A MATHEMATICAL MODEL OF THE CHEMOTHERAPEUTIC TREATMENT OF ACUTE MYELOBLASTIC LEUKEMIA

S. I. RUBINOW *and* J. L. LEBOWITZ

From the Graduate School of Medical Sciences, Cornell University, New York 10021

ABSTRACT Based on our previous mathematical model of the acute myeloblastic leukemic (AML) state in man, we superimpose a chemotherapeutic drug treatment regimen. Our calculations suggest that small changes in the protocol can have significant effects on the result of treatment. Thus, the optimal period between drug doses is the *S*-phase interval of the leukemic cells—about 20h—and the greater the number of doses administered in a given course treatment, the longer the rest interval should be before the next course is administered. For a patient with a "slow" growing AML cell population, remission can be achieved with one or two courses of treatment, and further suppression of the leukemic population can be achieved with continued courses of treatment. However, for patients with a "fast" growing AML cell population, a similar aggressive treatment regimen succeeds in achieving remission status only at the cost of very great toxic effects on the normal neutrophil population and its precursors.

INTRODUCTION

The knowledge that some chemotherapeutic agents such as arabinosyl cytosine (ara-C) are cell-cycle specific has provided a rational basis for drug-treatment protocols that depend on the kinetic properties of the cell population to be eliminated. In the hands of Skipper and his collaborators (1), such consideration has produced protocols that have succeeded in curing mice of L-1210 leukemia. A parallel development in the treatment of human leukemia has been the introduction of the L-2 protocol in the treatment of acute lymphoblastic leukemia (ALL) by investigators at the Memorial Sloan-Kettering Cancer Center (2–4). In addition, the L-6 protocol has been introduced for the treatment of acute myeloblastic leukemia (AML) and of related myeloid forms of this disease (5). These protocols have significantly extended both the incidence of remission and the mean survival time of all patients. Thus (6), the incidence of remission of 56% in previously untreated patients was achieved, with a median duration of remission of 10 mo. The median survival time of responders was 2 yr, whereas prior to 1966, the median survival time of adults with AML, was about 4 mo.

The essential rationale of the L-6 protocol has been previously reported (7, 8): Drug doses of the cycle-specific drug ara-C in combination with 6-thioguanine (TG) are administered sufficiently close together in time so that leukemic cells are prevented

from completing S-phase without being exposed to a lethal drug concentration. The duration of S-phase of leukemic cells is about 20 h (9). Treatments are continued until marrow depression or other toxic effects become too great, and a rest period is instituted, usually of 3 wk duration, to permit recovery of the normal marrow cells. The entire course of treatment is then repeated, if necessary, to a remission stage.

Aside from the significant achievement of extending the life of the patients involved, the important theoretical accomplishment of the introduction of these protocols is the principle that the protocol, which is to say the temporal course of administration of the chemotherapeutic agent, and not just the drug itself, is vital for the success of chemotherapy. The empirical nature of this accomplishment, achieved after many years of trial and error, leads very naturally to the suggestion that a mathematical model of the cell proliferation and treatment process could perhaps provide a completely deductive basis for success (or failure) of a chemotherapeutic drug regimen in the treatment of cancer. This conception has in fact appealed to a number of mathematically minded investigators of the cancer problem (10–14). The significance of mathematical modeling in understanding the kinetics of leukocyte proliferation and of the acute leukemic state has by now been generally recognized (15–18).

Here we shall describe our own efforts to model the essential kinetic features of the L-6 protocol. Our goal is to aid therapy and the medical chemotherapist, who is impelled to treat his leukemic patient in the best way he knows how, in the face of the many uncertainties about the nature of the disease state AML. Because of these uncertainties, we must make many presumptions and assumptions about the nature of the disease, as well as normal granulopoiesis. However, it is important to recognize that whether one detail of the model is correct or not is not so important as the general scheme: at the present time we are interested in suggesting improved strategies in chemotherapy, rather than the matching of a particular treatment regimen to a given patient.

Our model is purely a kinetic one that concerns itself with growth, birth, and death processes of cell populations, and associated homeostatic mechanisms. To represent the latter, only the existence of such control mechanisms is assumed, rather than the biological or biochemical means by which it is achieved. The search for such mechanisms, by a granulopoietic chalone (19), or by colony-stimulating factors (CSF) (20, 21) and CSF inhibitors (22), is of course being actively pursued in its own right. In previous work we have suggested a model of the neutrophil production system in normal man (23), as well as a model of the acute myeloblastic leukemic state (24). The basic features of our model can be described succinctly as follows. In the marrow of normal man there is a proliferative state and a nonproliferative state (see Fig. 1). The proliferative state consists of two compartments, an active or cycling compartment A and a resting compartment G_0. In G_0, the decision is made as to whether a precursor cell goes back to the active state and proliferates, or travels to the nonproliferative state, in which it matures, and is expelled to the blood as a young neutrophil. In the steady state, half of the cells leaving G_0 go to A and divide, while half go on to mature. If the population wishes to expand (contract), a greater (lesser) fraction of the

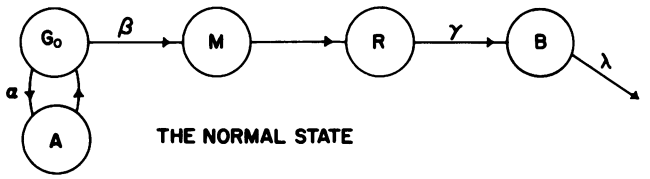

FIGURE 1 Schematic model of the normal neutrophil production system. The control functions α, β, and γ represent the fractional rate of release of cells along the indicated pathways, and depend on the total number of cells in the system (in the case of α and β), or in the blood (in the case of γ). λ is the time rate of cell disappearance from the blood compartment.

G_0 cells are sent to A than to the maturation compartment M. The decision as to which evantuality occurs depends homeostatically on whether the total population of neutrophils and precursors is greater or smaller than the prescribed total steady-state population number $\bar{N}$, where $\bar{N} \sim 10^{12}$ cells. There is also a mechanism in the nonproliferative state by means of which young neutrophils may be expelled to the blood, in response to need from the blood.

In the acute myeloblastic leukemic state, we adopt the point of view of Clarkson (7) that side by side with the normal neutrophil production system, there exists a distinct leukemic cell population. By and large it is a nonmaturing cell population, but it is controlled homeostatically in a manner similar to the normal population (see Fig. 2). However, the homeostatic level $\bar{N}'$ of the leukemic population is greater than the corresponding level of the normal cells, say $\bar{N}' \sim 3 \times 10^{12}$. Furthermore, the homeostatic control mechanism for the normal cells fails to recognize the leukemic cells as different from normal cells. Consequently, as the leukemic cells increase in their desire to reach their homeostatic level $\bar{N}'$, the normal cell production system is progressively curtailed as the leukemic cells approach and surpass the normal homeostatic level $\bar{N}$. Thus, the principal consequence of the exposure of the normal neutrophil population to the leukemic population is to destabilize the normal homeostatic control of the nonleukemic cell population. The combined system possesses a new stable state to which the population is (unfortunately) driven, in which all cells are leukemic, while normal neutrophils and their precursors disappear. Hence, we do not view the question as to whether leukemia is a neoplasm or a disorder of hemopoietic regulation as an

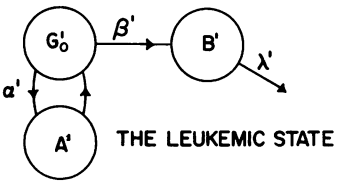

FIGURE 2 Schematic model of the leukemic cell population in the acute myeloblastic state. Primed compartments and control functions are counterparts of the normal neutrophil system. Leukemia marrow myeloblasts not actively proliferating are assumed to be in the resting state G_0'.

TABLE I

STEADY-STATE PARAMETERS OF THE NEUTROPHIL PRODUCTION SYSTEM IN A NORMAL 70 kg MAN*

Compartment	Mean transit time	Population no.
	h	
G_1	12	6.0×10^{10}
S	15	7.5×10^{10}
$G_2 + m$	3	1.5×10^{10}
A	30	1.51×10^{11}
G_0	20	1.01×10^{11}
M	96	4.85×10^{11}
R	90	4.54×10^{11}
B	9.7	0.49×10^{11}
Sum	246	1.24×10^{12}

*Taken from ref. 23.

either/or proposition (25). Rather, in our model, the existence of the neoplasm or leukemic cell population leads to destabilization of the normal regulated state.

The mathematical formulation and other details of the complete model can be found elsewhere (23, 24). The parameters that characterize the normal steady-state behavior of the neutrophil production system are summarized in Table I. The control functions α and β, which determine the fractional rates of cells leaving G_0 to enter either the compartments A or M, respectively, were represented either by a power law (23), or by a logarithmic law (24) with parameter values as shown in Table II. Previous experience with representing perturbations of the normal neutrophil system such as leukophoresis experiments, suggest that the power law, which has a more rapid rate of response than the logarithmic law, is more successful than the logarithmic law in doing so.

The principal effect of varying the parameters entering into either of these functions is to alter the fractional rate of exponential growth of the normal population, or recovery rate, in response to depletion as by chemotherapeutic insult. It can be shown (24) that this fractional growth rate is proportional to the difference $\alpha_1 - \beta_1$, where α_1 and β_1 are the dynamical parameters entering into the functions α and β. Thus,

TABLE II

PARAMETERS OF THE CONTROL FUNCTIONS* α AND β

Control function	α_0	α_1	β_1	ν	$\bar{N}$
	h^{-1}	h^{-1}	h^{-1}		
Logarithmic	0.05	0.0375	0.00417	—	1.24×10^{12}
Power	0.05	0.05	0.00417	3	1.24×10^{12}

*From refs. 23 and 24.

TABLE III

STEADY-STATE PARAMETERS OF THE LEUKEMIC CELL POPULATION IN AML*

Compartment	Mean transit time	Population no.
	h	
G_1'	0	0
S'	20	2.08×10^{11}
$G_2' + m'$	5	0.52×10^{11}
A'	25	2.60×10^{11}
G_0'	227	2.36×10^{12}
B'	36	3.75×10^{11}
Sum	288	3×10^{12}

*Taken from ref. 24.

the greater the excess of α_1 with respect to β_1, the greater is the recovery rate. The control functions α' and β' were represented by a logarithmic law.

The parameters determining the quasi-steady-state behavior of the leukemic cell population, characterizing the very late stages of AML, are given in Table III. By varying α_1' and β_1', models of leukemic cell populations with differing dynamical characteristics, that is to say natural growth rates and natural lifetimes, can be represented. Essentially two different models were investigated, a fast growing cell population and a slow growing cell population. The parameters α_1' and β_1' for these cases, together with the doubling time (in the presence of a normal neutrophil population) and mean lifetime (defined as the time needed for the population number to reach 10^{12}, starting from one cell), are given in Table IV.

The behavior of the leukemic blood cell population as a function of time is displayed in Figs. 3 and 4 for the two cases. This behavior is very similar to that of the total population. The normal blood cells maintain their normal level during the silent and unobserved period of exponential growth of the leukemic population, and then precipitously disappear when the leukemic population attains a detectable level of about 10^{11} cells.

In modeling a drug-treatment regimen, we superimpose a killing schedule on the natural history of the disease. Thus, we assume that the effect of administration of a

TABLE IV

PARAMETERS OF THE CONTROL FUNCTIONS OF TWO LEUKEMIC POPULATIONS

Model	α_0'	α_1'	β_1'	Doubling* time	Mean* lifetime	$\bar{N}'$
	h^{-1}	h^{-1}	h^{-1}	d	d	
Fast	0.0044	0.0044	0.00044	12	470	3×10^{12}
Slow	0.0044	0.0022	0.0011	56	1560	3×10^{12}

*Calculated from Equations 11 and 12 in ref. 24.

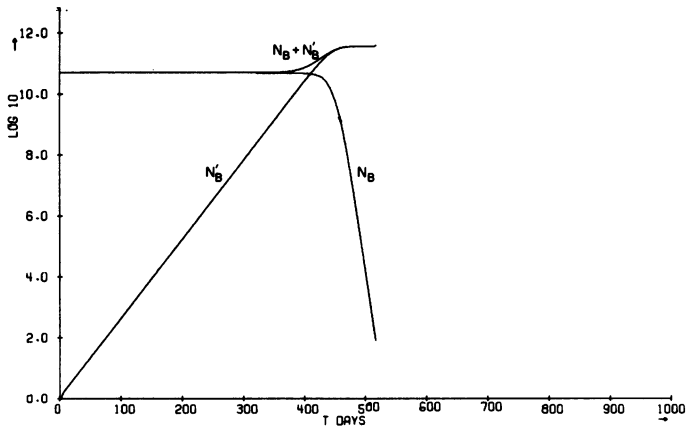

FIGURE 3 The ordinate represents, on a $\log_{10}$ scale, the number of normal neutrophils in the blood N_B, the number of leukemic myeloblasts N'_B, and the sum $N_B + N'_B$, as a function of time T in days, assuming 10 leukemic myeloblasts and introduced into the marrow at time zero. Parameters of the control functions α' and β', which determine the growth rate of this "fast" leukemic population, are given in Table IV.

dose of a drug or drug combination such as ara-C plus TG is to kill a fixed fraction f of all cells in S-phase, whether normal or leukemic. For purposes of calculation, the compartments A and A' are each subdivided into three compartments, namely, G_1, S, and $G_2 + m$. In all our calculations, it was assumed that $f = 0.9$ so that 90% of all cells in S were killed at the time of the drug administration. We considered the effect of treatment on both the fast and slow leukemic cell models. In simulating the L-6 protocol, we assumed that the drug combination was administered with a periodicity P for n times. Following this, a rest period of duration τ_R was imposed. We shall refer to the administration of a chemotherapeutic agent n times with periodicity P fol-

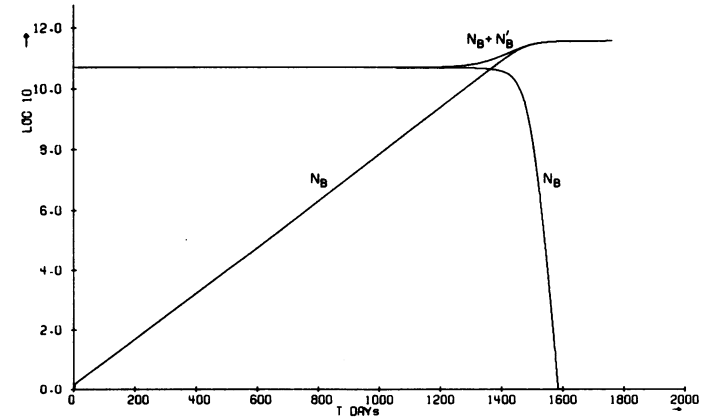

FIGURE 4 The same quantities as shown in Fig. 3 are here represented for the "slow" leukemic population of Table IV.

lowed by a rest period τ_R as a course of treatment. The regimen consisted of the course of treatment repeated six times. This corresponds to the most intensive treatment regimen attempted with the L-6 protocol. It is to be noted that the regimen contains two periodicities: a minor period equal to P, and a major period represented by the time interval between two successive rest periods. This major period equals $\tau_R + n P$.

In the clinic, the success of chemotherapy is measured firstly by the attainment of a remission status, which means the apparent elimination of leukemic myeloblasts from the blood and the reduction of myeloblasts in the marrow to normal levels. Such an apparent disappearance is attained if there is an approximately 100-fold decrease in the leukemic cell number. A precise clinical definition, which depends on the hemopoietic status of other cells, can be found elsewhere (5). For our purposes we shall conveniently define a state of remission as the reduction of the leukemic cell population to 10^{10} or less. We know from clinical experience that actual remissions can last for many months, and sometimes for years. Presumably, immunological or other factors are coming into play, not represented in our model, which make this possible. Hence, "success" in our model should be interpreted as the absolute reduction in the number of leukemic cells at a given time, while the toxic effect of chemotherapy is not too large: the normal population is at an acceptable level of depletion.

RESULTS OF CALCULATIONS

In attempting to assess the effects of the VAMP and BIKE chemotherapeutic protocols on patients with ALL, Freireich et al. (26) interpreted variability in observed remission time as a consequence of the variability in the number of cells killed in therapy. Such a view leaves unanswered the question as to why the same protocol applied to two different patients can differ by many orders of magnitude in the number of neoplastic cells killed. It would seem that an equally plausible interpretation is the one we have implicitly adopted herein: for a given protocol, variability in remission time is essentially a consequence of variability in doubling time.

There were several important effects that we attempted to investigate. First, we tried to examine the effect of variation of the periodicity P. Second, we varied the number of times n that the drug was administered. Third, we varied the time interval of rest period τ_R. Fig. 5 displays the temporal effect on the total populations of both the normal and leukemic cells of setting $P = 15$, 18, 20, or 24 (in units of hours). We had anticipated on naive grounds that the optimal periodicity for killing the leukemic population was $P = 20$, because the S-phase interval for the leukemic cells was 20 h, and hence such a schedule would kill leukemic cells at maximal efficiency. Of course, a periodicity of less than 20 h would also kill as many leukemic cells during a course of treatment, although the 20 h schedule extends over a longer period for a given number of drug administrations. However, the $P = 15$ schedule was expected to be most toxic for the normal cells, by the same argument, because the S-phase period of the normal cells was 15 h. It can be seen from Fig. 5 that these expectations were borne out by the calculations. The most severe depletion of the leukemic cells occurred for $P = 20$ hr.

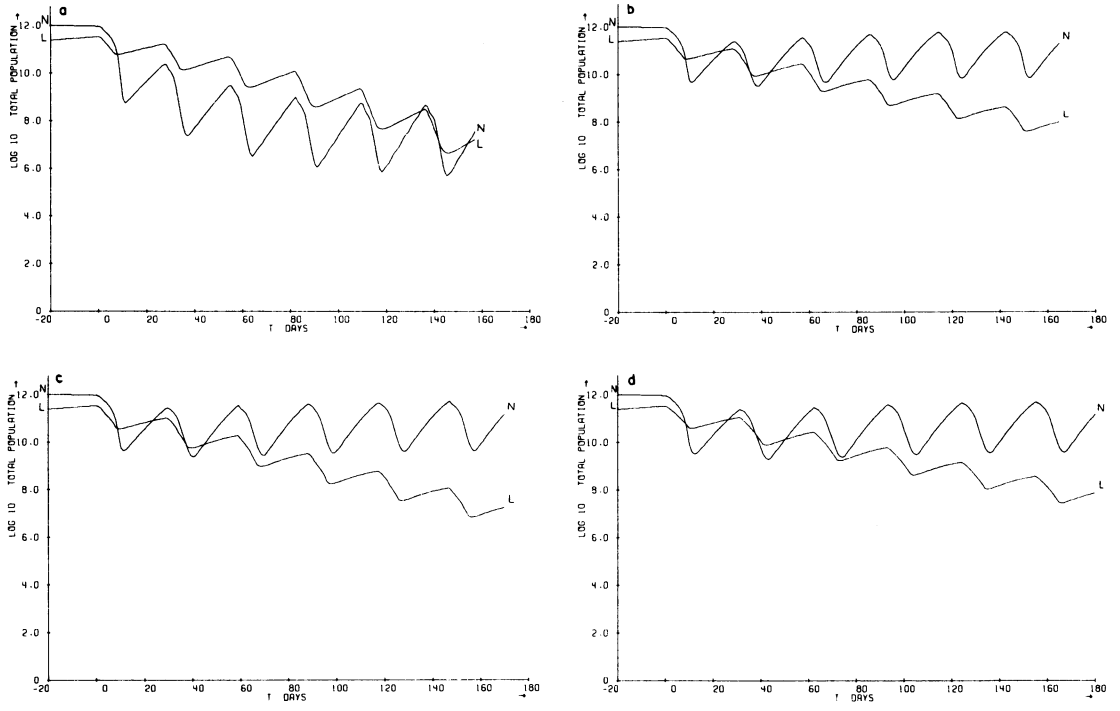

FIGURE 5 The ordinate represents, on a $\log_{10}$ scale, the total number of normal neutrophils and their precursors (labeled N) and the total number of leukemic myeloblasts (labeled L), as a function of time T during a drug regimen consisting of six courses of treatment. The treatment commences on day zero when the fraction of marrow leukemic myeloblasts (ratio of cells in $A' + G_0'$ to cells in $A + G_0 + M + R$) equals 0.25. The normal population is represented by the parameters of Table I and a logarithmic control function (see Table II), while the leukemic population is represented by the parameters of Table III and the "slow" model of Table IV. The treatment regimen parameters were as follows: Fraction of all cells f in S killed by a drug dose = 0.9; number of drug doses in each course of treatment was $n = 10$; rest period between successive courses of treatment was $\tau_R = 3$ wk; number of courses of treatment was six. (*a*) Periodicity between drug doses was $P = 15$ h; (*b*) $P = 18$; (*c*) $P = 20$; (*d*) $P = 24$.

In these calculations, the rest period τ_R was assumed to equal three wk, as in the actual L-6 protocol. The number of drug administrations in each major period was taken to be $n = 10$. The normal control functions were assumed to obey the logarithmic law. The leukemic population was represented by the slow model of Table II. It can be noted in the figures that the normal population always recovers much more rapidly than the leukemic population during the rest phases of the treatment. Perhaps slightly surprising is the comparison of Figs. 5*b* and 5*d*, which shows that the schedule with $P = 24$ appears to do as well as the schedule with $P = 18$. In fact, the former has a less toxic effect than the latter, as can be seen by comparing the minima in the normal population in the two cases.

The same schedule as above with $P = 20$ can not successfully deplete the fast growing leukemic population represented by the fast model, as shown in Fig. 6. Fur-

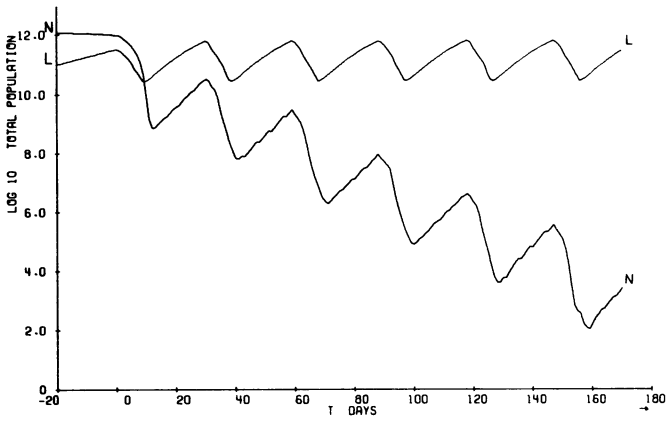

FIGURE 6 Same as Fig. 5 except that the normal population was represented by the power control function of Table IV, the leukemic population was represented by the "fast" model of Table IV, and $P = 20$.

thermore, the treatment has the additional undesirable quality of rapidly eliminating the normal population. The latter was modeled by a power law, with the same dynamical parameter values utilized in ref. 23 ($\alpha_0 = 0.05/\text{h}$, $\alpha_1 = 0.05$ h, $\beta_1 = 0.025$ h). Thus, the relative rapidity with which normal cells are sent into active phase in this model makes them more susceptible to the toxic effect of treatment. Also inimical to the recovery of the normal cell population during the rest periods is the presence of the relatively large leukemic cell population. Because normal cells identify leukemic cells as normal, the normal cell depletion does not appear as large to the control functions as it actually is.

In a further set of calculations, illustrated in Fig. 7, we retained the power law but increased the growth rate of the underpopulated normal cells by reducing the value of β_1 to 0.00417/h, and thus increasing the difference $\alpha_1 - \beta_1$. In addition, we extended the sequence of drug administrations to 20 in each of the major periods. For Fig. 7*a*, the recovery interval was assumed to be 3 wk. Although the normal population is here being eliminated, the effect of increasing n to 20 also leads to the elimination of the leukemic population. For Fig. 7*b*, the rest period was increased to 4 wk, with a concomitant dramatic improvement in the recovery behavior of the normal population, although the leukemic population is still being eliminated by this extremely intensive course of treatment. For Fig. 7*c*, the rest period was increased to 5 wk, and the results show that this period is too long. The leukemic cells are able to recover, and they are not reduced in number relative to the normal cells.

In the next set of calculations, illustrated in Fig. 8, the modeling of the normal population by a power law was retained, but the leukemic population was assumed to be the slow model. The treatment regimen is the same in this case as for that shown in Fig. 5*c*, so that the behavior of the leukemic population is predicatbly the same. However, it can be seen from a comparison of the behavior of the normal populations in

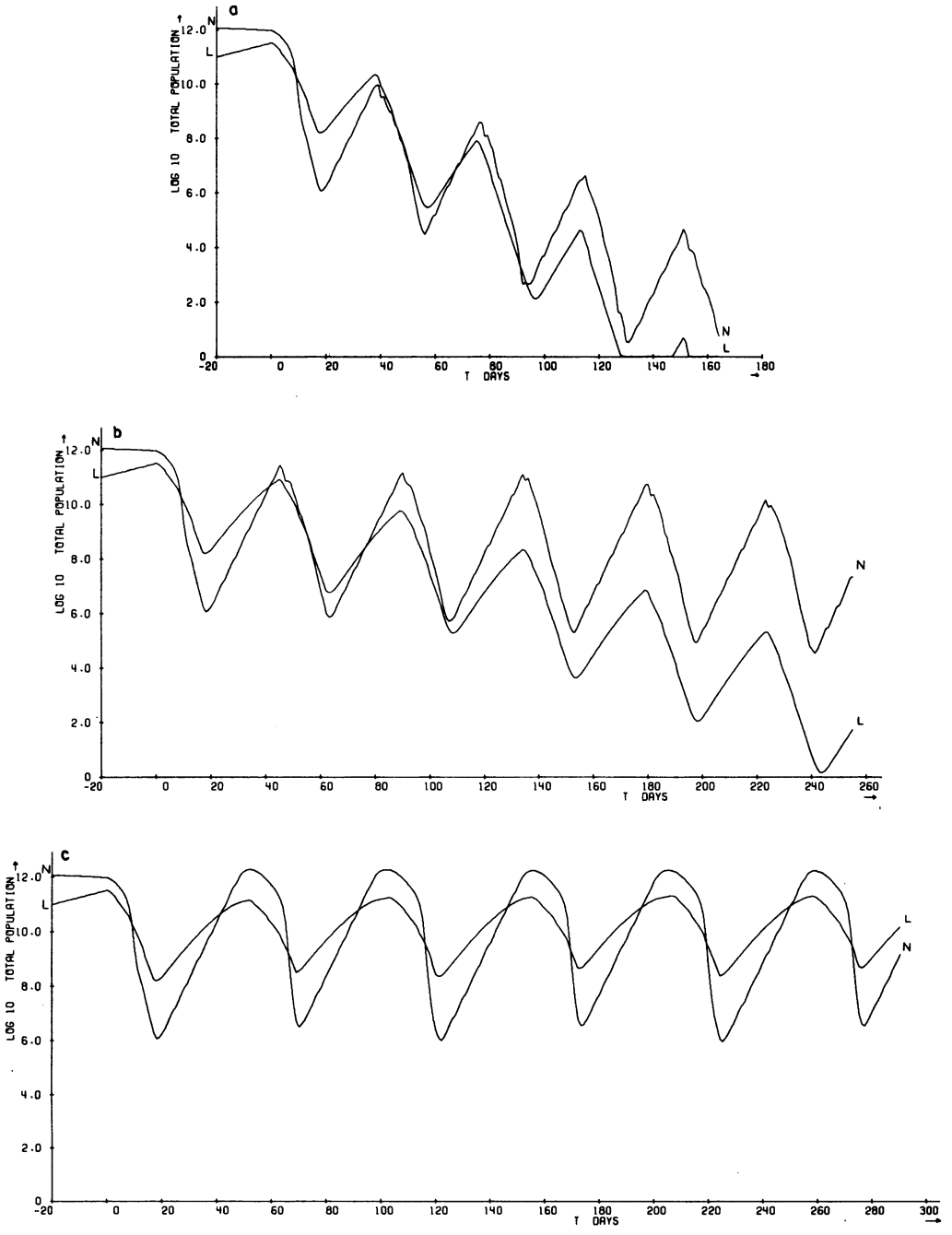

FIGURE 7 Same as for Fig. 6 except that $\beta_1 = 0.00417$/h, and the number of drug doses per treatment course $n = 20$. (*a*) The rest period was $\tau_R = 3$ wk; (*b*) $\tau_R = 4$ wk; (*c*) $\tau_R = 5$ wk.

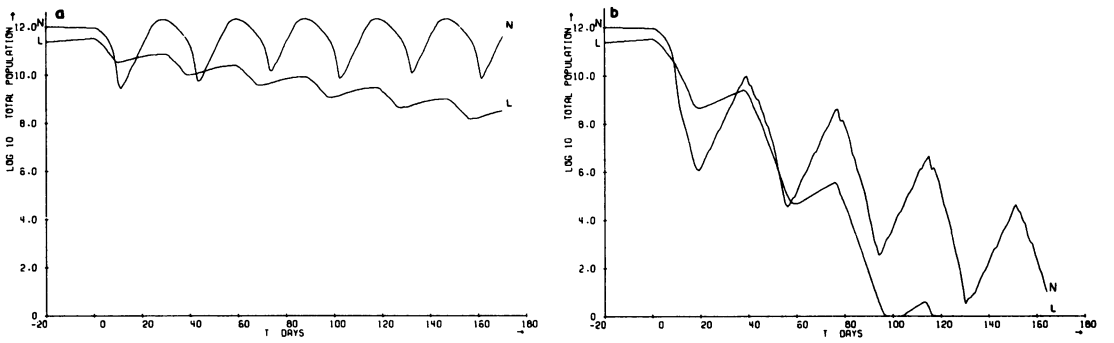

FIGURE 8 Same as for Fig. 5 *c* except that the normal population is represented by the power law of Table II. (*a*) $n = 10$; (*b*) $n = 20$.

Figs. 5*c* and 8*a* that the rate of recovery of the normal population following depletion from a course of treatment is more rapid for the power function. In both cases, it is seen that the total leukemic population is reduced to about 10^{10} cells after only one or two courses of treatment, in other words, a remission status is attained.

In Fig. 8*b* is shown the effect of the more aggressive treatment of the same population with n increased to 20. Here it is seen that the leukemic population is theoretically eliminated during the fifth course of treatment, although the toxic effect on the normal population is very great, and must be considered as unacceptable. (Perhaps the use of leukocyte transfusions or other support mechanisms could make such a course of treatment feasible.) We infer that the introduction of a 4 wk rest period in conjunction with $n = 20$ would benefit the normal population to a much greater extent than it would the leukemic population.

DISCUSSION AND COMPARISON WITH CLINICAL RESULTS

We are well aware of the many inadequacies of our model. Disease states such as smoldering leukemia may not be adequately represented by any set of parameter values. The toxic effect of chemotherapy on other cells in the body such as the epithelial cells in the gut is disregarded. The behavior of the leukemic population following the attainment of a state of remission is not correct, as we have indicated above. Variability of the S-phase is neglected. The possibility that a dose of ara-C inhibits cells from passing the $G_1 - S$ boundary (progression delay), as suggested by simulation studies of the effects of ara-C on L-1210 leukemia,[1] is not accounted for, although the model could be easily adapted to do so.

Nevertheless, as regards the kinetic characteristics of the normal neutrophil production system and of leukemic cells in AML, we believe our model does represent some present day experience in a reasonably semi-quantitative and realistic manner. Therefore, it seems fair to pose the following questions to it. What are the kinetic implica-

[1] Lincoln, T. Talk presented at Conference on Cell Kinetics and Cancer Chemotherapy, Annapolis, Md., Nov. 4–6, 1975.

tions of this knowledge in regard to chemotherapeutic regimens in the treatment of AML, and how can this knowledge be used to advantage? Can the L-6 protocol be improved merely by varying the temporal sequence of events, such as the major and minor periodicities, the duration of the rest period, the number of courses of treatment, and so forth? The analyses of our model of the L-6 protocol suggest that the answer to this last question is yes.

Our calculations show that significant changes occur with seemingly small alterations in scheduling parameters. For example, the theoretical results shown in Figs. 5–8 suggest that the optimum periodicity of drug doses is equal to that of the *S*-phase interval of leukemic cells, or 20 h. It is of interest to compare the latter conclusion with the actual practice of the L-6 regimen, which called for a periodicity of 12 h. Such a periodicity is roughly analogous to our calculations using a 15 h periodicity, which we found to be most unfavorable, because the toxic effect is severest. The remission rate achieved among 88 evaluable patients treated with the L-6 protocol was 56% (6). On the other hand, prior to the introduction of the L-6 protocol in 1970, of 36 evaluable patients treated with daily doses of ara-C plus TG, but without rest periods, 53% had complete or partial remissions. Hence, the use of a shorter period did not significantly increase the incidence of remission. In fact, the presumed advantage of the introduction of a rest period during treatment courses may have been counterbalanced by a disadvantage of utilizing a shorter period.

Our calculations also suggest that the more intensive a course of treatment is, the longer the rest period following it should be. We assumed, as in the actual L-6 protocol, that a course of 10 doses is followed by a rest interval of 3 wk duration. However, when 20 doses per course was utilized, then a longer rest period of about 4 wk duration is better than either 3 or 5 wk duration. In clinical practice the rest period apparently was variable (6), and depended on the clinical assessment of how well a patient had recuperated from the toxic effects of the previous dosage course. In this connection it should be noted that all our calculations were based on the initiation of therapy at a time when the marrow leukemic fraction equaled 0.25. In clinical practice, it can be presumed that the initiation of treatment could and often did occur at a later stage of the disease, when prognosis of therapeutic outcome is less favorable, from both a theoretical and empirical viewpoint, because the ability of the normal marrow to recover from the effects of treatment is considerably reduced.

It was very gratifying that two theoretical outcomes of our calculations were also observed in clinical practice. One was that in a case of favorable treatment, a remission is obtained after only one or two courses of treatment. In 20 out of the 49 observed remissions, 20 required exactly two courses of treatment. In all our calculations, the treatment was continued for six courses of treatment. In those cases where treatment was unfavorable after one or two courses because either the toxic effects were too great, or remission was not achieved, then continuing the treatment for six courses was usually even more detrimental to the normal population as compared with the leukemic population (see Figs. 6–7).

The L-6 protocol was actually carried out in several variations. In one of these,

regimen II, three additional courses of treatment were administered following the attainment of an M-1 marrow, and in nonresponders treatment was continued in an effort to achieve a remission status. This regimen was the least successful variation in achieving remission: the success rate was 18 out of 47 patients, or a 41% success rate. Furthermore, the median survival time of nonresponders was less than 2 mo. As suggested by Clarkson et al. (6), the more intensive treatment may have actually shortened survival time in these latter cases. A possible explanation, which is consistent with the results shown in Fig. 6, for example, is that in these cases the leukemic cell population is growing too rapidly and the toxicity effect is too large for the net effect of treatment to be beneficial.

However, the results shown in Figs. 5*b–d* and 8*a* suggest that, for a patient who does achieve a remission status, aggressive continuation of the chemotherapy with additional courses of treatment is advantageous, and in principle at least, as shown in Fig. 8*b*, could succeed in completely eliminating the neoplasm. Experience suggests that the better the remission status, the longer is the survival time. Hence, we conclude that the concept of aggressive continuation of chemotherapy should not be abandoned, but only for good responders, that is, individuals who do achieve remission status after two courses of treatment.

We found that for the fast growing leukemia, which had a natural lifetime of about 2 yr or so, treatment could be successful if very large toxic effects were acceptable. In contrast, treatment could be successful against the slow growing leukemia without such large toxic effects. This conclusion perhaps receives some clinical support from two recent studies of the correlations between kinetic parameters observed before the onset of treatment and the response to chemotherapy.[2] These investigators found that among those who achieved remission, an initial high labeling index (interpreted as a fast growing leukemia) was an unfavorable prognostic sign with regard to length of remission.

Our considerations emphasize once again our lack of knowledge of the dynamical behavior of the perturbed normal neutrophil population and of the AML cell population. The acquisition of such knowledge could be very beneficial in enhancing our understanding of the neutrophil system and in improving the strategy of treatment of AML by chemotherapy.

SUMMARY

We find that there are two important differences between the kinetic behavior of normal and leukemic cell populations that appear to be exploitable by means of regulation of chemotherapeutic protocols. One difference is that the normal population possesses a faster recovery rate from the cytocidal action of a course of treatment, than does the

[2]Vogler, W. R., W. B. Kremer, W. H. Knospe, G. A. Omura, and K. Tornyos. 1976. Synchronization with phase specific agents in leukemia and correlation with clinical response to chemotherapy. Submitted for publication; Hart, J. S., S. L. George, E. J. Freireich, G. P. Bodey, R. C. Nickerson, and E. Frei, III. 1976. Prognostic significance of pretreatment proliferative activity in adult acute leukemia. Submitted for publication.

leukemic population. However, in taking advantage of this difference, the length of the recovery period between two successive courses of treatment is a significant parameter that needs to be carefully adjusted. The second difference, which clinical investigators do not appear to have tried to take advantage of, is in the duration of *S*-phase in the two populations.

Dr. Rubinow is also affiliated with Sloan-Kettering Institute, New York 10021, and Dr. Lebowitz with the Physics Department, Belfer Graduate School of Sciences, Yeshiva University, New York 10019.

We wish to thank Dr. Bayard D. Clarkson for several helpful discussions of this work while it was in progress.

This work was supported in part by the National Cancer Institute, grant no. NCI R-5ROICA-12124-03.

Received for publication 14 April 1976.

REFERENCES

1. SKIPPER, H. E., F. M. SCHABEL, JR., and W. S. WILCOX. 1967. *Cancer Chemother. Rep.* **51**:125.
2. HAGHBIN, M., C. C. TAN, B. D. CLARKSON, V. MIKE, J. H. BURCHENAL, and M. L. MURPHY. 1974. Intensive chemotherapy in children with acute lymphoblastic leukemia (L-2 Protocol). *Cancer.* **33**: 1491.
3. GEE, T. S., M. HAGHBIN, M. D. DOWLING, I. CUNNINGHAM, M. P. MIDDLEMAN, and B. D. CLARKSON. 1976. Acute lymphoblastic leukemia in adults and children. Differences in response with a similar therapeutic regimen. *Cancer.* **37**:1256.
4. HAGHBIN, M., C. C. TAN, B. D. CLARKSON, V. MIKE, J. H. BURCHENAL, and M. L. MURPHY. 1975. Treatment of acute lymphoblastic leukemia in children with prophylactic intrathecal methotrexate and intensive systemic chemotherapy. *Cancer Res.* **35**:807.
5. GEE, T. S., K.-P. YU, and B. D. CLARKSON. 1969. Treatment of adult leukemia with arabinosylcytosine and thioguanine. *Cancer.* **23**:1019.
6. CLARKSON, B. D., M. D. DOWLING, T. S. GEE, I. B. CUNNINGHAM, and J. H. BURCHENAL. 1975. Treatment of acute leukemia in adults. *Cancer.* **36**:775.
7. CLARKSON, B. D. 1972. Acute myelocytic leukemia in adults. *Cancer.* **30**:1572.
8. CLARKSON, B. D., M. D. DOWLING, JR., T. S. GEE, and J. H. BURCHENAL. 1973. Treatment of acute myeloblastic leukemia. *Bibl. Haematol. No. 39.* 1098.
9. CLARKSON, B. D., and J. FRIED. 1971. Changing concepts of treatment in acute leukemia. *Med. Clin. N. Am.* **55**:561.
10. MERKLE, T. C., R. N. STUART, and J. W. GOFMAN. 1965. The calculation of treatment schedules for cancer chemotherapy. Lawrence Radiation Laboratory Report No. UCRL-14505, Livermore, Calif.
11. STUART, R. N., and T. C. MERKLE. 1965. The calculation of treatment schedules for cancer chemotherapy. Part II. Lawrence Radiation Laboratory Report No. UCRL-14505 Part II, Livermore, Calif.
12. SHACKNEY, S. E. 1970. A computer model for tumor growth and chemotherapy, and its application to L-1210 leukemia treated with cytosine arabinoside. *Cancer Chemother. Rep. Part 1.* **54**:399.
13. STEWARD, P. G., and G. M. HAHN. 1971. The application of age response functions to the optimization of treatment schedules. *Cell Tissue Kinet.* **4**:279.
14. AROESTY, J., T. LINCOLN, N. SHAPIRO, and G. BOCCIA. 1973. Tumor growth and chemotherapy: mathematical methods, computer simulations, and experimental foundations. *Math. Biosci.* **17**:243.
15. CRONKITE, E. P. 1973. Granulocytes. *In* Best and Taylor's Physiological Basis of Medical Practice. J. R. Brobeck, editor. Williams & Wilkins, Baltimore. 4–75.
16. LUKES, R., and J. W. PARKER. 1971. Disorders of the hematopoietic system. *In* Concepts of Disease. A Textbook of Human Pathology. 5th edition. J. G. Brunson and E. A. Gall, editors. Macmillan Company, New York. 881–954.
17. CRONKITE, E. P., and P. C. VINCENT. 1969. Granulocytopoiesis. *Ser. Haematol.* **2(4)**:3.

18. STEEL, G. G. 1973. Cytokinetics of neoplasia. *In* Cancer Medicine. J. F. Holland and E. Frei, III, editors. Lea and Febiger, Philadelphia. 125–140.
19. BULLOUGH, W. S. 1975. Mitotic control in mammalian tissues. *Biol. Rev.* **50**:99.
20. ROBINSON, W., D. METCALF, and T. R. BRADLEY. 1967. Stimulation by normal and leukemic mouse sera of colony formation in vitro by mouse bone marrow cells. *J. Cell Physiol.* **69**:83.
21. BRADLEY, T. R., D. METCALF, and W. ROBINSON. 1967. Stimulation by leukaemic sera of colony formation on solid agar cultures by proliferation of mouse bone marrow cells. *Nature (Lond.).* **213**:926.
22. CHAN, S. H., and D. METCALF. 1970. Inhibition of bone marrow colony formation by normal and leukaemic human serum. *Nature (Lond.).* **227**:845.
23. RUBINOW, S. I., and J. L. LEBOWITZ. 1975. A mathematical model of neutrophil production and control in normal man. *J. Math. Biol.* **1**:187.
24. RUBINOW, S. I., and J. L. LEBOWITZ. 1976. A mathematical model of the acute myeloblastic leukemic state in man. *Biophys. J.* **16**:897.
25. METCALF, D. 1971. The nature of leukaemia: neoplasm or disorder of haemopoietic regulation. *Med. J. Aust.* **2**:739.
26. FREIREICH, E. J., E. S. HENDERSON, M. R. KARON, and E. FREI. 1968. The treatment of acute leukemia considered with respect to cell population kinetics. *In* The Proliferation and Spread of Neoplastic Cells (21st Annual Symposium on Fundamental Cancer Research, 1967). Williams & Wilkins, Baltimore. 441–452.