

A MATHEMATICAL MODEL OF THE ACUTE MYELOBLASTIC LEUKEMIC STATE IN MAN

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ABSTRACT A dynamical mathematical model of the acute myeloblastic leukemic state is proposed in which normal neutrophils and their precursors, and leukemic myeloblasts, proliferate as distinct but interacting cell populations. Each population has a G_0 compartment, consisting of resting cells, that acts as a control center to determine the rate of proliferation. These rates are assumed to depend on the total number of cells in the combined populations. The presence of the leukemic population destabilizes the homeostatic state of the normal population, which is stable in the absence of leukemic cells, and drives the system to a new stable state consisting entirely of leukemic cells and no normal cells. Calculations based on the theory suggest that it is able to simulate the kinetic features of this disease state, at least in its typical manifestations.

INTRODUCTION

In a recent paper (1) we described a simple mathematical model of neutrophil production and control in normal man, designed to incorporate most of the known quantified kinetic parameters of granulocytopenesis, representing a variety of experiments. In this note we shall describe the dynamic or non-steady-state properties of the neutrophil production system in the abnormal state acute myeloblastic leukemia (AML) (a brief preliminary account of this work was presented in ref. 2). We emphasize at the outset that the leukemic state referred to throughout this work is a subset of the variety of myeloid leukemias that are clinically encountered. For example, we make no claim that our model is applicable to chronic myelogenous leukemia, or to unusual leukemic states such as those characterized by marrow hypoplasia.

The quantitative information regarding some kinetic aspects of this disease is extensive (3-5), and was significantly advanced by the pioneering radioactive labeling experiments of Cronkite and collaborators (6). We assume the reader is familiar with this work.

We adopt the point of view, advocated by Clarkson (7), that there exist side by side in AML two cell populations: the normal neutrophil cell system, and a population of leukemic blood cells (LBC). Each population is assumed to possess feedback control elements that regulate and control the total number of cells in the population. However, the leukemic cells are assumed to possess an aberrant set of kinetic parameters, different from those of the normal population. In other words, our fundamental point of view is that the leukemic state is not "uncontrolled growth," but rather, *controlled*

growth with an abnormal set of control elements. Such a viewpoint has already been put forth by others (8).

Various studies indicate the importance of colony-stimulating factor and colony-stimulating cells in regulating granulopoiesis, and illuminate the nature of the control system governing proliferative granulocytes in patients with AML (9–16). We do not consider such mechanisms explicitly, but only assume the existence of some control system, which is governed by the total population of the neutrophil system consisting of both proliferative and nonproliferative cells. This assumption is the most novel and critical one that we make, and one for which we cannot provide any direct experimental evidence, although there is some indication that leukemic cells do act to inhibit the colony-forming capacity of normal proliferative cells (13, 14, 16). The principal justification for our assumptions resides in the comparison we shall make subsequently of the deductions from our model with some of the known kinetic characteristics of AML.

MODEL OF THE NORMAL NEUTROPHIL POPULATION

We shall review briefly the properties of our model of the normal neutrophil production system in man (1). The five compartments comprising the model, together with their interconnections representing cell fluxes, are shown in Fig. 1. The proliferative pool consists of two compartments, an active compartment A and a resting compartment G_0 . Stem cell influx is assumed to be negligible, and the proliferative pool is self-maintaining. Following division of a cell in compartment A , the two daughter cells enter the G_0 phase, which acts as a control center, and from which cells leave at random to enter either the active phase A or the maturation compartment M at fractional rates α and β , respectively.

The maturation compartment M is a “pipeline,” in which all cells mature for a fixed time T_M and then enter the marrow reserve compartment R . The latter is, like G_0 , a “random” compartment, in which control is exercised on the rate per unit time γ at which cells leave to enter the blood compartment B . The compartments M and R together comprise the nonproliferating precursor cells of the system, normally found in the marrow.

The blood compartment B represents mature neutrophils in the circulating blood as well as the “marginal granulocyte compartment” composed of sequestered cells, possi-

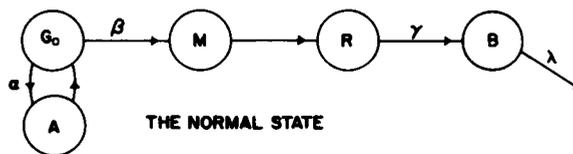


FIGURE 1 Schematic representation of the normal neutrophil production system. The active compartment A and the resting compartment G_0 comprise the self-maintaining marrow proliferative pool. The compartments labeled M and R represent the maturation and reserve pools of the marrow. The compartment B represents the blood and marginal granulocytes. The quantities α , β , γ , and λ represent release rates along the indicated pathways (from ref. 1).

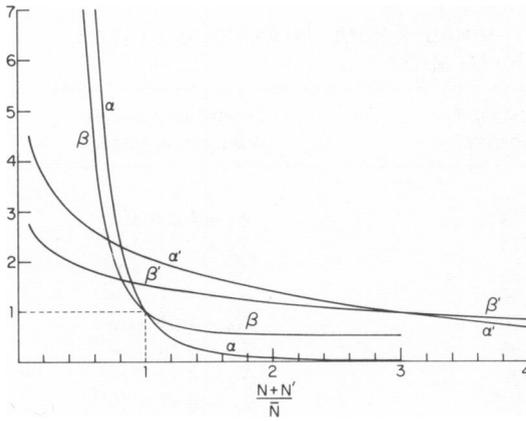


FIGURE 2

FIGURE 2 The normalized control functions α/α_0 , β/α_0 , α'/α'_0 , and β'/α'_0 , given by Eqs. 2 and 4, are shown as functions of the total normalized cell population $[N(t) + N'(t)]/\bar{N}$, consisting of both normal and leukemic cells. It was assumed that $\alpha_1/\alpha_0 = 2\beta_1/\alpha_0 = \alpha'_1/\alpha'_0 = 2\beta'_1/\alpha'_0 = 1$, and $\bar{N}'/\bar{N} = 3$. In the absence of leukemic cells and in the steady state, $N(t)/\bar{N} = 1$ and $\alpha/\alpha_0 = \beta/\alpha_0 = 1$.

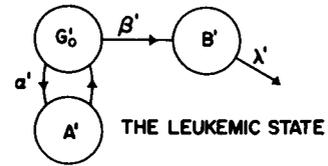


FIGURE 3

FIGURE 3 Schematic representation of the leukemic cell population in the acute myeloblastic leukemic state. The compartments A' and G_0 represent the actively proliferating and nonproliferating leukemic cell pools, respectively. Maturation is absent, and cells leave G_0 at fractional rates per unit time α' and β' to enter the active compartment A' and blood compartment B' , respectively. Cells leave the blood at random to die, at a fractional rate per unit time λ' .

bly on the walls of blood vessels. Compartment B is likewise a random compartment from which cells disappear or die at random at a fractional rate per unit time λ .

Control of proliferation is taken into account by making α and β depend on the total population of the entire system at any time, N . This dependence is illustrated in Fig. 2, which shows α and β plotted as a function of the total (normalized) population. In the absence of any leukemic cells, the abscissa represents the population number N/\bar{N} . \bar{N} is a prescribed parameter representing the total number of cells in the system in the steady state. In the steady state, $\alpha = \beta = \alpha_0$, a constant, i.e., for every cell sent out of the marrow proliferative pool to mature, a cell is sent to the active compartment to divide and replenish the proliferative pool. The shape of the curves α and β lead to the number \bar{N} being maintained in a stable manner (in the absence of leukemic cells) in response to perturbations.

The release rate γ of cells from the marrow reserve compartment depends on the number of cells in the blood compartment N_B , in a manner similar to the dependence of α or β on N . The steady-state value $\gamma = \bar{\gamma}$ is achieved when N_B equals its steady-state value \bar{N}_B .

The values of the parameters, chosen to represent most of the known quantitative kinetic observations of the neutrophil system in steady-state behavior, are shown in Table I. The deduced neutrophil production rate in the steady state is $n_0 = 5.0 \times 10^9$ cells/h. It should be borne in mind that in practice, G_0 cells are indistinguishable from

TABLE I
STEADY-STATE PARAMETERS OF THE NEUTROPHIL PRODUCTION SYSTEM
IN A 70 KG MAN*

| Compartment | Characteristic times inferred from observation | Population numbers deduced from model |
|-------------|---|---|
| | <i>h</i> | |
| G_1 | $T_1 = 12$ | $\bar{N}_1 = 6.0 \times 10^{10}$ |
| S | $T_S = 15$ | $\bar{N}_S = 7.5 \times 10^{10}$ |
| $G_2 + m$ | $T_2 = 3$ | $\bar{N}_2 = 1.5 \times 10^{10}$ |
| A | $T_A = 30$ | $\bar{N}_A = 1.51 \times 10^{11}$ |
| G_0 | $1/\alpha_0 = 20$ | $\bar{N}_0 = 1.01 \times 10^{11}$ |
| M | $T_M = 96$ | $\bar{N}_M = 4.85 \times 10^{11}$ |
| R | $1/\gamma_0 = 90$ | $\bar{N}_R = 4.54 \times 10^{11}$ |
| B | $1/\lambda = 9.7$ | $\bar{N}_{B\ddagger} = 0.49 \times 10^{11}$ |
| Sum | $T\ddot{\S} = 246$ | $\bar{N} = 1.24 \times 10^{12}$ |

*Taken from ref. 1.

‡Inferred from observation.

§ T is the total transit time.

G_1 cells. Therefore, there is an effective distribution of transit times in the proliferative state, resulting from the fact that the transit time in the G_0 compartment varies from cell to cell.

MODEL OF THE LEUKEMIC CELL POPULATION AND STEADY-STATE PROPERTIES

Leukemic myeloblasts are unable, by and large, to differentiate into maturer forms of neutrophil precursors. Consequently, we assume that the LBC behave like a proliferative pool only. The LBC are self-maintaining, and consist of an active compartment A' and a resting compartment G'_0 (see Fig. 3). In the resting state, the LBC leave at random to enter either the active compartment A' , or the blood compartment B' , at fractional rates α' and β' , respectively. Here the G'_0 compartment should perhaps be thought of as a nonproliferating compartment, from which cells are either committed to proliferate again (enter A') or to be released to the blood (enter B'). Cells in the blood are largely nonproliferative (8, 11, 17-20), and we assume this property is strictly true. (Proliferative blood cells can be thought of as belonging to A' or G'_0 .) They disappear from the blood at random, at a fractional rate per unit time λ' . The cells entering the blood are for the most part destined to die (3, 4, 21, 22). Leukemic cells may die even as they proliferate (4, 6, 21), although it is not possible to evaluate such loss quantitatively. It seems most plausible that the principal mechanism of cell loss is the release of cells to the blood. Therefore, in the interest of simplicity, we assume that cell loss during proliferation is negligible.

This model of the leukemic population was previously utilized (23) to represent the extensive and detailed kinetic observations, obtained with the aid of autoradiography, made by Clarkson et al. (21) of two adults with AML. In making this representation the leukemic cells were assumed to be in a quasi-steady state during the course of the

observations. The values of the steady-state parameters of the leukemic cell population so obtained are shown in Table II.

Other observations that are accounted for by the model are as follows. The production rate of LBC at the time of diagnosis $\sim 0.5\text{--}3 \times 10^9$ cells/h (17) ($\approx N'_B \lambda'$). The mean generation time of LBC is very long, perhaps of the order of 200 h, and measurably longer than that of neutrophil precursors (3, 4, 21, 22, 23, 25, 27, 28). There is no second wave seen in the labeled mitoses curve (21). If S-phase cells are initially labeled, some labeled cells show up in the blood a few hours later (17).

In order to represent the dynamics of the leukemic blast cell population, we assume that the control functions α' and β' depend on the total neutrophil precursor population in such a way as to make the leukemic cell population tend to a stable population number \bar{N}' , analogous to the behavior of the normal cell population by itself. However, the equilibrium number \bar{N}' is assumed to be substantially greater than the equilibrium number \bar{N} that characterizes the normal cell population. The control functions α and β are likewise assumed to depend on the total cell population, normal and leukemic. Thus, speaking anthropomorphically, we can say that normal cells are fooled by the leukemic cells, and recognize them as normal. The dependence of the control functions α , β , α' , and β' on the total normal plus leukemic cell population is illustrated in Fig. 2.

The system of differential equations which comprise our model are similar to those for the normal population (1), with the obvious extension of the number of compartments. They can be found in the Appendix. By specifying the characteristic control functions, the values of all the parameters of the model, and the initial state of the system at $t = 0$, the behavior of the system for all future times is found by integrating the equations. From such solutions the curves in Figs. 4–7 were obtained. It can be seen that cell fluxes from one compartment to another are represented at any moment, and evolve in time as the leukemic population increases. Such a dynamical model is to be

TABLE II
QUASI-STEADY-STATE PARAMETERS OF LEUKEMIC CELLS IN AML*

| Compartment | Mean cell lifetime | Number of cells at time of observation | Other references that support inferences of cell transit times |
|-------------|----------------------------|--|--|
| | <i>h</i> | | |
| G'_1 | $T'_1 = 0$ | $N'_1/(N'_0 + N'_A) = 0$ | |
| S' | $T'_s = 20$ | $N'_s/(N'_0 + N'_A) = 0.079$ | 5, 24 |
| $G'_2 + m'$ | $T'_2 = 5$ | $N'_2/(N'_0 + N'_A) = 0.020$ | 24, 25, 26 |
| A' | $T'_A = 25$ | $N'_A/(N'_0 + N'_A) = 0.099$ | |
| G'_0 | $1/\alpha'_0 = 227\dagger$ | $N'_0/(N'_0 + N'_A) = 0.901$ | |
| B' | $1/\lambda' = 36$ | $N'_B \S = 5.3 \times 10^{10}$ | 3, 17 |

*Taken from ref. 23 and inferred from the observations of Clarkson et al. (21).

†This quantity represents the mean lifetime defined as mean age of a cell in G_0 , or mean cell transit time. The mean interdivision time defined as the time interval between cell birth and subsequent division, is $1/2\alpha'_0 + T'_A = 139$ h.

§Mean number of leukemic cells observed in the blood of two adults.

contrasted with other simplistic representations of the growth of a single tumor population (29), that assume that the tumor is in steady exponential growth. It will be shown that the latter condition is satisfied only during the early unobserved growth phase of the LBC.

DYNAMICAL PROPERTIES OF THE MODEL

The explicit functional representation of the control functions α' and β' are given in the Appendix as Eqs. 2. The steady-state parameter \bar{N}' which appears in the control functions for the leukemic cells, is chosen to be 3×10^{12} , or 2.4 times larger than \bar{N} , the corresponding parameter of the normal cells. This value of \bar{N}' was chosen on the basis that the observed mean number of LBC present in children (10–14 yr old) who died with acute lymphocytic leukemia was 1.65×10^{12} cells (30). By extrapolation of weight, the mean number of cells at death in a 70 kg man with leukemia is inferred to be 2.9×10^{12} . Such an estimate is in agreement with other estimates of the number of LBC in adults in advanced stages of leukemia (4).

With this value of \bar{N}' , the qualitative effect on the normal population of the presence of the leukemic cell population can already be inferred from Fig. 2. Thus, suppose the normal population number is at its steady-state level \bar{N} , and a small number of leukemic cells are introduced, say 10, so that the total population is greater than \bar{N} . Then, so far as the normal cell control functions α and β are concerned, the total population is greater than its homeostatic level \bar{N} , β is greater than α , and the normal population production begins to turn off and operate below a self-sustaining level. The leukemic cells, on the other hand, recognize the total as being less than its steady-state level \bar{N}' , so that α' is greater than β' , and the leukemic population continues to increase. This results in a further decline in production of normal cells, with consequences that are ultimately devastating for the normal cell population.

What happens is seen graphically in Fig. 4, which shows the behavior of the normal blood neutrophil population number N_B , and the leukemic blood cell population number N'_B , as functions of the time t . Also shown is the total blood population number $N_B + N'_B$. Similar curves are obtained for the total populations of the normal and leukemic cells. The curves of the total leukemic population for three different sets of values of α'_i and β'_i (the rightmost curve corresponding to the case illustrated in Fig. 4) are shown in Fig. 5. The curves of Figs. 4 and 5 have the following qualitative features in common.

After a very short transient period, the LBC increase at a constant fractional rate, that is to say, they are in steady exponential growth for a long time, until a stationary growth phase appears, as N' approaches its steady-state level \bar{N}' . In the first phase no clinical manifestations appear since the leukemic cell population is negligible in comparison with the normal population, which remains at its steady-state level \bar{N} . It follows from Eqs. 2 that during this time, α' and β' are constant. It is shown in the Appendix that, under such conditions, the leukemic cell population grows at a constant rate, the excess of the birth rate over the death rate, proportional to $\alpha' - \beta'$ (see Eq. 11).

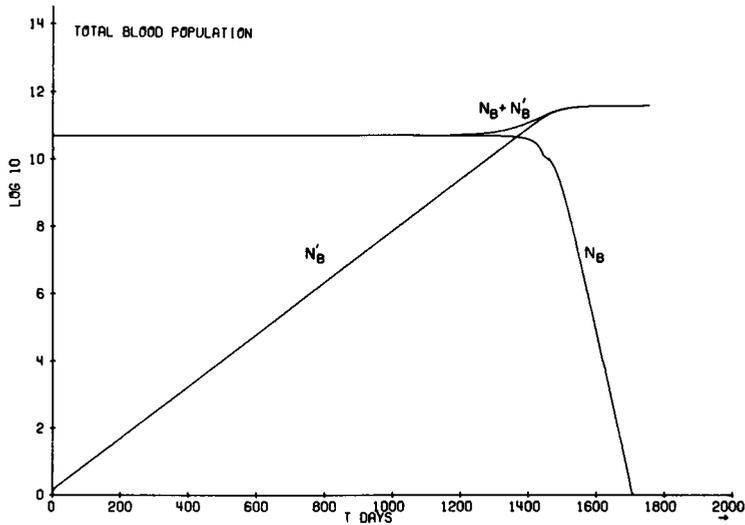


FIGURE 4 The behavior of the normal blood neutrophil population N_B , the leukemic blood cell population number N_B' , and the sum $N_B + N_B'$, as functions of the time. At $t = 0$, 10 leukemic cells are assumed to be introduced into the marrow, in S -phase, while the normal neutrophil cells and their precursors are in a steady state. The steady state parameters of the system are as given in Tables I and II. The functions α , β , α' , and β' are given by Eqs. 2 and 3 with $\alpha_0 = \alpha_1 = 2\beta_1 = 0.05/\text{h}$, $\nu = 4$, $\alpha'_0 = 0.0044/\text{h}$, $\alpha'_1 = 0.0022/\text{h}$, $\beta'_1 = 0.0011/\text{h}$, $\bar{N} = 1.24 \times 10^{12}$, and $\bar{N}' = 3 \times 10^{12}$.

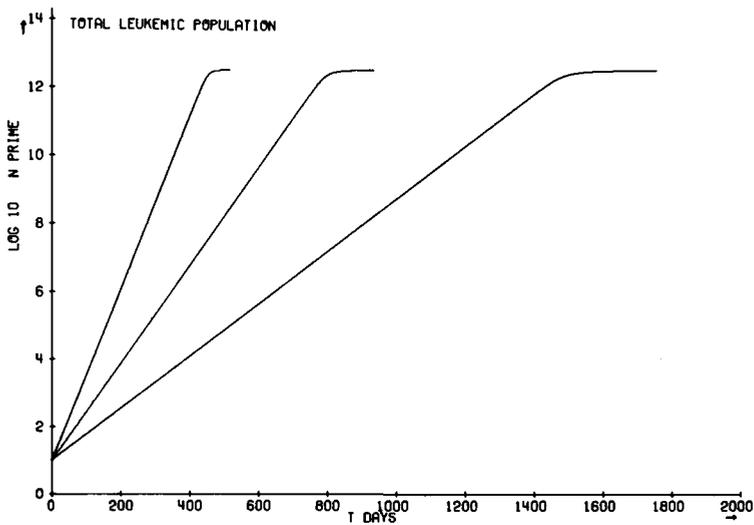


FIGURE 5 The curve on the right represents total leukemic blood cell population as a function of time for the same case as illustrated in Fig. 4. For the curve on the left, it was assumed that $\alpha'_1 = 0.0088/\text{h}$, and $\beta'_1 = 0.0044/\text{h}$, while for the middle curve, $\alpha'_1 = 0.0044/\text{h}$, and $\beta'_1 = 0.0022/\text{h}$. Other parameter values were chosen as for Fig. 4.

However, when N' becomes comparable to \bar{N} , the *presence* of the leukemic population in large numbers appears to the normal homeostatic mechanism of control of proliferation as an overpopulation of normal cells. Hence, the production rate is reduced below the self-maintenance level, and the normal population suffers a decline, as is seen for the normal blood neutrophils in Fig. 4. It is in this stage that diagnosis of the disease is usually made. The number of leukemic cells usually seen at first diagnosis varies from 10^{11} cells upwards (30). After this, the growth of the total leukemic population behaves in a Gompertzian manner, as observed in the growth of animal tumors (31–35), and the total LBC number slowly approaches its asymptotic limit \bar{N}' . (In fact, it can be shown mathematically that the differential equations for the populations in the G'_0 and A'_0 compartments are asymptotically Gompertzian in nature for large times.) Concurrently, the normal population rapidly disappears.

For the three growth curves shown in Fig. 5, the values of $\alpha'_1 - \beta'_1$ were chosen to be (reading from left to right), respectively, 0.0044/h, 0.0022/h, and 0.0011/h. These values correspond to mean doubling times (see Eqs. 11 and 12) of 12, 21, and 39 days, and mean lifetimes of 1.3, 2.3, and 4.3 yr, respectively. For Figs. 4 and 5, α and β were prescribed by Eqs. 3, but the curves are unaltered if Eqs. 4 are utilized instead. Unfortunately, almost no quantitative information exists that could fix the values of these parameters.

The possibility that the natural lifespan of leukemia, measured from the first (unobserved) appearance in the body of some leukemic cells, may be 5 yr or longer receives support from observations of the incidence of leukemia among survivors of the Hiroshima atomic bomb. It was found that the incidence of leukemia did not increase above its normal expected level until about 18 mo after exposure to the bomb, and that the increased incidence did not reach its peak until about 5–7 yr later (36).

Fig. 6 shows the behavior of the labeling index of the leukemic cells for each of the three cases cited, which is the ratio of leukemic cells in *S*-phase to the total leukemic marrow ($G'_0 + A'$) population. During the stage of the disease when the leukemic cell population is small compared with normal cell population and in steady exponential growth, both the number of leukemic cells in *S*-phase and the total leukemic marrow population maintain a fixed ratio, so that the labeling index remains constant, although at a level below that of the normal proliferating marrow cells. Ultimately, when the growth rate of the leukemic population declines and the population begins to approach its stationary phase, cells accumulate in G'_0 relative to S' , and the labeling index declines asymptotically to its new stationary level.

Although the labeling index in patients with AML is quite variable, in general its value is very low and below the value seen for normal myeloblasts (18, 19, 21, 37, 38). The mitotic activity is also low. Furthermore, the labeling index and mitotic index of LBC do decline as the disease progresses (3, 4, 22). In terms of the model, these observations suggest that the patients are being observed at different times during the declining phase of one of the labeling index curves shown in Fig. 6. Alternatively, the varying values of the labeling index could also reflect in part different intrinsic growth rates of the LBC (as represented by the different horizontal phases of the curves in Fig. 6).

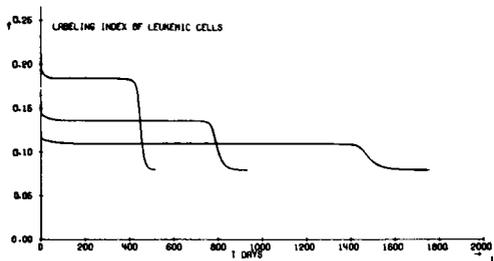


FIGURE 6

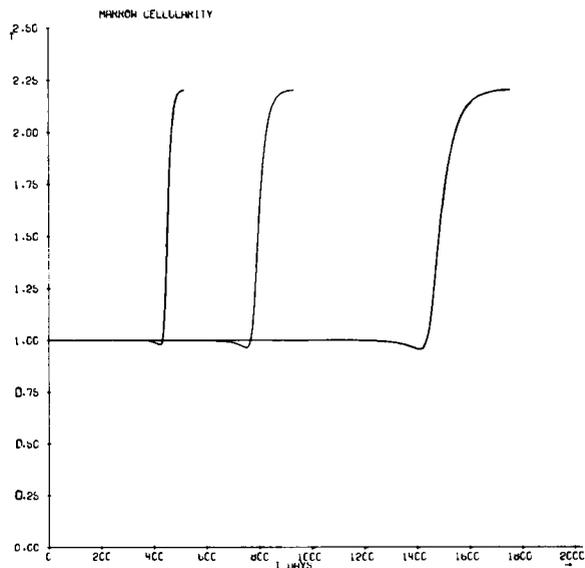


FIGURE 7

FIGURE 6 The labeling index of leukemic cells as a function of time for each of the three cases (reading from left to right) illustrated in Fig. 5.

FIGURE 7 The marrow cellularity as a function of time for each of the three cases (reading from left to right) illustrated in Fig. 5. The marrow cellularity is defined as the ratio of the total marrow population (normal plus leukemic cells) to the normal steady-state marrow population $\bar{N} - \bar{N}_B$.

In Fig. 7 is shown the marrow cellularity corresponding to the three cases displayed in Fig. 5. Here marrow cellularity is defined as the ratio of the total marrow population to the normal steady-state marrow population, which equals $\bar{N} - \bar{N}_B$. During the early stages of the disease, this ratio is seen to be unity, as we expect. With the initiation of the decline in the normal population, the marrow cellularity ratio momentarily declines. This decline occurs because the disappearance of the normal marrow population is temporarily greater than the increase in marrow population due to the leukemic cells. Subsequently, the marrow is overwhelmed by the continued increase in the leukemic cell population, especially those in G'_0 , and the cellularity rises sharply. In the advanced phase of the disease, the marrow cellularity ratio approaches a constant asymptotic value that depends on \bar{N}' , increasing or decreasing in direct proportion to it. Thus by appropriately increasing \bar{N}' , it is possible to produce marrow cellularities as much as 5 or 10 times normal, as seen in patients with AML in the advanced stage of the disease (B. D. Clarkson, personal communication).

DISCUSSION AND CONCLUSIONS

A mathematical model of the total neutrophil production has been introduced that is designed to represent the kinetic behavior of neutrophil cells and their precursors in the disease state, acute myeloblastic leukemia. The model makes a number of as-

sumptions regarding the mode of action of cells, the most critical of which are the following.

(i) There are two distinct populations, a normal cell population and a leukemic cell population, which function under a qualitatively similar but quantitatively different set of controls.

(ii) Each population has its own G_0 or resting compartment, which is a proliferative control center. In it, the decision is made as to whether a cell will enter an active proliferative compartment and subsequently divide, or whether the cell will not proliferate. In the latter case, a normal cell undergoes a period of maturation, enters the blood, and ultimately dies. If the cell is a leukemic cell, it enters the blood directly and ultimately dies.

(iii) The decision as to whether a cell proliferates or not (whatever the biochemical mechanism controlling this decision is eventually shown to be) depends on the total number of cells in the population.

(iv) Normal neutrophil precursors in G_0 do not distinguish leukemic cells, and regard them as part of the total population.

With the aid of these assumptions, the model appears able to successfully simulate some of the typical dynamical features of the acute myeloblastic leukemic state. The main effect of the interaction of the leukemic cell population, which possesses an aberrant set of kinetic parameters, with the normal population, is to destabilize the normal homeostatic control mechanisms of the latter population. The new stable state of the system, to which the population is (unfortunately) driven, is one in which there are no normal neutrophil cells or precursors, and all leukemic cells.

Because the model parameters are adjustable, different choices of values of these parameters permit a spectrum of realizations of the model. Thus, the variety of responses seen in humans can be accounted for by assigning different parameter values to different individuals. For example, longer or shorter natural histories are obtained as a result of slight changes in value of some of the dynamical parameters. It is possible that the "smoldering" form of leukemia, in which there may be no apparent progression of the disease for long periods of time, is characterized by a very long natural history. Alternatively, it is conceivable that the parameter \bar{N}' has a value that is initially about the same as \bar{N} , so that the normal neutrophil population tolerates the presence of the leukemia cells, which maintain themselves in a quasi-steady state near the level \bar{N} . The sudden transition, after a period of years, say, to the acute phase of the disease perhaps represents a sudden increase, for unknown reasons, in \bar{N}' to a value greater than \bar{N} .

The utility of a concrete mathematical model is that specific predictions about the natural history of the disease are made that may be susceptible to observational test, as for example, the assumptions listed above. Because of the successful qualitative simulation of the kinetic behavior of the disease, the concept of two distinct cell populations, normal and leukemic, is supported. At the present time, observations of kinetic features of leukemic cells in patients with AML must perforce be carried out when there are at least about 10^{10} or 10^{11} leukemic cells present, as otherwise, they are too few in number to be detected. The presence of this many leukemic cells implies

that a late stage of the disease is being observed, when the leukemic cells are already in the quasi-steady state phase of their Gompertzian growth. Hence, it should not surprise us that quantified knowledge of the dynamical properties of the system such as death rates, growth rates, and their temporal dependence still eludes investigators. Observations of the system when it is subjected to the large perturbations produced by chemotherapeutic drug doses can perhaps be helpful in this connection.

Furthermore, a mathematical model such as the one we have proposed can be applied to the simulation of the possible outcomes of various chemotherapeutic treatment regimens. Such simulation can be used for optimizing the treatment scheduling in the sense of maximizing the cytotoxic action of the drug on the leukemic population while minimizing the toxicity, or cytotoxic action of the drug on the normal population. This application of the model is the subject of a subsequent investigation.

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We thank Dr. Bayard D. Clarkson for a number of informative discussions while this work was in progress. We also wish to express our appreciation for the programming help of Edward Friedman.

This work was supported in part by NCI Grant No. 5 ROI CA 12124-01.

Received for publication 16 October 1975 and in revised form 15 March 1976.

APPENDIX

Mathematical Details of the Model

The mathematical formalism follows that of ref. 1, where a fuller discussion of relevant equations and their derivation can be found. Thus, cell density functions of the A' , G'_0 , and B' compartments are introduced, which when integrated over age or maturity variables, yield ordinary differential-difference equations for the total number of cells in each compartment, as follows.

$$\begin{aligned} dN'_A(t)/dt &= \alpha'(t)N'_0(t) - \begin{cases} f'(T'_A - t), & 0 < t < T'_A \\ \alpha'(t - T'_A)N'_0(t - T'_A), & t \geq T'_A \end{cases} \\ dN'_0(t)/dt &= -[\alpha'(t) + \beta'(t)]N'_0(t) + 2 \begin{cases} f'(T'_A - t), & 0 < t < T'_A, \\ \alpha'(t - T'_A)N'_0(t - T'_A), & t \geq T'_A, \end{cases} \\ dN'_B(t)/dt &= \beta'(t)N'_0(t) - \lambda'N'_B(t), \quad 0 < t. \end{aligned} \quad (1)$$

Here, N'_A , N'_0 , and N'_B represent the number of leukemic cells in the A' , G'_0 , and B' compartments, respectively, at time t , and $f'(a)$ represents the initial distribution of leukemic cells in compartment A' as a function of age a . The control functions α' and β' are defined as follows,

$$\begin{aligned} \alpha' &= \alpha'_0 + \alpha'_1 \log \frac{\bar{N}'}{N(t) + N'(t)}, \\ \beta' &= \alpha'_0 + \beta'_1 \log \frac{\bar{N}'}{N(t) + N'(t)}, \end{aligned} \quad (2)$$

where $N(t)$ is the total normal population of neutrophils and their precursors at time t , and $N'(t)$ is the total number of LBC, equal to $N_A(t) + N_0(t) + N_B(t)$.

The equations satisfied by the total populations of the normal compartments, which are similar to the above, are given in ref. 1. However, the functions α and β there are now defined in terms of both $N(t)$ and $N'(t)$ to be

$$\begin{aligned}\alpha(t) &= \alpha_0 + \alpha_1 \left(\left[\frac{\bar{N}}{N(t) + N'(t)} \right]^\nu - 1 \right), \\ \beta(t) &= \alpha_0 + \beta_1 \left(\left[\frac{\bar{N}}{N(t) + N'(t)} \right]^\nu - 1 \right),\end{aligned}\quad (3)$$

where ν is a positive number, or alternatively,

$$\begin{aligned}\alpha(t) &= \alpha_0 + \alpha_1 \log \left[\frac{\bar{N}}{N(t) + N'(t)} \right], \\ \beta(t) &= \alpha_0 + \beta_1 \log \left[\frac{\bar{N}}{N(t) + N'(t)} \right].\end{aligned}\quad (4)$$

Stability of the total population at the homeostatic level \bar{N} requires that $\alpha_1 > \beta_1$.

To represent those cells in the active compartment that are exclusively in S -phase, the active compartment is partitioned into three subcompartments consisting of the G_1 cells, the S -phase cells, and the $G_2 + m$ cells. Then the first Eq. 1 is replaced by the three equations

$$\begin{aligned}dN'_1(t)/dt &= \alpha'(t)N'_0(t) - J'_1(t), \\ dN'_s(t)/dt &= J'_1(t) - J'_s(t), \\ dN'_2(t)/dt &= J'_s(t) - J'_2(t),\end{aligned}\quad (5)$$

where

$$\begin{aligned}J'_1(t) &= \begin{cases} f'_1(T'_1 - t), & 0 < t \leq T'_1 \\ \alpha'(t - T'_1)N'_0(t - T'_1), & t > T'_1 \end{cases} \\ J'_s(t) &= \begin{cases} f'_s(T'_1 - t), & 0 < t \leq T'_s \\ f'_1(T'_1 + T'_s - t), & T'_s < t \leq T'_1 + T'_s \\ \alpha'(t - T'_1 - T'_s)N'_0(t - T'_1 - T'_s), & t > T'_1 + T'_s \end{cases} \\ J'_2(t) &= \begin{cases} f'_2(T'_2 - t), & 0 < t \leq T'_2 \\ f'_s(T'_s + T'_2 - t), & T'_2 < t \leq T'_2 + T'_s \\ f'_1(T'_A - t), & T'_2 + T'_s < t \leq T'_A \\ \alpha'(t - T'_A)N'_0(t - T'_A), & t > T'_A. \end{cases}\end{aligned}\quad (6)$$

Here $f'_1(a)$, $f'_s(a)$, and $f'_2(a)$ represent the three segments of $f'(a)$ in the three phases comprising A' . Eqs. 5 replace the first Eq. 1 in this expanded formulation, and are needed to obtain the labeling curves of Fig. 6. In addition, the second Eq. 1 is replaced by

$$dN'_0/dt = 2J'_2(t) - [\alpha'(t) + \beta'(t)]N'_0(t). \quad (7)$$

For a given choice of values of the parameters of the system and of initial conditions, Eqs. 1

and the corresponding equations for the normal compartments (Eqs. 28 and 29 of ref. 1), supplemented by Eqs. 3 and 4, were solved numerically with the aid of the CDC 6600 computer of the Courant Institute of Mathematical Sciences of New York University. Figs. 4-7 represent computer curves generated in this manner.

When $\bar{N}'(t)$ is small compared with \bar{N} , and the normal population is at its normal homeostatic level $N(t) = \bar{N}$, then α' and β' are essentially constant and given by Eqs. 2 as

$$\begin{aligned}\alpha' &= \bar{\alpha}' = \alpha'_0 + \alpha'_1 \log(\bar{N}'/\bar{N}), \\ \beta' &= \bar{\beta}' = \alpha'_0 + \beta'_1 \log(\bar{N}'/\bar{N}).\end{aligned}\quad (8)$$

Then it is possible to show that the leukemic compartment populations can exist in a state of steady exponential growth with growth rate γ , that is,

$$N'(t) = c e^{\gamma t}, \quad (9)$$

where c and γ are constants. γ is given as the solution to the transcendental equation

$$\bar{\alpha}' + \bar{\beta}' + \gamma = 2\bar{\alpha}' e^{-\gamma T'_A}, \quad (10)$$

with $\bar{\alpha}'$ and $\bar{\beta}'$ defined in Eq. 8. If $\gamma T'_A \ll 1$, then Eq. 10 can be simplified and solved explicitly for γ , that is,

$$\gamma = (\bar{\alpha}' - \bar{\beta}')/(1 + 2\bar{\alpha}' T'_A). \quad (11)$$

The doubling time is expressed in terms of γ as $\gamma^{-1} \log 2$. The natural lifetime of the acute myeloblastic state can be estimated as, essentially, the time τ it takes one cell to grow into 10^{12} cells. Thus, from Eq. 9, with $c = 1$ and $N'(\tau) = 10^{12}$,

$$\tau = \gamma^{-1} 12 \log 10 = 27.6 \gamma^{-1}. \quad (12)$$

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