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SOME MODELS IN HEMOPOIESIS: PREDICTIONS AND PROBLEMS

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INTRODUCTION

Cell kineticists interested in the hemopoietic system, like other biologists, are often skeptical of the work of biomathematicians. In reading through the modeling literature in hemopoiesis it is not difficult to see why. Biologically, some of the models are blatantly incorrect in their assumptions. Some are so complicated that insight into the role of various parameters and control elements in determining the behaviour of the model is difficult. Finally, many are presented in a fashion that makes then inaccessible to the biologist.

This is an unfortunate situation for at least two reasons. First, hematopoietic systems pose interesting, difficult, and unsolved problems for the mathematician. The systems involved contain time delays (due to the presence of the cell cycle and maturation times) as well as nonlinearities (nonlinearity is obvious because of the stability of the hemopoietic system in the face of experimental and clinical perturbations). Secondly, in my opinion the mathematician can offer some insight to the biologist into the way surprising modes of behavior may arise in systems that are inherently nonlinear and which may contain time delays. The origin of these behaviours is not always obvious.

Here, I illustrate the common threads in many different hematological models, and concentrate on areas where I feel contributions have been made that deserve the careful and thoughtful consideration of experimentalists. My personal bias is that in an area as complicated and poorly understood as hemopoiesis, models must be conceptually simple enough to give straightforward predictions, and thus allow the experimentalist some hope of designing experiments to test these predictions. This has guided my selection of some topics over others.

The outline of the paper is as follows. The next two sections contain a short description of the structure of the hemopoietic system and a discussion of some periodic hematological phenomena. The fourth section points out some common aspects of peripheral control models. In the fifth section classical and more recent notions concerning the nature of control within the

pluripotential stem cell population are examined. More complicated models of hemopoiesis are mentioned briefly, and then in the final section the connection between cellular proliferation and maturation is considered.

THE ARCHITECTURE OF THE NORMAL HEMATOPOIETIC SYSTEM[1,2]

The organization of normal hematopoiesis can be viewed as follows. It is generally believed that there exists a self maintaining pluripotential stem cell population capable of producing committed stem cells for the erythroid, myeloid and megakarocytic lines. These committed stem cell populations are not thought to be self maintaining and thus depend on a cellular influx from the pluripotential population for their continued existence. Neither the pluripotential nor the committed stem cells are morphologically identifiable, though there are *in vitro* assays for their presence.

With increasing maturation, committed stem cells acquire characteristics that allow them to be classified as recognizable proliferating precursors. In both the erythroid and myeloid series there are three recognizable precursors that are known to undergo cellular division. As maturation proceeds proliferative activity in these populations ceases, the cells enter a maturational phase, and the nucleus is expelled. In the myeloid series mature neutrophils are released from the marrow into the blood where they are apparently destroyed at random with a short half-life (~ 7 hours in humans). For the erythroid series this last step is different in that the mature circulating erythrocyte lives for a long time (~ 120 days in humans) before being destroyed. In the megakarocytic line the cellular division characterizing the recognizable erythroid and myeloid precursors is replaced by division of nuclear material alone, in which the nuclear DNA duplicates to a maximum of 32N. Megakarocytes produce platelets at all ploidy values above 8N with the majority of the production occurring at 16N.

In the erythroid series there is a well established *in vivo* hormonal control operating between the circulating erythrocyte mass and the erythroid stem cell. Decreases in hemoglobin levels lead to a decrease in arterial oxygen tension, which in turn triggers the release of a hormone called erythropoietin (EPO) by the kidney. EPO acts to increase the size of the committed erythroid stem cell population, though it is not clear if this is due to an increase in the cellular influx from the pluripotential stem cells, or an increase in the number of divisions within the erythroid stem cells, or both. It is also possible that EPO increases the velocity of maturation of the erythroid precursors. Ultimately the erythrocyte mass and, thus, the oxygen carrying capacity of the blood are increased.

In analogy with the erythroid series, negative feedback controls from the periphery to the committed stem cells have been postulated for both the myeloid and megakarocytic lines, via colony stimulating factor (CSF) and thrombopoietin respectively. A number of *in vitro* regulators have been demonstrated by various groups. However, the experimental evidence is complex and contradictory and there does not seem to be sufficient clarity in this area to definitively characterize the nature of the feedback in the *in vivo* situation. A number of authors have assumed that myeloid and megakarocytic peripheral control mechanisms must be similar to that operating in the erythroid series. In the absence of any clear evidence to the contrary it is a reasonable hypothesis.

In addition to these long range (from the mature cell to the committed stem cell) feedback mechanisms, short range control mechanisms have been postulated to exist within the pluripotential stem cells. Though the details are not clear, the pluripotential cells must have some means of sensing their numbers and making appropriate adjustments in production rates to maintain a stable population.

PERIODIC HEMATOLOGICAL DISEASES

Pathology in physiological system function is often marked by the onset of periodic behaviour in a normally constant system variable, or by the alteration of a normally periodic variable. The term dynamical disease has been applied to those pathologies characterized by the operation of an intact control system in a region of physiological parameter space that produces periodic behaviour [3-6]. The reason that dynamical diseases are of interest is two-fold: 1) By studying the qualitative properties of the oscillation under various experimental or clinical manipulations it may be possible to localize the origin of the oscillation to a particular portion of a complex control system; and 2) Having narrowed down the origin of the oscillations it may be possible to determine how they might arise by varying parameters in a mathematical model of that system. This procedure may give insight into the nature of the control system and thus lead to testable hypotheses. There are several periodic hematological disorders of this type[7].

Periodic hematopoiesis (also known as cyclical neutropenia) is a benign disease characterized by an oscillation in circulating neutrophil numbers from normal to low values with a period of 17 to 23 days in humans. In addition there is a concomitent oscillation of most of the other formed elements of the blood with the same period, but out of phase with one another. The observed phase differences are consistent with estimated differences in maturation times.

All grey collies have periodic hematopoiesis, and the only apparent difference between the canine and human forms of this disorder is the 11 to 12 day period of the former. Transplantation of grey collie marrow into an irradiated normal collie induces periodic hematopoiesis in the recipient, while the converse procedure results in normal hematological function for the grey collie. Thus it seems clear that some marrow component is responsible for the genesis of this disorder.

Circulating levels of EPO and the putative myeloid regulator CSF are known to cycle with the same period as the formed elements of the blood in both canine and human periodic hematopoiesis. However the fact that in the grey collie phlebotomy and hypertransfusion, which would respectively lower and elevate EPO and CSF levels, have no effect on the phase of the oscillation would indicate that there is no significant primary involvement of peripheral control loops in this disorder.

Periodic chronic myelogenous leukemia (periodic CML) is a variant of CML. In this condition, peripheral leukocyte and thrombocyte levels are not merely elevated, as in CML, but oscillate around elevated levels with a period of 35 to 70 days in the absence of any clinical intervention. In some patients there are also erythrocyte and lymphocyte oscillations. Leukopheresis, when tried in one patient, had no effect on the phase of the oscillation. This, combined with the observation of oscillations in the number of S phase myeloid colony forming cells in other patients, even in the absence of peripheral leukocyte oscillations, argues against an origin of periodic CML from the destabilization of a peripheral control system.

As an example of the experimental induction of oscillatory behaviour, it has been shown[8] that the chronic administration of red blood cell isoantibody to rabbits is marked in some by a steady depression of hemoglobin and reticulocyte levels, and in others by sustained oscillations in hemoglobin and reticulocytes with a period of 16 to 17 days. This procedure induces what is known as an autoimmune hemolytic anemia, and the most obvious effect of the procedure would be to increase the random destruction rate of erythrocytes.

PERIPHERAL CONTROL ELEMENTS

As a paradigm for the control exercised by the elements of the peripheral blood over their marrow production, many have used the following formulation (see Figure 1).

Let the density of circulating cells in the blood at time t be $Z(t)$ (cells/kg) and assume that their destruction rate is α (day^{-1}). Assume further that

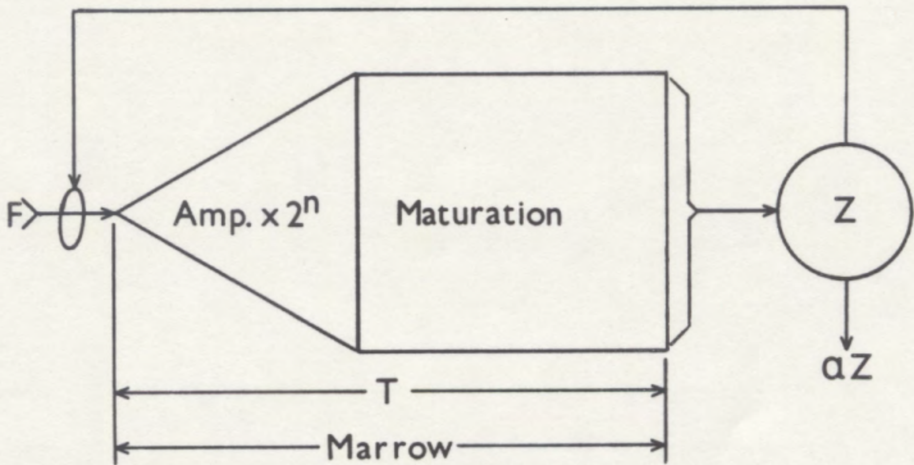

Fig. 1. A schematic representation of the peripheral control of blood cell production.

the influx F (cells/kg/day) from the pluripotential into the committed stem cells is controlled by the level of Z (e.g. via erythropoietin), that on the average each cell entering from the pluripotential population undergoes n mitoses before proliferation ceases, and that the total transit time from the entry of a cell into the committed stem cell population to the release of its mature progeny into the blood is T. Then the dynamics of Z(t) are governed by

$$\frac{dZ}{dt} = -\alpha Z(t) + \nu(Z_T) \qquad (1)$$

where $Z_T = Z(t-T)$ and

$$\nu(Z_T) = 2^n F(Z_T) \qquad (2)$$

is the current cellular flux into the blood (the production rate) in response to a demand created a time T in the past. One would intuitively expect that the production rate (ν) would be a monotone decreasing function of the size of the mature circulating population (Z_T), i.e. that low circulating cell numbers would induce a large cellular influx from the marrow that would steadily decrease as circulating cell numbers increased. A number of authors have considered such a model for the control of peripheral platelet[9], erythrocyte[10,11], and granulocyte[4,7,12] numbers. Through a combination of analytic and numerical techniques, it now appears[7,13,14] that the only two modes of behaviour

available for the circulating cell mass, $Z(t)$, from (1) with a decreasing production function ν is either an approach to a stable steady state Z^*, or to a stable limit cycle oscillation in $Z(t)$.

In two studies that assumed the production to be a decreasing function, the authors[10,11] estimated the parameter values corresponding to normal erythropoiesis and were able to demonstrate analytically and numerically that a simple increase in the peripheral erythrocyte destruction rate (α) leads to a Hopf bifurcation and an apparently stable oscillation identical in period to that observed in the reticulocyte count of rabbits with experimentally induced autoimmune hemolytic anemia[8].

Other studies[15-18] have employed equation 1, with a decreasing production function ν, and the additional assumption that the transit time (T) is made up of a constant portion (T_0) plus a variable portion (ΔT) that is an increasing but bounded function of circulating cell numbers:

$$T = T_0 + \Delta T\ (Z(t)) \tag{3}$$

This assumption of a variable transit time in the marrow is introduced to reproduce a variable release time from the marrow maturational compartment in the face of altered peripheral demands. These early studies, applied to granulopoiesis, attempted to explain cyclical neutropenia and periodic CML based on computer demonstrated oscillatory solutions to equations 1 and 3. However, from the properties of these two disorders discussed in the previous section, the studies are of doubtful validity.

Rather than assuming the transit time T is identical for each element of the population, a more realistic assumption is that there is a distribution of transit times through the population. In this case equation 1 is replaced with

$$\frac{dZ}{dt} = -\alpha Z(t) + \nu(y(t)) \tag{4}$$

where

$$y(t) = \int_{-\infty}^{t} g(t-t')\ Z\ (t')\ dt' \tag{5}$$

The function g gives the distribution of maturation times and if $g(t-t')$ is a delta function, $g(t-t') = \delta\ (t-t'-T)$, then equations (4) and (5) reduce to (1). This concept of a distribution of transit time values was applied[19] to a consideration of granulocyte-monocyte interactions and their possible role in the genesis of cyclical neutropenia.

Although little in the way of analytic work has been published, the assumption of maturation time dependent on the numbers of peripheral blood elements,

or of a distribution of maturation times, gives behaviour more stable than does equation 1 with a monotone decreasing production function ν and a constant transit time T. However, the previous conclusion concerning the two possible modes of behaviour of the circulating cell numbers (either an approach to a locally stable steady state or to a limit cycle) remains intact[20,21].

In all of these studies it was assumed that the production was a monotone decreasing function of circulating cell numbers a time T in the past. In yet another attempt[4,7] to understand periodic CML it was assumed that the production ν (Z_T) was a 'humped' function of Z_T, i.e. ν $(0) = 0$, $\lim \nu(Z_T) = 0$ as $Z_T \to \infty$, and for some single $Z^+ > 0$, ν (Z^+) has a maximum. Like other studies that have postulated a role for the peripheral control loop in producing the characteristics of periodic CML, this notion must be rejected. However, this fortuitous assumption of a humped form for the production revealed a broader spectrum of behaviour for equation 1 than when $\nu(Z_T)$ was simply monotone decreasing. Briefly, with a humped $\nu(Z_T)$ the solutions of (1) may either be stable, periodic (with many different periods), or aperiodic as a single parameter is varied[4,7,22,23]. This is a concrete example of a simple deterministic control system whose behaviour may be quite complicated. Thus when faced with complex data we need not necessarily invoke the operation of complicated control systems[24] for their origin.

These studies of peripheral control, approximated by equation 1 (or by equations 4 and 5), make the clear prediction that it may be possible to experimentally induce oscillations in these systems by altering any one of a number of parameters. The one parameter that seems most accessible is the circulating cell destruction rate, α. A carefully designed <u>in vivo</u> experiment would therefore involve a procedure to increase the cell destruction rate to, and maintain it at, various known constant levels in individual animals, and then to monitor the number of circulating cells on a daily basis. The data from such experiments would yield valuable information concerning the dynamics and control of the particular system under study, and similar experiments could be designed for erythrocytes, neutrophils, and platelets.

STEM CELL MODELS

Howard and Pelc[25] were the first to observe that the cell cycle could be viewed as containing four discrete phases: the DNA synthesis phase (S), the mitotic period (M), the phase between the completion of M and the initiation of S (known as G1), and the period between the completion of S and the beginning of M (known as G2). Cells were viewed as progressing through these stages in a

sequential and orderly fashion. Using regenerating liver as a model for the cell cycle Lajtha et al.[26] expanded this model by including a resting (G0) phase into which all cells entered after mitosis, and from which cells were randomly recruited into G1. They applied this model to the bone marrow stem cell population, speculating that cells differentiated out of the G0 phase and that the population of cells must be autoregulatory, so any loss of cells from the population would eventually result in a compensatory movement of cells from G0 into the active proliferative phase. They incorporated these hypotheses into a discrete time mathematical model and examined the behaviour of the hypothetical stem cell population after acute and chronic radiation damage.

Lebowitz and Rubinow[27] extended this G0 model [by allowing for the possibility of random cellular death during the proliferative phase, and that some cells might enter G1 directly after mitosis (the G0 shunt)] and used their formulation to predict cell cycle times from autoradiographic grain count distributions. Rubinow[28] later extended this work to include a distribution of intermitotic times and applied his results to a description of the α curve[29].

A simplified version of the G0 model, assuming a fixed time τ (days) for cells to traverse the proliferating portion of the cell cycle and no G0 shunt, is illustrated in Figure 2. P(t) and N(t) denote the size (cells/kg) of

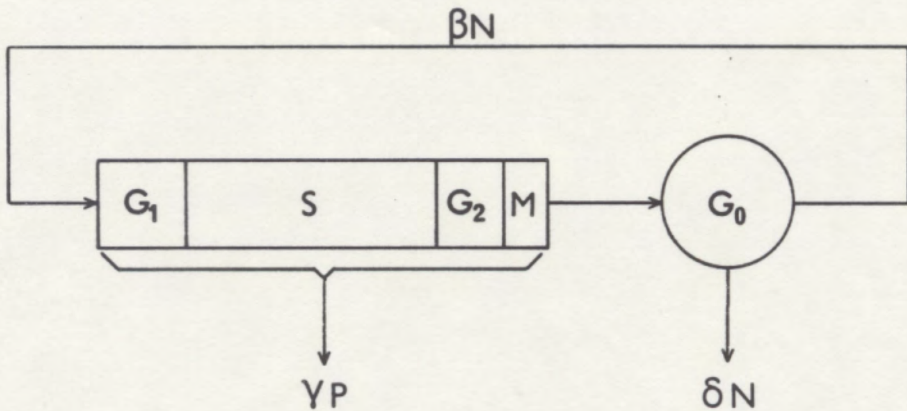

Fig. 2. A diagramatic representation of the elements in a G0 cell cycle model.

proliferating and G0 phase cell populations respectively, δ (day^{-1}) is the rate of differentiation out of G0, and β (day^{-1}) is the rate of cell reentry into G1 from G0. Under exceptional circumstances cells may be removed (die) at a rate

$\gamma(\text{day}^{-1})$ from the proliferating phase. Under these assumptions the model is described by

$$\frac{dN}{dt} = -(\beta + \delta) N(t) + 2\beta_\tau N_\tau e^{-\gamma\tau} \quad (6)$$

and

$$\frac{dP}{dt} = -\gamma P + \beta N - \beta_\tau N_\tau e^{-\gamma\tau} \quad (7)$$

where, as before, subscripted quantities are evaluated at a time τ in the past. Elements of control are usually introduced through β and/or δ.

In one of the first studies to seriously look at the question of stem cell control alone,[30] it was assumed there was no proliferating cell death ($\gamma = 0$) and that G0 phase cells produce a mitotic inhibitory substance (chalone, concentration C) which is catabolized at a constant rate. Thus equation 7 is supplemented with

$$\frac{dC}{dt} = -\mu C + \sigma N$$

and the cell reentry rate from G0 to G1, β (C), is a decreasing function of the mitotic inhibitor concentration, C. Based on analog computer simulations it was noted that the G0 phase cell numbers (N) might either approach a steady state or exhibit apparently stable oscillatory behaviour. There was no evaluation of the role various model parameters might play in determining the stability of the steady state, or the period of the oscillatory solutions when the steady state is unstable.

A later study[31] assumed that the production of mitotic inhibitor was not rate limiting on the time scales of importance so $C = (\delta/\mu) N$ and thus $\beta = \beta(N)$. Assuming a particular decreasing function for β and that $\gamma = 0$, it was possible to determine the steady state proliferating and G0 populations, their local stability in the face of various parameter changes, and to calculate the expected period of any oscillations occurring when stability was lost. In this study a central question was whether the dynamics of the pluripotential stem cells could account for the characteristics of periodic hematopoiesis. Under the assumption of no proliferating cell death ($\gamma = 0$), it was impossible to produce the characteristics of human or canine periodic hematopoiesis by varying a single parameter at a time, keeping all others at their estimated normal values. However, by setting all model parameters at their normal values and only assuming irreversible cell loss from the proliferating phase of the stem cell compartment it was possible to quantitatively reproduce both the period and amplitude of human and canine periodic hematopoiesis. This model predicted dynamical behaviour is borne out by the characteristics of peripheral

blood cell oscillations induced in dogs[32] and humans[33] by the chronic administration of drugs which selectively kill proliferating phase cells. A central question is, of course, whether this predicted behaviour will persist in the face of more realistic assumptions concerning the cell cycle. A stability analysis of the model including a distribution of cell cycle times demonstrates that the predicted behaviour is retained[34].

The qualitative clinical characteristics of periodic CML discussed previously have led to the hypothesis that the source of the cycling may be within pluripotential cells, just as the ultimate defect in CML is thought to be[2]. An analysis of grain count data from acute myelogenous leukemic myeloblasts, the first recognizable proliferating myeloid precursor, led to the conclusion that their cell cycle time (τ) is greatly elevated over that of the normal myeloblast [35]. Other studies have come to the same conclusion, and estimates for the cell cycle time in the leukemic state place it as high as four times normal.

Under the assumption that an elevation of the leukemic myeloblast cell cycle time may reflect a similar change within the pluripotential population, it then becomes of interest to examine the expected dynamics of the pluripotential stem cell with an increased cell cycle time (τ) and other parameters held at their normal values. When this analysis was carried out[36], it was predicted that the pluripotential cell population numbers should become unstable and start to oscillate with a period of about 12 days once the cell cycle time exceeds approximately 2.6 days. As noted previously the typical period found in periodic CML ranges from 30 to 70 days. Thus, at first glance it would seem that a simple elevation in the cell cycle time could not be responsible for the observed periodicities in periodic CML. One must note, however, that in all of the clinical studies of periodic CML blood samples have been taken at intervals ranging from 3 to 14 days, and thus aliasing may represent a source of error in these studies. These observations suggest that the period of peripheral oscillations in periodic CML may be significantly less than the reported periods. If this question is to be resolved it will be necessary to collect data from CML patients on a daily basis as has been done in the studies of periodic hematopoiesis.

Necas and co-workers[37-39] have examined the dynamics of the *in vivo* assay for the pluripotential cell in the mouse (the CFU-S) after selective ablation of S phase cells with hydroxyurea. From these results it was hypothesized that the population of S phase cells must play a significant role in the control of pluripotential cell numbers. Necas et al.[40] have examined the dynamics of a Lebowitz-Rubinow G0 phase cell cycle model under the assumption that the G1

reentry rate (β) is a function of the number of cells in S phase. To avoid depopulation of the pluripotential cells they further assumed that the rate of cellular differentiation out of G0 (δ) is dependent on G0 population numbers. With their parameter estimations they were able to achieve a close match between computer predicted model behaviour and actual CFU-S behaviour following hydroxurea and total body irradiation. These results, coupled with earlier work assuming pluripotential control by G0 phase cell numbers, raise the possibility that pluripotential dynamics are controlled by the entire population. The recent _in vitro_ demonstration of a cell number dependent competitive interaction between EPO and CSF[41] is relevant in this regard.

As in the case of the peripheral control systems, these theoretical studies of stem cell dynamics make the very clear prediction that oscillatory regimes may be encountered as various cell cycle parameters are altered. The one parameter over which we can exercise control with assurance is the rate of cell death during the proliferative phase of the cell cycle, γ. The use of cell cycle specific drugs at different doseage levels within a population of animals, coupled with daily peripheral blood counts, may yield data analogous to that previously noted incidently in humans[33]. If it is possible to induce such bifurcations in stem cell behaviour, we may learn a great deal about stem cell dynamics by studying the resulting oscillations.

COUPLED STEM CELL AND PERIPHERAL CONTROL MODELS

To my knowledge the first outline of a coupled stem cell-peripheral control loop was by Lajtha and Oliver[42] for the erythroid series. It was postulated that the pluripotential population controlled its own size, and that EPO controlled the rate of differentiation out of the pluripotential compartment. This model was later quantified to examine the effects of irradiation on the erythron[43].

Kirk et al.[44] proposed a formulation of the Lajtha-Oliver model for the erythron that coupled elements discussed in the previous two sections. This model was conceived to examine the possible origin of the reticulocyte and hemoglobin oscillations in rabbits[8] discussed earlier. Computer simulations of this model[44-46] revealed that the possible modes of behavior were numerous, but a lack of analytic results makes it difficult to understand the role of various parameters in determining system behaviour. An identical formulation has been examined for the pluripotential stem cell-megakarocyte control system[47].

Probably the most complete and rigorously developed model including aspects of stem cell and peripheral control, as well as control over release rate, is that of Rubinow and Lebowitz[48] for neutrophil production in man. This model was used to examine a number of processes, including the response to irradiation and the effects of leukopheresis. In a variant of this model[49,50], the growth of a small leukemic clone of cells and its eventual domination of normal granulopoiesis was examined. Under the assumption that the leukemic cells had an elevated steady state, and a long sojurn in G0 compared to normal, it was predicted that in acute myelogenous leukemia one to four years might elapse between the establishment of a leukemic clone and its eventual growth to a clinically detectable level.

CELLULAR MATURATION AND PROLIFERATION

In the studies mentioned above no detailed assumptions were made concerning the connection between cellular proliferation and maturation within the committed hematopoietic lines.

Among cell kineticists interested in hematopoietic function it is a commonly held belief that maturation and proliferation within the recognizable proliferating erythroid and neutrophilic precursors may be schematically represented as in Figure 3. Thus, within each recognizable proliferating compartment, every cell entering from the previous morphological stage must pass through mitosis at least once. Further, the transition between morphological compartments occurs postmitotically. This may be termed a sequential model.

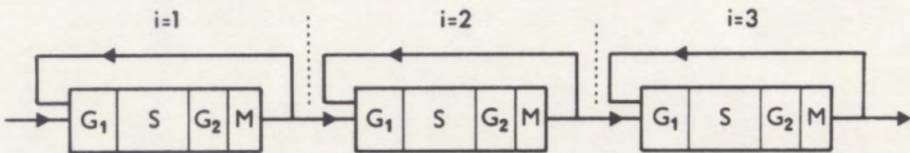

Fig. 3. Diagrammatic representation of the sequential model. i = 1 corresponds to the most immature recognizable morphological category (proerythroblast or myeloblast), i = 2 to the basophilic erythroblast or promyelocyte, and i = 3 to the last proliferating compartment (polychromatic erythroblast or myelocyte). The cellular input to the i = 1 category is presumed to come from the appropriate stem cell compartment, while the cellular efflux from the last proliferating compartment (i = 3) is taken as the cellular production rate.

The sequential model provides a very definite framework within which to analyze available cell kinetic data (i.e. labeling indices, DNA synthesis times,

mitotic indices, and mitotic times). Further, the model places clear restrictions on these data. Cronkite[51], and then Rubinow[52], pointed out that there were significant discrepancies between the available cell kinetic data and a sequential model for cellular maturation and proliferation. Later Rubinow and Lebowitz[48] reanalyzed these data for human neutrophil precursors and concluded "... that it is premature, at the present time, to put forward a detailed model of the proliferative compartments which includes distinct stem, myeloblast, promyelocyte, and myelocyte compartments". More recent studies have reemphasized these discrepancies for human neutrophilic precursors[53-55], and human, guinea pig, and rat erythroid precursors[53,54]. It now seems totally clear for both erythroid and neutrophilic precursors, viewed within the context of a sequential model, that: 1) S and M phase data within each morphologically recognizable proliferating compartment are inconsistent with each other; and 2) Either set of data (S or M) for the entire recognizable proliferating population of cells is inconsistent with known cellular production rates. We are thus faced with at least two possible alternatives: Either the data are incorrect, or the sequential model is incorrect.

The origin of this sequential model in a hematological context is not easy to trace, but at least one definite alternative was proposed 20 years ago. In their qualitative formulation of the kinetics of erythropoiesis Lajtha and Oliver[42] suggested that the transition between morphologically distinguishable cell types was not dependent on mitosis and might occur throughout the cell cycle. This would be properly called a random maturation model.

This concept of random maturation was reintroduced in a number of experimental studies of erythroid precursors in the embryonic[56], young[57], and mature[58-60] rat; the mouse[61]; and in studies of the neutrophilic precursors in the rat[62]. More recent studies have specifically incorporated the hypothesis of random maturation into extensive models of human granulopoiesis[63,64], and erythropoiesis in the mouse[65], and one included self regulatory and EPO control mechanisms to examine strategies for minimizing the transient effects of acute proliferating cell depopulation[66].

In spite of the demonstrated failure of a sequential model to account for the available data, and the reasonable hypothesis that the model is incorrect, some of these attempts to explore the consequences of a random maturation model have met with surprisingly bitter criticism[67,68]. The recent demonstration[69] that a large body of steady state cell kinetic data inconsistent with a sequential model is consistent with a random maturation model re-opens this question. Whatever the eventual resolution of these discrepancies, we will

gain in our understanding of this most interesting system.

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