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IMMUNOLOGICAL SURVEILLANCE AND NEOPLASTIC DEVELOPMENT

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1. **Introduction.** In 1908 Ehrlich suggested that one of the functions of the immune system is to prevent the development of neoplasia; see [8]. It appears that his remarks went unnoticed until the late 1950's. Thomas [17] pointed out that it is unlikely that transplantation immunity developed as a means of defending one animal against surgically transplanted homografts from another animal. He said: "It is a universal requirement of multicellular organism—to preserve uniformity of cell type . . . the phenomena of homograft rejection will turn out to represent a primary mechanism for natural defense against neoplasia." This suggests that immunity as we know it in vertebrates had not necessarily evolved to be a primary defense against invasion by micro-organisms. Burnet [2, 3] has elaborated on the immune surveillance concept. Observations indicate that many malignant cells possess antigens which are distinct from those on their (normal) progenitors. In principle, the concept suggests that, under certain circumstances, these antigens elicit an immune response and this cell mediated immunity might play a major role in combating incipient neoplastic lesions.

The immunological surveillance concept came to be widely accepted by 1970. There are a number of reviews of the extensive data which apparently support the concept; see e.g., [18]. Burnet [3] provided a background of the historical and theoretical aspects of immunological surveillance in neoplastic development.

However, in [12], on the basis of the available evidence, it was suggested that the concept should be questioned for there were situations in which the immune system apparently facilitated the development of tumors. More detailed investigations by Prehn followed in [13] and [14]. Other related work appears in [10], [9] and [19]. The most recent critical surveys of the concept of immune surveillance and neoplasia appear to be those contained in [5] and [1]; see [7] for specific mathematical problems in this area.

DeLisi [5] presents a significant amount of evidence which conflicts with the immune surveillance concept. For example, it is found that, when varying doses of tumor are transplanted into normal syngeneic recipients, the probability of survival does not increase monotonically

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with the dose. A sufficiently small dose (even of the order of 40 cells) sometimes has a better chance of survival than doses which are more than one hundred times greater. There is no obvious explanation for this "sneaking through" phenomenon. The reader is referred to [5] for considerably more details of the conflicting evidence.

2. **A Mathematical Model for Tumor-Lymphocyte Interaction.** Since there is a certain amount of evidence (pro and con) for the immune surveillance concept it is of interest to study a dynamical mathematical model of a simple system. Such a model is developed and analyzed in [6]. DeLisi and Rescigno consider the dynamics of a solid tumor in the presence of a specifically reactive lymphocyte population which is stimulated by, and antagonistic to, the tumor. They assume that the interaction between lymphocytes and tumor cells takes place on the surface of the spherical tumor. For the situation of a steady rate of lymphocytes entering the system (as might be expected in an *in vivo* situation) their mathematical model takes the form

$$\frac{dx}{dt} = -\lambda_1(x - x_0) + \frac{\alpha_1 x y^{2/3}}{1 + x}\left(1 - \frac{x}{x_c}\right) = f_1(x, y),$$

$$\frac{dy}{dt} = \lambda_2 y - \frac{\alpha_2 x y^{2/3}}{1 + x} = y^{2/3} g(x, y),$$

where λ_1, α_1, λ_2 and α_2 are constant (positive) parameters with dimension of $(\text{time})^{-1}$, t is the time variable, x_c (>0) is proportional to the maximum number of lymphocytes, x_0 (>0) is proportional to the source strength, x (>0) is proportional to the number of lymphocytes and y (>0) is proportional to the number of tumor cells. The full assumptions and details leading to these two equations are in [6] or [16, Chapter 12].

The two differential equations for x and y exhibit a rich collection of behaviors in the phase plane. For example, $(x_0, 0)$ is a locally stable critical point, (x_1, y_1) and (x_3, y_3) are saddle points, and (x_2, y_2) is a center; the abscissae of these four critical points are arranged as $x_0 < x_1 < x_2 < x_3$. Of special interest is the fact that there is a limit cycle surrounding S_2. This result was not anticipated and it seems somewhat surprising that (depending on certain combinations of the parameters and constants in the equations) there could possibly exist sustained oscillations for both the lymphocyte and tumor cell populations. It is not yet known if real tumors have ranges of the numerical values of λ_1, λ_2 etc. which are in accordance with the requirements in the mathematical model of these quantities to produce limit cycle oscillations. (Mathematically, the existence and stability of the limit cycle

can be demonstrated by appeal to the Hopf bifurcation theorem.)

The assorted phase plane behaviors make predictions about the possible results involving syngeneic tumor transplants (i.e., transplantation of a tumor from a donor to a genetically identical recipient), in accordance with the experimental evidence. Also, if prior to transplantation the recipient is treated with lymphocytes, which are specifically reactive against the tumor (so-called adaptive transfer) the model predicts that the chance of survival increases, again in agreement with experimental observation. In fact it is encouraging that there are many points of agreement between the mathematical model and experimental results.

The complete mathematical analysis of the phase plane behaviors is in Chapter 12 of [16].

In the differential equations the effect of the spherical geometry of the tumor occurs via the two-thirds power of y. For a non-spherical tumor the ratio of surface area to volume is of the form (radius)$^{\nu}$. Accordingly if 2/3 is replaced by ν then the equations for the interaction of lymphocytes with the non-spherical tumor take the form

$$\frac{dx}{dt} = -\lambda_1(x - x_0) + \frac{\alpha_1 y^{\nu} x}{1 + x}\left(1 - \frac{x}{x_c}\right),$$

$$\frac{dy}{dt} = \lambda_2 y - \frac{\alpha_2 x y^{\nu}}{1 + x}.$$

There is no difficulty in analyzing the phase plane behaviors of these equations.

A growing tumor tends to become vascularised and have its own circulation, see, e.g., [11]. Lymphocytes are transported by the circulation to portions of the interior of a solid tumor and so one would anticipate an interaction between the lymphocytes and tumor cells throughout the tumor and *not* just on its surface, as DeLisi and Rescigno have assumed. However, a growing solid tumor is a complicated entity to mathematically model and it remains a challenge to develop more biologically realistic models, which are also amenable to mathematical investigation.

3. **Cytotoxic Drug Interaction with Immune Surveillance.** Define

$$U(t - a) = \begin{cases} 0, & t - a < 0, \\ 1, & 0 < t - a < b - a, \quad 0 < a < b. \end{cases}$$

Assume that a cell cycle *nonspecific* drug is injected into a patient at time t_0. The simplest assumption on the drug kinetics is that the drug concentration decays exponentially. This can be represented mathemati-

cally by the equation $dv/dt = -\beta v$, where β^{-1} is the characteristic time constant for the drug and v is its concentration. If the magnitude of the dosage is v_0 at $t = t_0$ then

$$v(t) = v_0 \exp[-\beta(t - t_0)]\, U(t - t_0).$$

For m equally spaced injections of equal size then

$$v(t) = v_0 \sum_{i=1}^{m} \exp[-\beta\,(t - (i - 1)T - t_0)]$$

$$U[t - (i - 1)T - t_0],$$

where T is the time interval between doses.

It is reasonable, in a first approximation, to assume that the action of the (drug) control agent at time t is proportional to the number of tumor cells at time t (and hence also to $y(t)$) and to express it in the form $f(v)y$. Here $f(v)$ is the rate of control per the nondimensional level y and is a function of the control variable v, which may now be interpreted as the actual magnitude of the cycle nonspecific drug level at the tumor site. The rate of control, $f(v)$, is often of a saturating type with

$$f(v) = pv/(q + v), \quad p > 0,\ q > 0$$

and p and q are constants.

The basic equations now take the form

$$\dot{x} = f_1(x, y) - \gamma_1 f(v)x,$$

$$\dot{y} = y^{2/3} g(x, y) - \gamma_2 f(v)y,$$

where, in the first equation, the second term indicates that the drug will have the effect of diminishing the rate of increase of mature lymphocytes. In these equations the quantity v is a function of time of the form shown earlier for equally spaced injections. Accordingly in order to make progress the differential equations need to be integrated numerically for appropriate values of the parameters λ_1, λ_2 etc. Unhappily, this information does not yet appear to be available, even for breast carcinomas.

A different type of problem may now be considered. One may specify that, over a treatment period involving kT, k a positive integer, the level of lymphocytes must not fall below a preassigned number and simultaneously the level of tumor cells must be below a given number. Such a problem leads to an "optimal" control problem for the determination of the level of $v(t)$ which optimizes the appropriate performance

criterion subject to the corresponding system equations. Of course there are many optimization problems that can be formulated. Again there is the difficulty in that one does not have information on the numerical ranges of the parameters in the mathematical model.

Extensions to problems involving cell cycle specific drugs and the combination of different drugs involve similar difficulties.

4. **A Three Level Population Dynamics Model.** To account for the occurrence of *de novo* tumors, Rescigno and DeLisi [15] introduce a three population model—immature lymphocytes (L_1), mature lymphocytes (L_2) and tumor cells. There is no restriction to spherical geometry. In terms of the non-dimensional numbers x (proportional to L_1) y (proportional to L_2) and z which is proportional to the total number of tumor cells their basic equations take the form

$$\dot{x} = -\lambda_1(x - x_0) + \alpha_1[yz/(1 + y)] \exp(-y/y_c),$$

$$\dot{y} = \lambda_1 x - \alpha_3 y, \quad \dot{z} = (\lambda_2 - \alpha_2 y)z/(1 + y),$$

where x_0 is representative of the source of immature lymphocytes and λ_1, λ_2, α_1, α_2, α_3 and y_0 are positive constants; also $x > 0$, $y > 0$, and $z > 0$.

When $x_0 < \alpha_3\lambda_2/\alpha_2\lambda_1$ there are two critical points in the first octant, which is divided into eight regions by the intersections of the planes and surface given by the solution of $\dot{x} = \dot{y} = \dot{z} = 0$. It can be demonstrated that (1) a limit cycle oscillation exists with the closed curve passing through four of these regions (2) a separate limit cycle exists which passes through a set of four regions different from those in (1). Once information on ranges of the constants λ_1, etc., is known it will be possible to examine the nature of these sustained oscillations in greater detail. The interesting feature in the mathematical model is that these limit cycles occur. No satisfactory biological explanation for the occurrence of these limit cycles has been proposed. For details of the derivation of the basic equations, analysis of stability and definitions of the eight regions see [16, Chapter 12].

It is apparent that the effects of cytotoxic drugs on the present immune surveillance model can be handled by the approaches of the previous section. More complicated optimal control problems can also be formulated.

Although the role of the host immune response to the growth of spontaneous human tumors is unknown, at the present time, there is active research in this area.

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