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Minimizing Therapeutically Induced Anemia

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Abstract. A model for erythroid production based on a continuous maturation-proliferation scheme is developed. The model includes a simple control mechanism operating at the proliferating cell level, and analytic solutions for the time dependent response of the model are derived. Using this model, the response of the erythron to a massive depletion of the proliferating cell compartment (due for example to cytostatic drugs or radiation) is calculated. It is demonstrated that a therapeutic measure designed to decrease the erythroid precursor maturation velocity may considerably ameliorate the deleterious effects of proliferating cell destruction. One way to decrease the erythroid cell maturation rate would be by having the patient breathe in an oxygen enriched atmosphere.

Key words: Erythrocyte maturation-proliferation – Partial differential equations – Anemia

I. Introduction

In hematology, the classical concept concerning the connection between cellular maturation and proliferation within the recognizable proliferating cellular compartments has been a sequential one. In this model it is assumed that within each morphological category of proliferating cells, cells may either enter cycle from the previous compartment or after mitosis in the compartment in question. Cells progress through cycle ($G1 \to S \to G2 \to M$) in a completely sequential fashion, and following mitosis some daughter cells pass to the next morphological compartment while others reenter $G1$ in the same compartment.

Cronkite (1964), Rubinow and Lebowitz (1975) and Mackey and Dörmer (1981a) have all pointed out that this model is inconsistent with the existing cell kinetic data from a number of species. Blackett and co-workers (Tarbutt and Blackett, 1968; Constable and Blackett, 1972) have speculated that maturation within the rat erythroid and neutrophilic proliferating precursors is continuous, with cells passing from one morphological stage to the next at any point in the cell cycle. Mackey and Dörmer (1981b) used this concept to analyze the cell kinetic data from proliferating erythroid precursors in a number of species, and found satisfactory agreement between the data and the model.

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Here, the notion of continuous maturation throughout the cell cycle is extended to a model for the entire erythron, including the stem cells, the recognizable proliferating and non-proliferating erythroid precursors of the bone marrow, and the circulating erythrocytes (part II). In III, the steady state behaviour for the model is derived, while in part IV the behaviour of the model is determined following a massive depletion of the proliferating precursors (stem cells plus recognizable cells) due, for example, to the action of a cytostatic drug or radiation. Finally, in part V a simple strategy for minimizing the potentially lethal effects of such an assult is described.

II. Formulation of a Continuous Maturation-Proliferation Model for the Erythron

A. Biological Preliminaries

Here, some salient features of erythroid maturation are briefly reviewed for those unfamiliar with the process. For a more extensive treatment, consult Ważewska-Czyżewska (1981).

The most primative (i.e., least differentiated) cell type within the hematopoietic system is the pluripotential stem cell (PPSC). Cells in the PPSC population differentiate into less primative committed precursors for erythrocytes, neutrophils-macrophages, megakaryocytes, and lymphocytes, though the specific triggers for this differentiation process are not understood.

Once a cell from the PPSC is committed into the erythroid line, it is designated as an erythroid committed stem cell (CSC-E). Cells within the CSC-E undergo an unknown number of divisions, and mature with respect to their hemoglobin (Hb) synthesis rate and Hb content. Cells within the PPSC and CSC-E are not morphologically characterized, though there are *in vitro* assays for the CSC-E.

The first morphologically recognizable erythroid precursor is the proerythroblast (Pro EB), followed by the basophillic erythroblast (Baso EB) and polychromatic erythroblast (Poly EB). All three (Pro EB, Baso EB, and Poly EB) are capable of cell division, and as the maturation level increases the Hb content per cell increases. Following these, the next recognizable erythroid precursor is the orthochromatic erythroblast (Ortho EB), and the transition between the Poly EB and the Ortho EB marks the point at which proliferative ability is lost. The Ortho EB are followed, morphologically, by the reticulocytes and finally by the erythrocytes. The primary location of all of these cells is in the bone marrow, save the erythrocytes which are circulating in the blood. Approximately half of the reticulocytes are in the circulation.

Little is known concerning the kinetic characteristics of the PPSC and CSC-E, though some efforts have been made to estimate their properties (Blumenson, 1973; Mackey, 1978). The total average cellular transit time through the recognizable proliferating precursors (Pro EB + Baso EB + Poly EB) is estimated to be 1.6 days (Mackey and Dörmer, 1981b), while the Ortho EB-Reticulocyte transit time is about 2 days. The mature circulating erythrocyte has a lifespan of 120 days (Wintrobe, 1976), after which it is rapidly destroyed.

The short range controls operating to maintain the erythron in a steady state are poorly understood. However, a conservative interpretation of the *in vitro*

and *in vivo* data (Fried et al., 1973; Mackey, 1978; McCulloch et al., 1974; Patt and Maloney, 1972; Vos, 1972; Vassort et al., 1973) implies that there is a mechanism operating within the stem cells such that the relative proliferation rate is a decreasing function of the number of stem cells. Long range control of the erythron is considerably better understood. In response to a fall in arterial oxygen concentration, occasioned e.g. by a fall in circulating erythrocyte numbers, the kidneys synthesize and release the hormone erythropoietin (EPO). EPO, in turn, apparently acts on all of the proliferating cells (CSC-E, Pro EB, Baso EB, and Poly EB) to produce an increase in cellular production via an increase in maturation velocity.

B. The Model

With the above remarks in mind, the following formulation is suggested for the maturation-proliferation process within the erythron.

Each cell is assumed to be characterized by two independent variables: m, the maturation level; and a, the age. Immediately following mitosis a cell has an age $a = 0$. Cellular age increases with velocity V_a until at age $a = a_0$ mitosis occurs and two daughter cells of age $a = 0$ are produced. With respect to maturation, cells are presumed to enter the CSC-E at a maturation level $m = m_0$, and progress in maturation at a velocity V_m until the boundary $m = m_1$, marking the loss of proliferative potential between the Poly EB and Ortho EB. Maturation continues past this point, still at a velocity V_m, until maturation level $m = m_2$ is reached which denotes the end of the life time of the mature erythrocyte.

Let the density of cells of age a and maturity m at time $\bar{t}$ be $n(\bar{t}, m, a)$, so n must satisfy the conservation equation

$$\frac{\partial n}{\partial \bar{t}} + \frac{\partial}{\partial m}[V_m n] + \frac{\partial}{\partial a}[V_a n] = 0 \tag{1}$$

in conjunction with the boundary condition

$$n(\bar{t}, m, 0) = 2n(\bar{t}, m, a_0) \tag{2}$$

from mitosis. The total number of cells at a given maturation level m at time $\bar{t}$ is clearly

$$N(\bar{t}, m) = \int_0^{a_0} n(\bar{t}, m, a)\, da \tag{3}$$

so, under the assumption that the velocity of maturation, V_m, is independent of a and that V_a is continuous integration over a in (1) gives, using (2),

$$\frac{\partial N}{\partial \bar{t}} + \frac{\partial (V_m N)}{\partial m} = V_a(\bar{t}, m, a_0) n(\bar{t}, m, a_0). \tag{4}$$

Equation (4) may be rewritten in the form

$$\frac{\partial N}{\partial \bar{t}} + V_m \frac{\partial N}{\partial m} = \left[p(\bar{t}, m, N) - \frac{\partial V_m}{\partial m} \right] N \tag{5}$$

where the relative proliferation rate $p(\bar{t}, m, N)$ is given by

$$p(\bar{t}, m, N) = \frac{V_a(\bar{t}, m, a_0) n(\bar{t}, m, a_0)}{N(\bar{t}, m)}. \tag{6}$$

Here, the behaviour of the erythron hemoglobin levels as a function of maturation level is approximated by taking

$$V_m(\bar{t}, m) = \begin{cases} r(m - m_0) & \text{for } m_0 \leqslant m < m_1 \\ r(m_1 - m_0) & \text{for } m_1 < m. \end{cases} \tag{7}$$

Secondly, it is assumed that the relative proliferation rate is given by

$$p(\bar{t}, m, N) = \begin{cases} A(1 - BN), & m_0 \leqslant m < m_1 \\ 0, & m_1 \leqslant m < m_2 \\ -\infty, & m_2 \leqslant m. \end{cases} \tag{8}$$

The first part of (8) merely reflects the nature of the short range proliferative control; the second the fact that proliferation does not occur within the Ortho EB, reticulocytes, and erythrocytes; and the last that erythrocyte destruction is very rapid at the end of their lifespan. Thus, the behaviour of this model for the erythron is specified by equations (5), (7), and (8) in conjunction with an initial condition $N(t = 0, m) = N_0(m)$. Lasota (1981) has shown that there exists a unique and globally stable solution to the system (5), (7), (8) if $N_0(0) > 0$.

It will prove convenient to work with dimensionless variables in investigating the properties of this system, so let

$$x = \frac{m - m_0}{m_1 - m_0}, \qquad \lambda = A/r,$$

$$t = r\bar{t}, \qquad c = V_m/r(m_1 - m_0),$$

$$u(t, x) = BN, \qquad L + 1 = \frac{m_2 - m_0}{m_1 - m_0}.$$

Thus Eqs. (5), (7), and (8) become

$$\frac{\partial u}{\partial t} + c(t, x)\frac{\partial u}{\partial x} = \left[p(t, x, u) - \frac{\partial c}{\partial x} \right] u(t, x) \tag{9}$$

$$c(t, x) = \begin{cases} x, & 0 \leqslant x < 1 \\ 1, & 1 \leqslant x \end{cases} \tag{10}$$

and

$$p(t, x, u) = \begin{cases} \lambda(1 - u), & 0 \leqslant x < 1 \\ 0, & 1 \leqslant x < L + 1 \\ -\infty, & L + 1 \leqslant x \end{cases} \tag{11}$$

respectively.

III. Behaviour of the Normal Erythron

Combining Eqs. (9) through (11) gives

$$\frac{\partial u}{\partial t} + c(t, x)\frac{\partial u}{\partial x} = f(t, x, u) \tag{12}$$

where

$$f(t,x,u)=\begin{cases}[\lambda(1-u)-1]u, & 0\leqslant x<1\\ 0, & 1\leqslant x<L+1\\ -\infty, & L+1\leqslant x\end{cases} \tag{13}$$

and $c(t,x)$ is given by (10).

Starting with an initial distribution $u(0,x)=v(x)$ it is straightforward to show that the solution to (12), (13) is

$$u(t,x)=\begin{cases}\dfrac{v(xe^{-t})(\lambda-1)e^{(\lambda-1)t}}{(\lambda-1)+\lambda v(xe^{-t})[e^{(\lambda-1)t}-1]}, & 0\leqslant x<1\\ \dfrac{v(xe^{-(t-x+1)})(\lambda-1)e^{(\lambda-1)(t-x+1)}}{(\lambda-1)+\lambda v(xe^{-(t-x+1)})[e^{(\lambda-1)(t-x+1)}-1]}, & 1\leqslant x<1+t\\ v(x-t-1), & 1+t\leqslant x<L+1\\ 0, & L+1\leqslant x\end{cases} \tag{14}$$

and thus in a steady state

$$u(t,x)\underset{t\to\infty}{\to}\frac{\lambda-1}{\lambda}\equiv u_0, \qquad 0\leqslant x<L+1 \tag{15}$$

if $v(0)\neq 0$. Clearly $\lambda>1$ for the steady state to be biologically meaningful, which just means that the maximum proliferation rate must be greater than the rate of maturation.

In terms of the functioning of the body, the quantity of importance is the total number of erythrocytes as these are the cells responsible for the transport of oxygen. This is given to a good approximation by the total number of nonproliferating cells,

$$U(t)=\int_1^{L+1}u(t,x)\,dx \tag{16}$$

with $u(t,x)$ from (14) and an appropriate initial distribution $v(x)$. After the steady-state has been attained, the total number of nonproliferating cells is just

$$U_0(t\to\infty)=L\left(\frac{\lambda-1}{\lambda}\right). \tag{17}$$

IV. The Effects of Proliferative Cell Depletion

It is common clinical practice to administer cytostatic drugs or radiotherapy to patients with a number of proliferative disorders, and these therapies are designed around the fact that these drugs kill proliferative cells. One of the frequent consequences of such therapy is a massive anemia. Alternately, in healthy people large fractions of the proliferative cell population may be accidently destroyed due, e.g., to radiation or exposure to a number of organic chemicals. In addition to the killing of proliferative cells, either by accident or by design, it may sometimes

happen that the maximum proliferative rate A of the remaining cells is substantially decreased (Boggs and Boggs, 1976; Morley et al., 1975).

To examine the response of the maturation-proliferation model presented here in such a situation, assume that a fraction θ of the normal proliferating cell population remains (i.e., $1-\theta$ were removed by some means at $t=0$) and that those remaining are now characterized by a new λ given by $\lambda' = A'/r$.

Now, to determine the behaviour of the system it is necessary to solve (12) and (13) with the initial condition

$$v(s) = \begin{cases} \theta\dfrac{\lambda-1}{\lambda}, & 0 \leqslant x < 1 \\ \dfrac{\lambda-1}{\lambda}, & 1 \leqslant x < L+1 \\ 0, & L+1 \leqslant x \end{cases} \tag{18}$$

taking care to note that the factor λ in (13) must be replaced by λ'.

Using (14) it is quite straightforward to show that the required solution is

$$u(t,x) = \begin{cases} \dfrac{(\lambda'-1)\theta\left(\dfrac{\lambda-1}{\lambda}\right)e^{(\lambda'-1)t}}{(\lambda'-1)+\lambda'\theta\left(\dfrac{\lambda-1}{\lambda}\right)[e^{(\lambda'-1)t}-1]}, & 0 \leqslant x < 1 \\ \dfrac{(\lambda'-1)\theta\left(\dfrac{\lambda-1}{\lambda}\right)e^{(\lambda'-1)(t-x+1)}}{(\lambda'-1)+\lambda'\theta\left(\dfrac{\lambda-1}{\lambda}\right)[e^{(\lambda'-1)(t-x+1)}-1]}, & 1 \leqslant x < t+1 \\ \dfrac{\lambda-1}{\lambda}, & t+1 \leqslant x < L+1 \\ 0, & L+1 \leqslant x. \end{cases} \tag{19}$$

As in the normal erythron, the damaged system still approches a steady state distribution, for

$$u(t,x) \underset{t\to\infty}{\to} \frac{\lambda'-1}{\lambda'} \equiv u_1, \qquad 0 \leqslant x < L+1 \tag{20}$$

and thus the new steady state number of nonproliferating cells will be given by

$$U_{1,ss} = U_1(t\to\infty) = L\frac{\lambda'-1}{\lambda'}. \tag{21}$$

Another quantity of more immediate interest from the hematological point of view, however, is the minimum value to which the nonproliferating population will fall before re-establishing the new steady state given by (21). An analysis of the computed $U_1(t)$ based on the solution (19) shows, as expected intuitively, that the minimum value of $U_1(t)$ will occur at $t=L$. This minimum value is easily

calculated to be

$$U_{1,\min}(t = L) = \frac{1}{\lambda'} \ln \left[\frac{u_1 - \theta u_0}{u_1} + \theta \frac{u_0}{u_1} e^{(\lambda' - 1)L} \right] \tag{22}$$

where u_0, u_1 are defined in (17) and (20) respectively.

V. Maximizing the Minimum Number of Non-Proliferative Cells

The ultimate consequence of a destruction of a large fraction of the proliferating phase cells with an accompanying reduction in the maximum proliferation rate from A to A' will be the establishment of a new steady state $U_{1,ss}$, related to the normal steady state $U_{0,ss}$ by

$$U_{1,ss} = U_{0,ss} \frac{1 - \frac{1}{\lambda'}}{1 - \frac{1}{\lambda}}. \tag{23}$$

This new steady state may be appreciably less than the normal steady state, but still adequate to maintain life.

However, the most immediate threat to life may occur during the transient following the destruction of the proliferating cells, when $U_1(t)$ reaches its minimum value $U_{1,\min}$, given by (22). It may happen that $U_{1,\min}$ is so small that it precludes the maintenance of life without some form of direct intervention.

It would appear that any procedure that could decrease the velocity of maturation r below its normal value should have the effect of lessening the severity of $U_{1,\min}$. To investigate the nature of this process we now assume that in addition to killing a fraction $1 - \theta$ of the proliferating phase cells at $t = 0$, and reducing their maximum proliferative rate to A', some means of decreasing their velocity of maturation to r' is also instituted at $t = 0$. In this case the dimensionless maturation velocity $c(t, x)$ is not continuous in x, and must be determined by the continuity condition that equates the influx of cells from the left at $x = 1$ to the efflux of cells to the right; i.e. $c(t, 1-)u(t, 1-) = c(t, 1+)u(t, 1+)$, where

$$c(t, 1 \pm) = \lim_{\varepsilon \to 0} c(t, 1 \pm \varepsilon), u(t, 1 \pm) = \lim_{\varepsilon \to 0} u(t, 1 \pm \varepsilon).$$

Thus the behaviour of the system will be described by the solutions of (12) with

$$c(t, x) = \begin{cases} \frac{r'}{r} x, & 0 \leqslant x < 1 \\ 1, & 1 \leqslant xL + 1 \end{cases} \tag{24}$$

and

$$f(t, x, u) = \begin{cases} [\lambda'(1 - u) - (r'/r)]u, & 0 \leqslant x < 1 \\ 0, & 1 \leqslant x < L + 1 \\ -\infty, & L + 1 \leqslant x. \end{cases} \tag{25}$$

The initial condition is again given by (18).

Set $\alpha = r'/r$ so the solution to (12), (24), and (25) with (18) is given by

$$u(t,x) = \begin{cases} \dfrac{(\lambda' - \alpha)\theta\left(\dfrac{\lambda-1}{\lambda}\right)e^{(\lambda'-\alpha)t}}{(\lambda'-\alpha) + \lambda'\theta\left(\dfrac{\lambda-1}{\lambda}\right)[e^{(\lambda'-\alpha)t} - 1]}, & 0 \leqslant x < 1 \\ \dfrac{\alpha(\lambda'-\alpha)\theta\left(\dfrac{\lambda-1}{\lambda}\right)[e^{(\lambda'-\alpha)(t-x+1)}]}{(\lambda'-\alpha) + \lambda'\theta\left(\dfrac{\lambda-1}{\lambda}\right)[e^{(\lambda'-\alpha)(t-x+1)} - 1]}, & 1 \leqslant x < t+1 \\ \dfrac{\lambda-1}{\lambda}, & t+1 \leqslant x < L+1 \\ 0, & L+1 \leqslant x. \end{cases} \tag{26}$$

Now the distribution $u(t,x)$ will approach a steady state

$$u(t,x) \underset{t\to\infty}{\to} \alpha\frac{\lambda'-\alpha}{\lambda'} \equiv u_2, \qquad 1 \leqslant x < L+1 \tag{27}$$

and it is evident from a comparison of (20) and (27) that a decrease in the maturation rate from r to r' may either increase u_2 above u_1 or decrease it. It is quite easy to show that the steady state u_2 will have its maximum value exactly when $\alpha = \lambda'/2$, or $r' = A'/2$.

The minimum value that the total number of non-proliferating cells will reach following destruction, but with a concommitant reduction in maturation rate to r', also occurs at $t = L$ and is given by

$$U_{2,\min}(t = L) = \frac{\alpha}{\lambda'}\ln\left\{\frac{u_2 - \theta\alpha u_0}{u_2} + \frac{\theta\alpha u_0}{u_2}e^{(\lambda'-\alpha)L}\right\}. \tag{28}$$

Determining the value of α that will maximize the minimum $U_{2,\min}$ is generally impossible analytically, though it is clear that $\alpha = \lambda'/2$ will maximize the steady state

$$U_{2,ss} = L\alpha\frac{\lambda'-\alpha}{\lambda'}. \tag{29}$$

However, an estimation of some of the parameters appearing in our model allows considerable insight into the usefulness of decreasing r in severe cases of proliferating cell depletion and damage.

Within the erythrocytes, the total transit time for the non-proliferating cells is approximately 122 days, while it is about 2 – 3 days for the proliferating cells. Thus $L \simeq \frac{122}{3} - 1 \simeq 40$. λ is difficult to estimate because of the unknown numbers of divisions within the CSC-E populations. We assume the normal steady state is optimal so $\lambda = 2$. With these values $u_0 = \frac{1}{2}$ and $U_0 = 20$.

In Table 1 we have tabulated, with $L \simeq 40$, the predicted minimum and steady state normalized values of the non-proliferating erythroid cells with and without

Table 1. A comparison of the usefulness of a therapy consisting of a reduction of proliferating erythroid precursor maturation rate to its optimal value for two levels of cellular destruction (θ) and various levels of the maximal proliferation rate (λ'). * implies that there is no non-zero steady state as the total number of non-proliferating cells approaches zero as $t \to \infty$. See text for further details

	$U_{1,ss}$ (no therapy)	$U_{2,ss}$ (with therapy)	$U_{1,\min}$ (no therapy)		$U_{2,\min}$ (with therapy)	
			$\theta = 0.01$	$\theta = 0.10$	$\theta = 0.01$	$\theta = 0.10$
2	20.00	20.00	17.70	18.85	17.70	18.85
1.9	18.95	19.00	16.55	17.76	16.70	17.85
1.8	17.78	18.00	15.28	16.56	15.70	16.85
1.7	16.47	17.00	13.88	15.23	14.70	15.85
1.6	15.00	16.00	12.30	13.74	13.70	14.85
1.5	13.33	15.00	10.53	12.07	12.70	13.85
1.4	11.43	14.00	8.54	10.18	11.70	12.85
1.3	9.23	13.00	6.28	8.05	10.70	11.85
1.2	6.67	12.00	3.75	5.66	9.70	10.85
1.15	5.22	11.50	2.43	4.39	9.20	10.35
1.10	3.64	11.00	1.25	3.11	8.70	9.85
1.05	1.90	10.50	0.49	1.95	8.20	9.35
1.00	0.00	10.00	*	*	7.70	8.85
0.95	0.00	9.50	*	*	7.20	8.35
0.90	0.00	9.00	*	*	6.70	7.85

therapy (therapy to maximize the steady state value of U, $\alpha = \lambda'/2$) at two different destruction levels (90% and 99%), and assuming varying degrees of damage to the proliferative potential of the proliferating erythroid precursors. As is clear from the previous formulae (21) and (29), the steady state values depend only on the degree of reduction in the proliferative potential while the minimum values during the transient approach to the steady state depend on λ' as well as the extent of destruction within the proliferative cell compartment.

An examination of the values in Table 1 shows that a therapy designed to decrease the rate of maturation to the optimal value ($\alpha = \lambda/2$) required to maximize the normalized steady state number of non-proliferating erythroid cells has a dramatic effect on the entire time dependent approach of the non-proliferating cell numbers to equilibrium. The efficacy of such a procedure becomes especially strong in the case of a high degree of proliferative cell destruction (small θ) combined with a large drop in maximal proliferative rate (small λ'). Throughout we have assumed that the depletion of the proliferating cell population affected all of these cells uniformly (c.f. equation (18)). One could also assume that the damage by cytostatic drugs or radiotherapy is more severe in the less mature cells, i.e. $v(x) = \theta x u$, $0 \leqslant x < 1$, after depletion. In this case all of the above calculations may be carried through in a similar manner and it is found that the effects of therapy detailed in Table 1 become even more dramatic.

How might such a therapy be realized? For the erythrocytes, to decrease the maturation rate it should be sufficient to have the patient breathe in an oxygen enriched environment. As a consequence of the increased arterial oxygen levels, there should be a decrease in the renal production of EPO, and a consequent

reduction in the rate of maturation. Such a therapy, based on the theoretical conclusions of this paper, has been successfully used on patients suffering from induced anemias. The clinical details of this treatment may by found in Ważewska-Czyżewska (1981).

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