that consists of incompressible cells held together by adhesive forces. Mitosis or cell proliferation acts like a source of incompressible fluid, necrosis has the role of a fluid sink and the fluid domain or tumor size varies in extent to accommodate any imbalance in net production.

The mathematical model incorporates the following approximations:

(i) All living tumor cells are identical and each is to be considered an incompressible structure of constant volume.

(ii) Cell division occurs "instantaneously" relative to the growth time of the tumor, and each daughter cell occupies the same volume as any other cell of the population.

(iii) The proliferation rate of cell volume by mitosis is described by a source distribution $S(\sigma, \beta)$ which is a function only of the local nutrient and inhibitor concentrations. This function describes the rate at which cell volume is produced by mitosis per unit volume of living cells.

(Although the explicit functional form of $S(\sigma, \beta)$ has yet to be given, the assumptions already made imply that $S(\sigma, \beta) = 0$ for $\beta > \beta_l$, and for consistency, $S(\sigma, \beta) \equiv 0$ for $\sigma < \sigma_l$. It remains only to approximate $S(\sigma, \beta)$ for $\sigma > \sigma_l$ and $\beta < \beta_l$.)

The necrotic core is composed of dead cells and cellular material in various stages of disintegration and dissolution. This phenomenon is not well understood, but the debris, described as jelly-like, is capable of supporting the pressure exerted on it by the outer viable layers. The complex molecules which form the structure of a live cell are assumed to degenerate in death to simpler permeable compounds. This implies a continuing loss of cell volume that must be compensated by a material flow. The information available at present does not permit or justify a detailed description of the death process and for this reason the simplest approximations are made to characterize necrosis and its effects in tumour growth.

(iv) The necrotic core "loses" cell volume at a rate that at any time is proportional to the core volume. Moreover, this loss occurs at a uniform rate throughout the region of necrosis. The proportionality constant is denoted by 3λ strictly for convenience. (A rapid decrease in cell volume may accompany the death of a cell, like a deflating balloon and this is discussed in the Appendix.)

If the mass density of living cells is constant and equal to the density of the necrotic debris, the conservation of mass with distributed sources and sinks is equivalent to the conservation of volume. In words, the conservation law is as follows:

$$A = B + C - D - E$$

with A = the total volume of living cells at any time t;
B = the initial volume of living cells at time $t = 0$;
C = the total volume of cells produced in $t \geq 0$;
D = the total volume of necrotic debris at time t;
E = the total volume lost in the necrotic core in $t \geq 0$.

In order to convert this statement into a mathematical equation the following notation is introduced (see Figure 1):

Let $R_0(t)$ be the outer radius of the nodule at any time t. $R_0(0)$ is then the initial radius of the tumor.

Let $R_i(t)$ be the radius of the necrotic core. Since death occurs when the nutrient level σ falls below the critical value σ_l, $R_i(t)$ is defined by the relationship

$$\sigma(R_i(t), t) = \sigma_l$$

If $\sigma > \sigma_l$ everywhere, then $R_i(t) \equiv 0$.

Let $R_g(t)$ be the radius at which cell proliferation ceases because the concentration of chemical inhibitor in the domain of living cells reaches the critical level β_l. By definition

$$\beta(R_g(t), t) = \beta_l.$$

For $R_g(t) \leq R_i(t)$, the critical level β_l lies within the necrotic core and the katabolite has no effect on living cells. If $\beta < \beta_l$ everywhere, then $R_g \equiv 0$.

Let $\max(a, b)$ denote the larger of the two positive numbers a, b.

The mathematical forms of the various terms in conservation law above are then as follows:

$$A = \frac{4\pi}{3}(R_0^3(t) - R_i^3(t));$$

$$B = \frac{4\pi}{3}R_0^3(0);$$

$$C = 4\pi \int_0^t dt \int_{\max(R_i(t),R_g(t))}^{R_0(t)} S(\sigma, \beta) r^2 \, dr;$$

$$D = \frac{4\pi}{3}R_i^3(t);$$

$$E = \frac{4\pi}{3}\int_0^t 3\lambda R_i^3(t) \, dt.$$

Replacement of the word phrases by their mathematical forms leads, upon simplification, to the conservation of volume equation which governs the growth of the tumor:

$$R_0^3(t) = R_0^3(0) + 3\int_0^t dt \int_{\max(R_i(t),R_g(t))}^{R_0(t)} S(\sigma, \beta) r^2 \, dr - \int_0^t 3\lambda R_i^3(t) \, dt. \tag{3.1}$$

A more useful form is the time derivative of this equation:

$$R_0^2 \frac{dR_0}{dt} = \int_{\max(R_i,R_g)}^{R_0} S(\sigma, \beta) r^2 \, dr - \lambda R_i^3. \tag{3.2}$$

The conservation of mass can also be given in terms that refer only to the movement and flow of live cells:

The rate at which the volume of live cells increases

= the rate at which volume of live cells is produced − the volume rate at which live cells die to replenish the volume loss in the necrotic center.

Only the second term on the right-hand side requires further explanation. If U is the velocity of a cell at the necrotic interface, $R_i'(t) - U$ is its *relative* velocity with respect to this moving surface. Therefore, $-4\pi R_i^2(R_i' - U)$ represents the "dying" rate at which cell volume is forced to flow out of the viable domain into the necrotic core in order to replenish the volume lost there. The rate equation is then

$$\frac{4\pi}{3}\frac{d}{dt}(R_0^3 - R_i^3) = \int_{\max(R_i,R_g)}^{R_0} Sr^2 \, dr - 4\pi R_i^2(R_i' - U).$$

The comparison of this with (3.2) shows that

$$U = -\lambda R_i(t), \tag{3.3}$$

is the inward migratory velocity of cells at the necrotic interface. A mass conservation law that accounts for a volume contraction of cells upon death is given in the Appendix.

4. Growth retardation due to necrosis

In the first model, the chemical inhibitor is assumed to be a produce of necrosis. Again the simplest approximations are made:

(i) The chemical inhibitor $\beta(r, t)$ is produced in the necrotic core, $r \leq R_i(t)$, at a constant rate per unit volume, P.

(ii) The diffusivity of any chemical is uniformly constant throughout the tumor and the adjacent medium. The diffusivities of $\sigma(r, t)$ and $\beta(r, t)$ are the constants k and κ, respectively.

(iii) The nutrient σ is consumed by living cells at a constant rate per unit volume, A. (Variations in consumption between viable and growing cells are considered in the Appendix.)

(iv) The rate of cell proliferation per unit volume in the growth region is a constant, s. In terms of the step function

$$H(x) = 1, \quad x \geq 0; \qquad H(x) = 0, \quad x < 0;$$

the source distribution for new cells (or new volume) due to mitosis is approximated by

$$S(\sigma, \beta) = sH(\sigma - \sigma_l)H(\beta_l - \beta). \tag{4.1}$$

(v) The composition of the ambient medium is held fixed (by mixing, etc.) throughout any experiment. The concentrations of nutrient and inhibitor at the outer surface of the tumor are the constants, σ_∞ and zero, respectively.

The data available at present doesn't really warrant much more sophisticated and elaborate approximations although these are relatively easy to formulate. At present, a theory with as few unspecified constants as possible provides the most useful information because the parameters of a simple model can be determined from the experiments while those of a complex model cannot.

With the source function as given in (4.1) the mass conservation law, equation (3.2), can be written as

$$R_0^2 \frac{dR_0}{dt} = \frac{s}{3}[R_0^3 - \max(R_i^3, R_g^3)] - \lambda R_i^3. \tag{4.2}$$

The assumption of diffusive equilibrium implies that the equations for concentrations σ, β are,

$$\frac{1}{r^2}\frac{\partial}{\partial r} r^2 \frac{\partial}{\partial r}\sigma(r, t) = \frac{A}{k} H(r - R_i(t))H(R_0(t) - r), \tag{4.3}$$

$$\frac{1}{r^2}\frac{\partial}{\partial r} r^2 \frac{\partial}{\partial r}\beta(r, t) = -\frac{P}{\kappa} H(R_i(t) - r). \tag{4.4}$$

The boundary conditions require σ, $\partial\sigma/\partial r$, β, $\partial\beta/\partial r$ to be continuous across every interface and in particular $\sigma = \sigma_\infty$, $\beta = 0$ at $r = R_0(t)$; all functions are bounded at the origin. By definition $R_g(t)$ and $R_i(t)$ satisfy

$$\begin{aligned} \beta(R_g, t) &= \beta_l, \\ \sigma(R_i, t) &= \sigma_l, \end{aligned} \tag{4.5}$$

if solutions exist; otherwise, $R_g \equiv 0$, $R_i \equiv 0$.

Since time derivatives have been neglected in the diffusion equations, the only initial condition required is the value of $R_0(0)$. The initial size of the tumor is always assumed to be so small that $R_i(0) = 0$, $R_g(0) = 0$.

The solutions of the differential equations (4.3) and (4.4) are:

$$R_i(t) \le r \le R_0(t) \begin{cases} \sigma = \sigma_\infty - \dfrac{A}{6k}(R_0^2 - r^2) + \dfrac{AR_i^3}{3k}\left(\dfrac{1}{r} - \dfrac{1}{R_0}\right), & (4.6) \\ \beta = \dfrac{PR_i^3}{3\kappa}\left(\dfrac{1}{r} - \dfrac{1}{R_0}\right); & (4.7) \end{cases}$$

$$r \le R_i(t) \begin{cases} \sigma = \sigma_l, & (4.8) \\ \beta = \dfrac{PR_i^3}{3\kappa}\left(\dfrac{3}{2R_i} - \dfrac{1}{2}\dfrac{r^2}{R_i^3} - \dfrac{1}{R_0}\right); & (4.9) \end{cases}$$

where in particular

$$\sigma_\infty - \sigma_l = \frac{A}{3k}\left[\frac{1}{2}(R_0^2 - R_i^2) - \frac{R_i^2}{R_0}(R_0 - R_i)\right]. \tag{4.10}$$

Growth retardation of live cells occurs when $R_g(t) \ge R_i(t)$; the precise condition obtained from (4.5) is

$$\beta_l = \frac{P}{3\kappa}R_i^3\left(\frac{1}{R_g} - \frac{1}{R_0}\right). \tag{4.11}$$

In principal, the problem is now solved. The last two formulas relate both $R_g(t)$ and $R_i(t)$ to the outer radius $R_0(t)$ and their replacement in (4.2) enables the integration of that equation. The procedure is elementary but the calculation is not trivial. At least three stages of development must be examined separately (depending on the value of $\max(R_i, R_g)$) and all special cases, conditions, and constraints sorted out. Qualitatively, the period of exponential growth is followed by central necrosis and a build-up of inhibitory chemical which, if and when it exceeds the critical level, introduces the final phase of growth retardation. A quantitative description requires more effort, but since the mathematics involved is straightforward only the barest details of analysis are presented here.

The value of the outer radius at which central necrosis first occurs is

$$R_c = \left[\frac{6k}{A}(\sigma_\infty - \sigma_l)\right]^{1/2}. \tag{4.12}$$

Following Burton [1], it is convenient to use this distance in making the problem dimensionless and to this end new variables are introduced

$$\xi = \frac{R_0(t)}{R_c}, \qquad \zeta = \frac{R_g(t)}{R_c}, \qquad \eta = \frac{R_i(t)}{R_c}. \tag{4.13}$$

In this notation, the initial radius of the colony is $\xi(0) = R_0(0)/R_c$, the development of the necrotic core begins when $\xi = 1$ and continues for all $\xi > 1$. Growth retardation due to the presence of a chemical inhibitor occurs only when, and if, $\zeta \geq \eta$ and in all circumstances, $\xi \geq \zeta$, $\xi \geq \eta$.

The dimensionalization is completed by replacing time t by

$$\tau = st, \qquad \frac{d}{dt} = s\frac{d}{d\tau}. \tag{4.14}$$

Since $1/s$ is essentially related to the "doubling" time for pure exponential growth of the population, τ measures time with respect to this basic unit.

As a result of substituting these variables in all equations and boundary conditions, two basic dimensionless numbers appear

$$Q^2 = \frac{\beta_1 \kappa A}{(\sigma_\infty - \sigma_1)kP}, \qquad \gamma = \frac{\lambda}{s}. \tag{4.15}$$

The solution then takes the form exemplified by

$$\xi = \xi(\tau, Q, \gamma) \quad \text{with} \quad R_0(t) = R_c\xi(\tau, Q, \gamma), \quad \text{etc.}$$

The specification of parameters relates the theory to any particular experimental situation, i.e., cell strain, nutrient levels, etc.

The dimensionless versions of equations (4.2), (4.10) and (4.11) are

$$\xi^2\frac{d\xi}{d\tau} = \tfrac{1}{3}(\xi^3 - \max(\zeta^3, \eta^3)) - \gamma\eta^3, \tag{4.16}$$

$$\begin{aligned} 1 &= \xi^2 - \eta^2 + 2\eta^3\left(\frac{1}{\xi} - \frac{1}{\eta}\right), \quad \xi \geq 1 \text{ only;} \\ \frac{Q^2}{2} &= \eta^3\left(\frac{1}{\zeta} - \frac{1}{\xi}\right), \quad \xi \geq \zeta \geq 1, \quad \zeta \geq \eta \text{ only.} \end{aligned} \tag{4.17}$$

In order for the inhibitor to retard the growth of living cells, the concentration of β must reach the critical value β_1 at the necrotic interface $r = R_i(t)$ at some point in the development of the tumor. This occurs when (and if) $\zeta = \eta$ at which time the outer radius is $\xi = \xi_* > 1$. The physical interpretation is that β builds up and diffuses faster than the necrotic core expands. This second critical radius ξ_* is calculated from (4.16) and (4.17). With $\zeta = \eta$, it follows that

$$\xi_* = Q(2x_*^2(1 - x_*))^{-1/2}$$

where

$$x_* = \left(1 + 3\left(1 + \frac{8}{9Q^2}\right)^{1/2}\right) \Big/ \left(4\left(1 + \frac{1}{Q^2}\right)\right). \tag{4.18}$$

The tumor does not reach this crucial size when the rate of volume loss in the necrotic core is sufficiently large. In this event, the nodule consists of only two distinct layers—an inner sphere of cellular debris enveloped by a growth layer of active mitosis that contains all the live cells. A criterion for such a situation, derived below, involves the relative magnitudes of the parameters Q and γ, that characterize competing physical processes.

The variables

$$x = \eta/\xi, \quad y = \zeta/\xi \tag{4.19}$$

facilitate the mathematical operations and allow the various stages of tumor development to be described succinctly. Only a summary of results is given here; the analytical details are not difficult to reproduce.

Phase I: A period of exponential growth of the tumor until the onset of necrosis.

Range of variables:

$$\xi(0) \leq \xi(\tau) \leq 1.$$

Constraints:

$$\eta \equiv 0, \qquad \zeta \equiv 0.$$

Growth equation:

$$3\xi^2 \frac{d\xi}{d\tau} = \xi^3.$$

Method: Explicit integration.

Solution:

$$\xi(\tau) = \xi(0)\, e^{\tau/3}, \qquad \eta(\tau) = \zeta(\tau) \equiv 0. \tag{4.20}$$

Time period:

$$0 \leq \tau \leq \tau_1 = -3 \log \xi(0).$$

Discussion: The tumor grows at an exponential rate until the first cell at the center of the sphere dies from lack of sufficient nutrient.

Phase II: A period of growth retardation of the tumor due to the death of cells, which lasts from the onset of necrosis until the inhibitor concentration at the necrotic interface reaches the critical level or the tumor achieves a steady state.

Range of variables:

$$1 \leq \xi \leq \min(\xi_*, \xi_l), \qquad 0 \leq x \leq \min(x_*, x_l)$$

where

$$x_l = (1 + 3\gamma)^{-1/3}, \qquad x_* = \left(1 + 3\left(1 + \frac{8}{9Q^2}\right)^{1/2}\right) \Big/ 4(1 + 1/Q^2), \tag{4.21}$$

$$\xi = F(x) = [(1 - x)^2(1 + 2x)]^{-1/2}, \tag{4.22}$$

and

$$\xi_l = F(x_l), \qquad \xi_* = F(x_*).$$

Constraints: For

$$\zeta \leq \eta, \qquad 1 = \xi^2 - \eta^2 + 2\eta^3\left(\frac{1}{\xi} - \frac{1}{\eta}\right).$$

Growth equation:

$$3\xi^2\frac{d\xi}{d\tau} = \xi^3 - (1 + 3\gamma)\eta^3$$

with

$$\xi = 1, \qquad x = 0 \quad \text{at} \quad \tau = \tau_1 = -3\log\xi(0).$$

Method: Change of variable to x and exact integration to obtain x as an implicit function of time.

Formulation:

$$\frac{9x}{(1 + 2x)(1 - x)(1 - (1 + 3\gamma)x^3)}\frac{dx}{d\tau} = 1, \tag{4.23}$$

Solution:

$$\begin{aligned}\frac{3}{2}x_l^2\frac{(1 + x_l + 4x_l^2)}{(1 - x_l + 3x_l^2 + 2x_l^3 + 4x_l^4)}\log\left[\left(\frac{x}{x_l}\right)^2 + \frac{x}{x_l} + 1\right] \\ - \frac{3^{3/2}x_l(1 - x_l)}{1 - x_l + 3x_l^2 + 2x_l^3 + 4x_l^4}\left[\tan^{-1}\frac{1}{\sqrt{3}}\left(\frac{2x}{x_l} + 1\right) - \tan^{-1}\frac{1}{\sqrt{3}}\right] \\ - \frac{3x_l^2}{(1 + x_l - 2x_l^2)}\log\left(1 - \frac{x}{x_l}\right) - \frac{12x_l^3}{1 + 8x_l^3}\log(1 + 2x) \\ + \frac{3x_l^3}{1 - x_l^3}\log(1 - x) = \tau - \tau_1.\end{aligned} \tag{4.24}$$

Time period: If $x_l < x_*$ then the elapsed time, $\tau - \tau_1$, ranges from zero to infinity. However, most of the development is completed when $\tau - \tau_1 = O(1/\gamma)$ (and γ is small).

If $x_* < x_l$, the second stage ends at time $\tau = \tau_*$ when $x = x_*$.

Discussion: Tumor growth in the second phase, as described in (4.23) and (4.24), is illustrated in Figure 2 for several values of γ. The growth either proceeds to a final steady state or it terminates at some point with the onset of phase III. The cutoff condition depends on the values of γ and Q.

(a) If $x_l < x_*$ then the tumor grows to its steady state given by $x_\infty = x_l, \xi_\infty = \xi_l$. Since chemical retardation is not a factor in this case, the final nodule consists of only two distinct regions, a spherical shell of growing cells that surrounds the inner necrotic core. Complete cell proliferation is required to balance the volume loss in necrosis. The radius of the tumor is finite for all $\gamma \neq 0$ and the approach

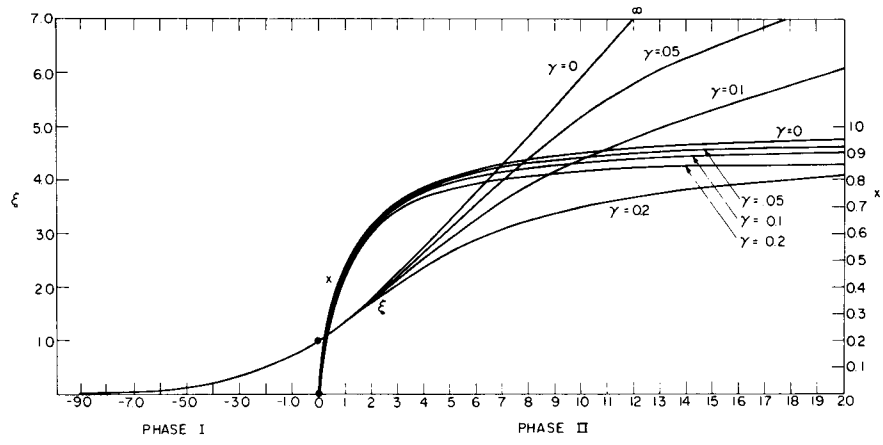

Figure 2. Phases I and II in the development of a solid carcinoma with growth retardation due to necrotic debris.

to the dormant state is exponential with the characteristic time scale $O(1/\gamma)$. For the special value $\gamma = 0$, i.e., $x_l = 1, \xi_l = \infty$, the steady state radius is infinite, the layer of growing cells is infinitesimally thin and (4.24) reduces to

$$\log(x^2 + x + 1) - \tfrac{4}{3}\log(1 + 2x) - \tfrac{2}{3}\log(1 - x) + \frac{x}{1 - x} = \tau - \tau_1. \quad (4.25)$$

This is the exact time-dependent solution of an analogous problem considered by Burton [1]. (The asymptotic approach to steady state is, in this circumstance, algebraic and $x \sim \tau/(1 + \tau), \xi \sim \tau/\sqrt{3}$).

(b) If $x_l > x_*$, which in view of experimental information is of greatest interest, phase II lasts until the concentration β_l is reached at the necrotic interface. This occurs when the tumor radius is $\xi_*(Q)$ as given in (4.18). The cut-off conditions depend only on Q and are shown in Figure 3.

For nodular carcinomas grown in vitro, $Q < 1, \gamma < 1$ appears to be the relevant parameter range and for these values, the second stage is of a fairly short duration. The tumor grows almost linearly with time during this interval which has been described accordingly as a phase of linear growth.

Phase III: A period of retarded tumor growth due to the death of cells *and* chemical inhibition of mitosis, which begins when $\beta = \beta_l$ at the necrotic interface and lasts until the dormant steady state is achieved.

Range of variables: $\xi_* \leq \xi \leq \xi_\infty$, $x_* \leq x \leq x_\infty$ where ξ_∞, x_∞ are the steady state values.

Constraints:

$$\xi \geq \zeta \geq \eta, x_l > x_*$$

$$1 = \xi^2 - \eta^2 + 2\eta^3\left(\frac{1}{\xi} - \frac{1}{\eta}\right)$$

$$\tfrac{1}{2}Q^2 = \eta^3\left(\frac{1}{\zeta} - \frac{1}{\eta}\right)$$

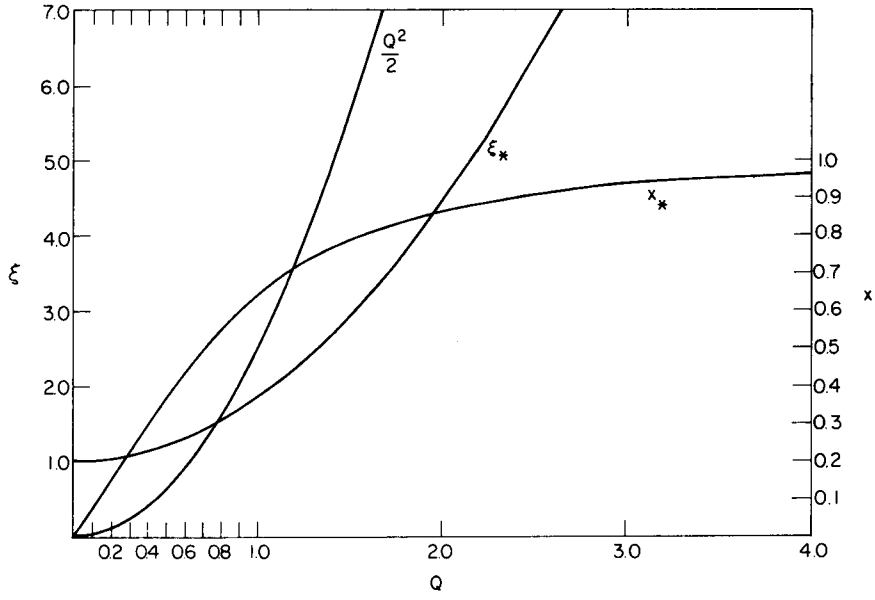

Figure 3. Critical values ξ_* and x_* versus Q at the end of phase II and the onset of phase III.

Growth equation:

$$3\xi^2 \frac{d\xi}{d\tau} = \xi^3 - \zeta^3 - 3\gamma\eta^3. \tag{4.25}$$

with initial conditions $\xi = \xi_*, x = x_*, \zeta = \eta$ at $\tau = \tau_* = \tau_2$.

Method: Change of variables to x, y and *numerical* integration to obtain all variables as functions of time.

Formulation:

$$\frac{9x}{(1 + 2x)(1 - x)} \frac{dx}{d\tau} = 1 - y^3 - 3\gamma x^3$$

$$\xi = [(1 - x^2)(1 + 2x)]^{-1/2}, \qquad \frac{Q^2}{2\xi^2} = x^3\left(\frac{1}{y} - 1\right) \tag{4.26}$$

with $x = x_* = y, \xi = \xi_*$ at $\tau = \tau_*$ (see (4.21) and (4.24)).

Solution: The numerical integration proceeds forward in time until solution curves asymptote to their final steady state values, $x_\infty, y_\infty, \xi_\infty$ which are solutions to the preceding system of equations with $dx/d\tau = 0$.

If γ and Q are moderately small and

$$\mu = \frac{Q^2}{2\gamma} \tag{4.27}$$

then an excellent approximate equation for the steady state is

$$\mu(1 - x_\infty)^2(1 + 2x_\infty) = x_\infty^6 \tag{4.28}$$

Figure 4 shows the corresponding values of $\mu, x_\infty, \xi_\infty$, the thickness of the viable layer $\xi_\infty - \eta_\infty$, and the radius η_∞ of the necrotic core. The thickness of the spherical shell of proliferating cells is

$$\xi_\infty - \zeta_\infty = \left(\frac{Q^2\gamma}{2}\right)^{1/2} = \mu^{1/2}\gamma. \tag{4.29}$$

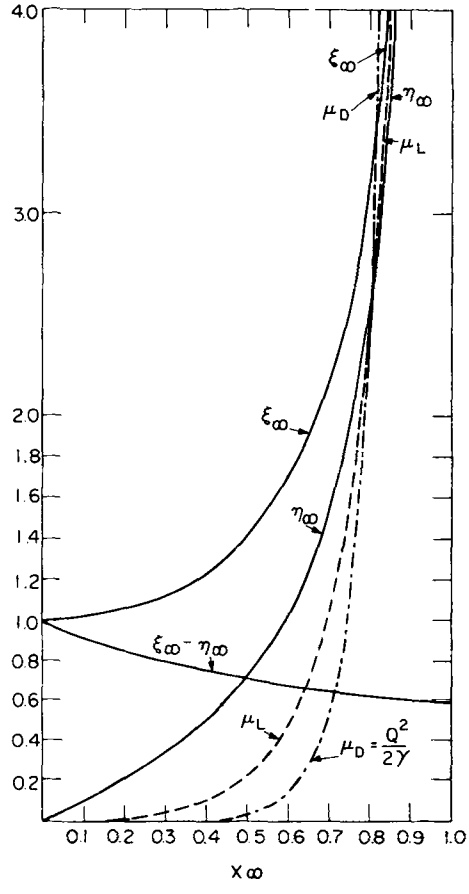

Figure 4. Steady state values of the outer radius of the tumor ξ_∞, the inner radius of the necrotic core η_∞, and the thickness of the viable layer, $\xi_\infty - \eta_\infty$, versus x_∞. Values of $Q^2/2\gamma$ corresponding to the models of § 4 and § 5 are the curves labelled μ_D and μ_L, respectively.

Some useful asymptotic formulas are:

for

$$\mu \ll 1, x_\infty \simeq \mu^{1/6}, \qquad \xi_\infty \simeq 1 - \mu^{1/2}\gamma, \qquad \xi_\infty - \eta_\infty \simeq 1 - \mu^{1/6},$$

$$y_\infty \simeq 1 - \mu^{1/2}\gamma;$$

for

$$\mu \gg 1, x_\infty \simeq 1 - (3\mu)^{-1/2}, \qquad \xi_\infty \simeq \mu^{1/2}, \qquad \xi_\infty - \eta_\infty \simeq 3^{-1/2}, \qquad y_\infty \simeq 1 - \gamma.$$

Time period: Although an infinite time interval is required to reach the steady state, the third state is essentially completed in a time the order of $1/\gamma$.

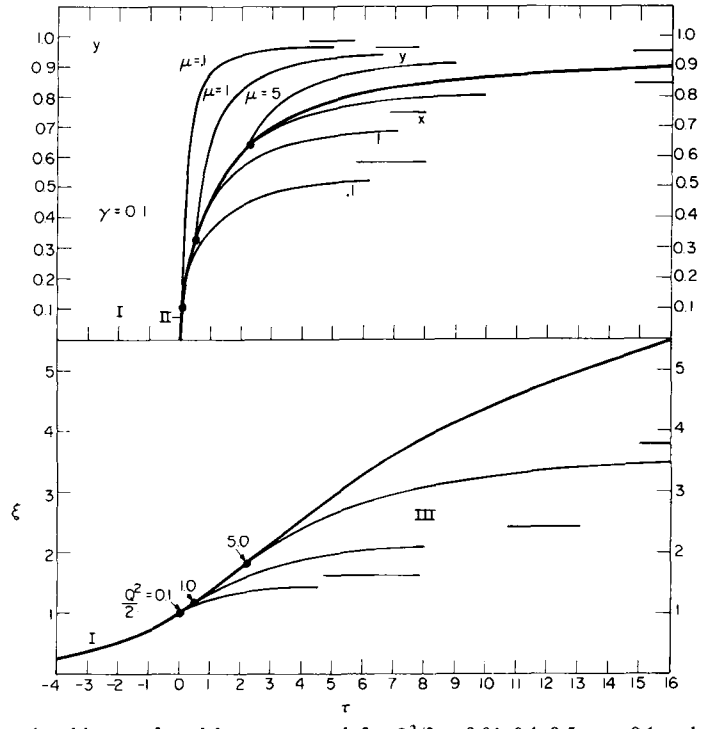

Figure 5. Complete history of model tumor growth for $Q^2/2 = 0.01, 0.1, 0.5$; $\gamma = 0.1$ and $\mu = 0.1, 1.5$. Phase II, which begins at $\tau = 0$ in relative time, ends with the bifurcation of the curves for y and x. Stage II is short in each of the three cases and the growth rate is approximately linear.

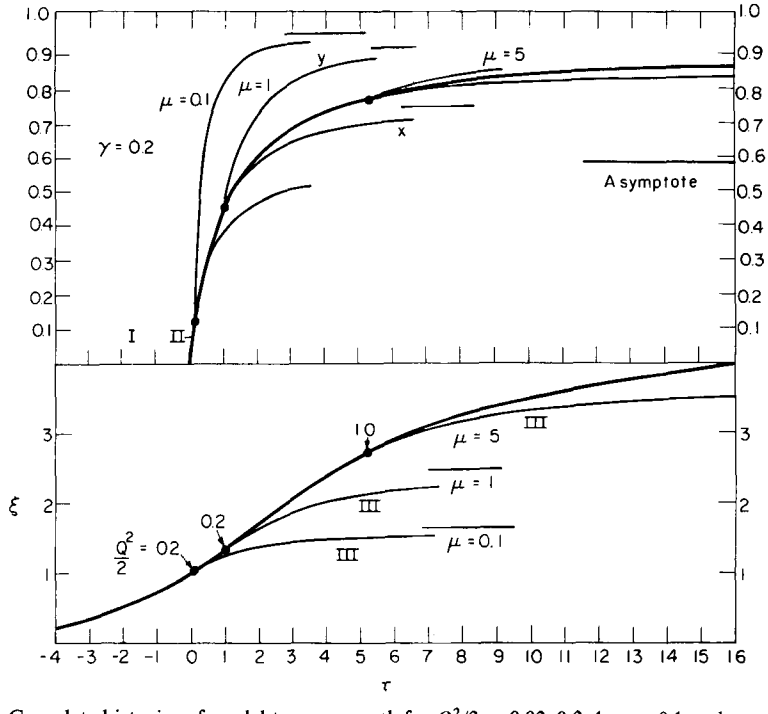

Figure 6. Complete histories of model tumor growth for $Q^2/2 = 0.02, 0.2, 1$; $\gamma = 0.1$ and $\mu = 0.1, 1, 5$.

Discussion: The development of the tumor in phase II is specified by the value of γ and the corresponding growth curves are shown in Fig. 2. If $x_* < x_l$, the third and final stage is marked by the onset of mitotic inhibition, that is $R_g = R_i$ or $y = x = x_*(Q)$ and $\xi = \xi_*(Q)$. The point of transition on any particular phase II growth curve depends only on the magnitude of Q and may be obtained from Figure 3. Thereafter, the radius R_g expands quickly towards its asymptote while the growth rates of $\xi(\tau)$, $x(\tau)$ diminish. These effects are shown in Figures 5 and 6 which are complete histories of model tumor growth at representative and realistic parameter settings. (The final layer of growing cells, given by (4.29), is known to be thin and examination of cross-sections of nodules in the steady state indicate that λ and Q are moderately small.)

The rate of volume loss per unit volume in the necrotic core controls the rapidity at which the steady state is approached. In dimensional units, $t = O(1/\lambda)$ characterizes the main period of activity in the last phase of growth.

5. Growth retardation due to wastes from living cells

The chemical inhibitor is now assumed to be a product solely of the metabolic processes of living cells and no katabolites are associated with necrosis. Only assumption (i) in the model of Section 4 is changed to read as follows:

(i) The inhibitor $\beta(r, t)$ is produced by living cells at a constant rate P per unit volume.

For spherical nodules, the inhibitor is produced in the annular shell of viable cells, $R_i(t) \leq r \leq R_0(t)$. The diffusion equation (4.4) is replaced by

$$\frac{1}{r^2}\frac{\partial}{\partial r}r^2\frac{\partial}{\partial r}\beta(r, t) = -\frac{P}{\kappa}H(R_0(t) - r)H(r - R_i(t)). \tag{5.1}$$

All other equations and boundary conditions remain the same. The solution of the problem is now

$$R_i(t) \leq r \leq R_0(t)\begin{cases}\sigma = \sigma_\infty - \dfrac{A}{6k}(R_0^2 - r^2) + \dfrac{AR_i^3}{3k}\left(\dfrac{1}{r} - \dfrac{1}{R_0}\right), \\ \beta = \dfrac{P}{3\kappa}\left[\dfrac{1}{2}(R_0^2 - r^2) - R_i^3\left(\dfrac{1}{r} - \dfrac{1}{R_0}\right)\right];\end{cases} \tag{5.2}$$

$$r \leq R_i(t)\begin{cases}\sigma = \sigma_l, \\ \beta = \beta_i(t)\end{cases} \tag{5.3}$$

It follows from the boundary conditions that for $R_i > 0$.

$$\beta_i = \frac{P}{3\kappa}\left[\frac{1}{2}(R_0^2 - R_i^2) - R_i^3\left(\frac{1}{R_i} - \frac{1}{R_0}\right)\right], \tag{5.4}$$

$$\sigma_\infty - \sigma_l = \frac{A}{3k}\left[\frac{1}{2}(R_0^2 - R_i^2) - \frac{R_i^2}{R_0}(R_0 - R_i)\right], \tag{5.5}$$

and if $\beta > \beta_l$ somewhere, the growth radius is given by

$$\beta_l = \frac{P}{3\kappa}\left[\frac{1}{2}(R_0^2 - R_g^2) - R_i^3\left(\frac{1}{R_i} - \frac{1}{R_g}\right)\right]. \tag{5.6}$$

Once again let R_c denote the outer radius when $\sigma = \sigma_l$ at the center of the nodule and necrosis due to nutritional deficiency begins. The problem is made dimensionless as before so that (5.5) and (5.6) become

$$1 = \xi^2 - \eta^2 + 2\eta^3\left(\frac{1}{\xi} - \frac{1}{\eta}\right), \qquad \text{for } \xi \geq 1, \tag{5.7}$$

$$Q^2 = \xi^2 - \zeta^2 + 2\eta^3\left(\frac{1}{\xi} - \frac{1}{\zeta}\right), \qquad \text{for } \zeta > \eta. \tag{5.8}$$

The growth equation is still

$$\xi^2\frac{d\xi}{d\tau} = \frac{1}{3}(\xi^3 - \max(\zeta^3, \eta^3)) - \gamma\eta^3, \tag{5.9}$$

although the conditions relating the radii R_0, R_g, R_i are modified. It remains to describe the different stages of tumor development.

In this model, the metabolic wastes of viable cells is the source of katabolite within the tumor. For this reason, growth retardation can take place before central necrosis. Indeed, if the core concentration of inhibitor does not reach the critical level β_l by the onset of necrosis, growth retardation *never* occurs. To see this, suppose that there is retardation and $\beta = \beta_l$ in the spherical annulus of live cells, that is $R_i \leq R_g \leq R_0$ or $\eta \leq \zeta \leq \xi$. The result of subtracting (5.8) from (5.7) is, upon rearrangement,

$$1 - Q^2 = \frac{1}{\zeta}(\zeta - \eta)^2(\zeta + 2\eta)$$

which shows that $Q^2 \leq 1$ is a necessary condition for growth inhibition. For values $Q^2 > 1$, the level $\beta = \beta_l$ is never attained; if $Q^2 = 1$, $\eta = \zeta \leq \xi$ and $R_i(t) \equiv R_g(t)$ for all time.

There are three phases of development in tumors which exhibit growth retardation. The first is a period of exponential growth which lasts until the concentration of inhibitor at the center of the nodule reaches the critical level β_l. This is followed by a period of retarded growth, during which the tumor consists of an outer mantle of dividing cells and an inner viable core. In the third stage, marked by the onset of central necrosis, the tumor evolves into its final steady state.

Growth inhibition caused by nutrient deficiency has exactly the same effects on the tumor as that of a katabolite from metabolic wastes. As a matter of fact, let $\sigma > \sigma_g$ be a necessary condition on nutrient concentration for the growth of cells, then the identifications

$$\beta = \sigma_\infty - \sigma, \qquad \beta_l = \sigma_\infty - \sigma_g, \qquad A = -P, \qquad k = \kappa$$

transform the model under discussion to one with retardation due to nutrient deficiency.

The results of analysis for each phase of development are summarized next.

Phase I: A period of exponential growth of the tumor until the inhibitor concentration at $r = 0$ reaches the critical level for retardation.

Range of variables:

$$\xi(0) \leq \xi \leq Q.$$

Constraints:

$$\eta \equiv 0, \qquad \zeta \equiv 0.$$

Growth equation:

$$3\xi^2 \frac{d\xi}{d\tau} = \xi^3.$$

Method: Explicit integration.
Solution:

$$\xi(\tau) = \xi(0)\, e^{\tau/3}, \qquad \eta \equiv 0 \equiv \zeta.$$

Time period:

$$0 \leq \tau \leq 3 \log(Q/\xi(0)) = \tau_1.$$

Discussion: The tumor develops at an exponential rate until growth retardation occurs at the center of the spherical nodule (which happens before the onset of central nectrosis, i.e., $\xi \leq 1$).

Phase II: A period of retarded growth due to the accumulation of wastes from the living cells in excess of critical concentration, which lasts until a necrotic core forms.
Range of variables:

$$Q \leq \xi \leq 1, \qquad 0 \leq y \leq (1 - Q^2)^{1/2}.$$

Constraints:

$$x \equiv 0, \qquad Q \leq 1, \qquad Q^2 = \xi^2 - \zeta^2.$$

Growth equation:

$$3\xi^2 \frac{d\xi}{d\tau} = \xi^3 - \zeta^3. \tag{5.10}$$

Method: Change of variable to y and exact integration to obtain y as an implicit function of time.
Formulation:

$$\frac{3y}{(1 - y^2)(1 - y^3)} \frac{dy}{d\tau} = 1 \tag{5.11}$$

with

$$y = 0 \text{ at } \tau = \tau_1, \quad \text{and} \quad \xi = Q(1 - y^2)^{-1/2}.$$

Solution:

$$\frac{2y}{1 - y} - 3 \log(1 - y^2) + 2 \log(1 - y^3) - \frac{4}{\sqrt{3}} \left[\tan^{-1} \frac{2y + 1}{\sqrt{3}} - \tan^{-1} \frac{1}{\sqrt{3}} \right] = 4(\tau - \tau_1). \tag{5.12}$$

Time period: This phase ends at time τ_2 when $y = (1 - Q^2)^{1/2}$. For small Q, $\tau_2 - \tau_1 \sim 1/Q^2$.

Discussion: For $Q < 1$, the effect of the inhibitor is to change the initial exponential growth rate to one that is approximately linear in time. This phase begins at $\tau = \tau_1$ and $\xi = Q$ and ends when $\xi = 1, \tau = \tau_2$, with the death of the first cell from nutrient deficiency. Typical growth curves in this phase are shown in Figure 7.

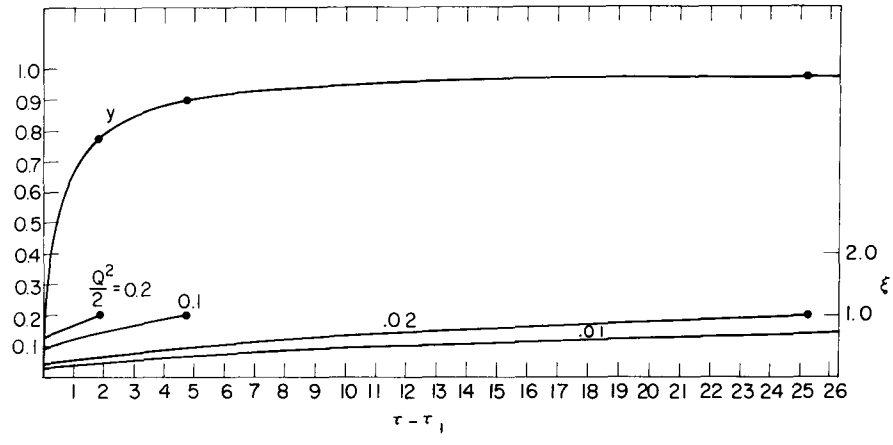

Figure 7. Phase II in the development of a tumor with retardation due to the metabolic wastes of live cells. This stage begins when $\xi = Q$ (the cutoff for the exponential growth period) and ends at $\xi = 1$ and the onset of central necrosis.

The thickness of the layer of dividing cells, measured by $1 - y$, decreases very rapidly and can be characterized as "thin" after an elapsed time of only one or two units. The duration of the second phase approaches zero as Q nears one. For $Q \geq 1$, there is no such period of retardation due to the action of a katabolite because the concentration of inhibitor never reaches the critical level. In this situation, the exponential phase ends with the onset of central necrosis which marks the next and final stage of development.

Phase III: A period of retarded growth due to chemical inhibition of mitosis *and* the death of cells which begins when $\sigma = \sigma_I$ at the center of the nodule and lasts until the steady state is achieved.

Range of variables:

$$1 \leq \xi \leq \xi_\infty, \qquad (1 - Q^2) \leq y \leq y_\infty, \qquad 0 \leq x \leq x_\infty$$

Constraints:

$$\xi \geq \zeta \geq \eta \geq 0,$$

$$1 = \xi^2 - \eta^2 + 2\eta^3\left(\frac{1}{\xi} - \frac{1}{\eta}\right),$$

$$Q^2 = \xi^2 - \zeta^2 + 2\eta^3\left(\frac{1}{\xi} - \frac{1}{\zeta}\right).$$

Growth equation:

$$3\xi^2\frac{d\xi}{d\tau} = \xi^3 - \zeta^3 - 3\gamma\eta^3.$$

Method: Change of variables to ξ, y, x and *numerical* integration to obtain all variables as functions of time.

Formulation:

$$\frac{9x}{(1+2x)(1-x)}\frac{dx}{d\tau} = 1 - y^3 - 3\gamma x^3, \tag{5.13}$$

$$\xi = ((1-x)^2(1+2x))^{-1/2}, \qquad \frac{Q^2}{\xi^2} = 1 - y^2 - 2x^3\left(\frac{1-y}{y}\right), \tag{5.14}$$

with $x = 0$ at $\tau = \tau_2$ (and $y = (1 - Q^2)^{1/2}$, $\xi = 1$).

Solution: The numerical integration proceeds forward in time until the solution curves asymptote to their steady state values x_∞, y_∞, ξ_∞, which are solutions of the preceding system of equations with $dx/d\tau = 0$. For γ and Q moderately small, and $\mu = Q^2/(2\gamma)$ an excellent approximation to the steady state is

$$\mu(1 - x_\infty)(1 + 2x_\infty) = x_\infty^3(1 + x_\infty + x_\infty^2) \tag{5.15}$$

Figure 4 shows the corresponding values of μ, x_∞, ξ_∞, the thickness of the viable layer $\xi_\infty - \eta_\infty$ and the radius η_∞ of the necrotic core. Useful asymptotic formulas may be derived from the approximations $x_\infty \simeq \mu^{1/3}$ for μ small and $x_\infty \simeq 1 - 1/\mu$ for μ large.

Time period: Although an infinite time interval is required to reach the steady state, the final stage of development is essentially completed when $\tau = O(1/\gamma)$.

Discussion: The rate of volume loss per unit volume in the necrotic core controls the rapidity at which the steady state is approached in phase III. In dimensional units the characteristic time interval of major activity is $\tau = O(1/\gamma)$. Complete histories of model tumor growth are shown in Figure 8 for experimental parameter

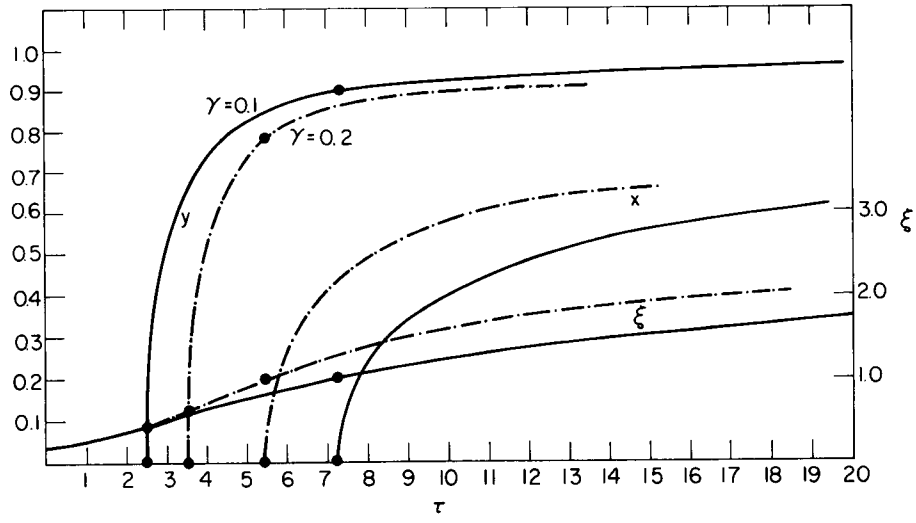

Figure 8. Complete histories of two model tumors corresponding to $Q^2/2\gamma = 1$ and $\gamma = 0.1$, $\gamma = 0.2$. Growth retardation is due to the metabolic wastes of live cells. The three growth phases are separated by large dots.

settings. Stage III, which begins with $\xi = 1$, exhibits a very rapid increase in the size of the necrotic core. However, the layer of proliferating cells is thin at the outset and remains so during the entire evolution. For $Q > 1$, the approach to the steady state is the same as for $Q = 1$, (i.e., $y \equiv x$). In this case, (5.13) becomes

$$\frac{9x}{(1 + 2x)(1 - x)} \frac{dx}{d\tau} = 1 - \left(\frac{x}{x_l}\right)^3$$

where $x_l = (1 + 3\gamma)^{-1/3}$ and the initial condition is $x = 0$ at $\tau = \tau_1 (\equiv \tau_2)$. This problem was solved in the last section, see equation (4.22) and (4.23).

6. Conclusion

By way of conclusion, we illustrate the use of theoretical models in the analysis of a prototype experiment. The objective is to infer the major internal processes affecting tumor growth from the most easily obtained data which are assumed to be

(i) measurements of the outer radius of the nodule as a function of time, i.e., $R_0(t)$;

(ii) a cross section of the final dormant state which provides the final values of R_0, R_g and R_i (tumor radius, growth radius, and radius of the necrotic core as shown in Figure 1).

From the steady state structure of the nodule, that is the radii $R_0(\infty)$, $R_g(\infty)$ and $R_i(\infty)$, two dimensionless values are obtained

$$x_\infty = R_i/R_0, \qquad y_\infty = R_g/R_0.$$

The values of γ and ξ_∞, *which are the same for both models considered,* are then determined from the relationships

$$\xi_\infty = [(1 - x_\infty)^2(1 + 2x_\infty)]^{-1/2}, \qquad y_\infty^3 = 1 - 3\gamma x_\infty^3.$$

However, the value of Q does depend on the model employed, and is calculated from either (4.28) or (5.15).

The outer radius R_c at which central necrosis first occurs can be computed from the scaling rule $R_c = R_0(\infty)/\xi_\infty$. Direct measurements of R_c by histological examinations of nodules in their early phase of growth should confirm this theoretical prediction whatever particular cell strain is used in the experiment.

Since all parameters have now been specified, the growth of a tumor as described by each of the theoretical models may be determined and the curves $R_0(t)$ and $\xi(t)$, graphed. Although the final steady state is the same, the evolutions can be markedly different, depending on the respective values of Q, and a typical example is shown in Figure 9. The comparison of theoretical and experimental growth curves to the *same dormant state* may be decisive evidence in answering the question of whether retardation is due primarily to metabolic wastes or necrosis. (The theory can be readily modified if it turned out that both sources contribute to growth inhibition. Indeed other more complex possibilities are formulated in the Appendix.)

Examination of the nodule at the onset of necrosis should be the best method to decide between the alternative hypotheses of retardation. If growth retardation is observed *before* central necrosis develops, then the implied source of inhibition is the metabolic wastes of live cells. On the other hand, the observation of growth retardation *after* the formation of a necrotic core implies that inhibition is a

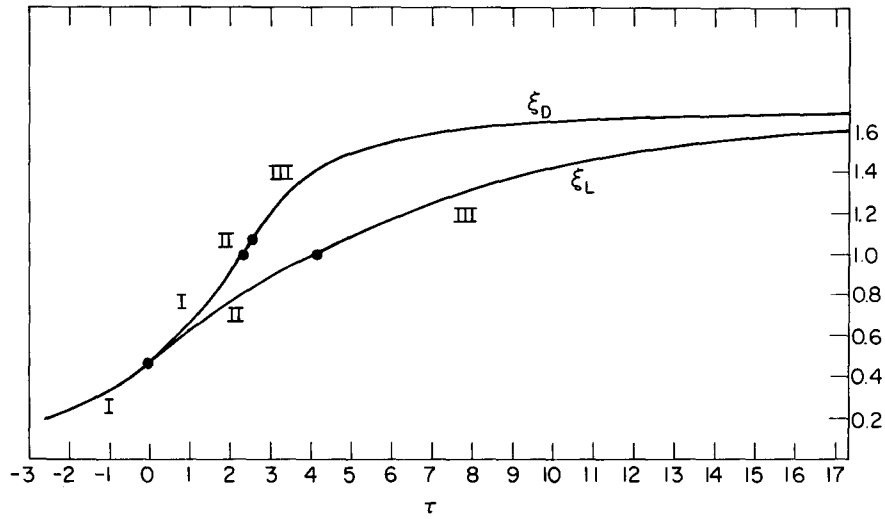

Figure 9. Models of tumor growth to a common steady state. The outer radius is ξ_D, when retardation is due to necrotic debris, and ξ_L when the source of inhibition is metabolic wastes. Time is measured from the point of bifurcation. Values are $y_\infty = 0{\cdot}95$, $x_\infty = 0{\cdot}6$, $\gamma = 0{\cdot}2201$; $Q^2/2 = 0{\cdot}0323$ for ξ_D and $Q^2/2 = 0{\cdot}1062$ for ξ_L.

consequence of necrosis. However, these may be difficult measurements to make with the exactness required because the interfaces that separate proliferating from merely viable cells, or live cells from dead cells, are probably not sharply defined initially when the radii R_g, and R_i are small. The surface $R_g(t)$ is after all an idealiza-

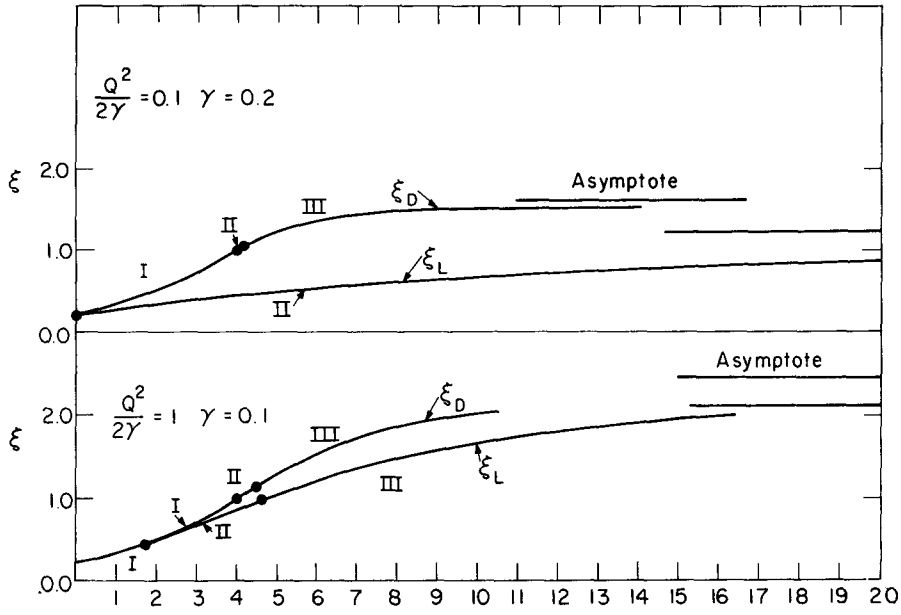

Figure 10. Models of tumor growth for the same parametric values; ξ_D, ξ_L are the outer radii when inhibition is due to dead material or the metabolic wastes of live cells. The three growth phases are separated by large dots. (Phase III for ξ_L in the upper graph begins at time $\tau = 25.3$.)

tion of a thin transition zone, of a certain thickness $L \ll R_0(\infty)$, wherein the mitotic index declines rapidly. The position of the interface is hard to define when $R_g(t) = O(L)$. For this reason, and others, the complete growth history may prove surer and more informative about growth retardation than observations made within a very short definite interval of time. However, Sutherland et al. [10] describe inhibition "shortly after" necrosis.

If the parameters Q and γ are determined a priori (say by directly measuring the rate constants involved) the two models discussed here predict different steady states for the solid tumor. Moreover the characteristic time scales of the transient evolutions can differ by an order of magnitude as illustrated in Figure 10.

Many mathematical models can be constructed by modifying any one of the assumptions or approximations made thus far. A few possibilities will suffice: diffusion constants need not be uniform or for that matter constant; cell proliferation can vary continuously with nutrient and inhibitor concentrations; a cell may collapse upon dying; disintegration and volume loss in the core can depend on position or the elapsed time since death of the cell. Clearly, a greater fund of experimental data is required to select new and perhaps more relevant assumptions as the basis for further theoretical study.

Appendix

The mathematical models examined can be adapted to include processes that are probably important but about which there is as yet little quantitative data. Some of these are as follows:

Let the mass density of necrotic debris, ρ_d, be greater than the corresponding density ρ, of living cells, i.e., $c = \rho_d/\rho > 1$. Since it then takes c cubic centimeters of living cells to make up one cubic centimeter of debris in the necrotic core, the death process involves a volume reduction (analogous to squashing tin cans). The generalization of the conservation of mass law (3.2) to account for such a contraction (all other factors remaining the same) is

$$R_0^2 R_0' = \int_{\max(R_i, R_g)}^{R_0} S(\sigma, \beta) r^2 \, dr - (c - 1) R_i^2 R_i' - c\lambda R_i^3.$$

The velocity at which cells flow across the necrotic interface and die is then

$$U = -(c - 1)R_i' - c\lambda R_i$$

Cell proliferation and the dependence of mitosis on nutrient and inhibitor concentrations can be described by the source distribution

$$S(\sigma, \beta) = s\left(\frac{\sigma - \sigma_l}{\sigma_\infty - \sigma_l}\right)^n \left(\frac{\beta_l - \beta}{\beta_l}\right)^m H(\sigma - \sigma_l) H(\beta_l - \beta),$$

where n, and m are positive constants (to be determined).

Dividing cells must consume more nutrient than those that are viable but dormant. Let A be the rate of nutrient consumption per unit volume that is necessary for sustenence, and $\alpha S(\sigma, \beta)$ represent the additional rate consumption for growth. The diffusion law for nutrient σ is then

$$\frac{\partial \sigma}{\partial t} - \nabla \cdot k \nabla \sigma = -(A + \sigma S) H(r - R_i) H(R_0 - r)$$

where for completeness the time derivative is included and k is not assumed to be constant. Likewise, let the production rates of inhibitor in the necrotic core and by live cells be P_d and P respectively. The diffusion law for the katabolite becomes

$$\frac{\partial \beta}{\partial t} - \nabla \cdot \kappa \nabla \beta = PH(r - R_i)H(R_0 - r) - P_d H(R_i - r).$$

The boundary conditions require that $\kappa\beta_r$, $k\sigma_r$, β, σ are all continuous across the surfaces $r = R_0$, and $r = R_g$. The possibility of an instantaneous and massive release of chemical inhibitor when cells die upon crossing the necrotic interface can be expressed by the condition

$$\kappa\beta_r \Big]_{R_i-}^{R_i+} = -\nu(R_i'(t) - U)H(R_i'(t) - U),$$

where ν is an appropriate rate constant. (The quantities $k\sigma_r$, σ, β are continuous at this surface.)

All functions are bounded at the origin, and initial conditions must be prescribed. If the time derivatives σ_t, β_t are neglected, the general problem is easily solved. However, the effort would be justified, in terms of what is learned, only with more hard data.

7. Acknowledgment

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References

1. Burton, A. C. (1966). Rate of growth of solid tumours as a problem of diffusion. Growth **30**, 157–176.
2. Carslaw, H. S. and Jaeger, J. C. (1959). Conduction of Heat in Solids, Oxford Univ. Press.
3. Crank, J. (1956). The Mathematics of Diffusion. Oxford Univ. Press.
4. Folkman, J. (1971). Tumor angiogenesis: therapeutic implications. New Eng. J. of Med. **285**, 1182–1186.
5. Folkman, J. Anti-angiogenesis: new concept for therapy of solid tumors. Ann. Surg. (in press).
6. Folkman, J., Merler, E., Abernathy, C., et al.: (1971). Isolation of a tumor factor responsible for angiogenesis. J. Exp. Med. **133**, 275–288.
7. Hill, A. V. (1928). The diffusion of oxygen and lactic acid through tissues. Proc. Roy. Soc. Lind. B. **104**, 39–96.
8. Inch, W. R., McCredie, J. A., and Sutherland, R. M. (1970). Growth of nodular carcinomas in rodents compared with multi-cell spheroids in tissue culture. Growth **34**, 271–282.
9. Sutherland, R. M., Inch, W. B. and McCredie, J. A. (1970). A multi-component radiation survival curve using an in vitro turnover model. Int'l J. of Radiation Bio. **18**, 491–495.
10. Sutherland, R. M., McCredie, J. A., and Inch, W. R. (1971). Growth of multicell spheroids in tissue culture as a model of nodular carcinomas. J. Nat. Cancer Inst. **46**, 113–120.
11. Thomlinson, R. H. and Gray, L. H. (1955). The histological structure of some human lung cancers and the possible implications for radio therapy. Brit. J. Cancer, **9**, 539–549.