

TUMOR GROWTH PATTERNS IN MULTIPLE MYELOMA

JAMES A. HOKANSON, PhD,*|| BARRY W. BROWN, PhD,* JAMES R. THOMPSON, PhD,[†]
BENJAMIN DREWINKO, MD, PhD,[‡] AND RAYMOND ALEXANIAN, MD[§]

Serial changes in tumor mass were evaluated in 61 patients with multiple myeloma who had received intermittent courses of melphalan-prednisone until death. The variations in the kinetics of tumor reduction and relapse could be explained by a mathematical model based on two cell populations, one sensitive to and one resistant to chemotherapy. For all responding patients, the median tumor halving-time was 1.3 months and the median doubling time was 2.9 months. The duration of a constant tumor mass during remission was brief in most patients. A larger fraction of resistant cells prior to therapy was associated with a slower tumor doubling-time during relapse. With a constant fractional reduction of sensitive cells and a tumor halving-time of one month or less, all cells sensitive to alkylating agents would be eliminated with 3 years of uninterrupted intermittent therapy.

Cancer 39:1077-1084, 1977.

CLARIFICATION OF THE GROWTH KINETICS OF human cancer may provide a more rational basis for future improvements in treatment. Multiple myeloma is a malignant disorder involving plasma cells which, because of the production of a measurable marker protein, provides a useful model for the study of tumor growth kinetics. The kinetics of tumor change were analyzed in 61 myeloma patients who had received a standard program of chemotherapy until death. A mathematical model based on the concept of two malignant cell populations, one drug-sensitive and one drug-resistant, was used to describe the data. Results indicated an initial rapid decrease in tumor mass with therapy, followed by a short period of steady-state tumor mass during remission, and then a relapse mani-

fested by unimpeded growth of a drug resistant cell population.

METHODS OF STUDY

Sixty-one patients with multiple myeloma in whom chemotherapy had been initiated between 1965 and 1973 were studied. All patients with sufficient data for analysis were included. This excluded only patients who died within 6 months of initiation of therapy and patients without 6 or more sequential determinations of myeloma protein levels. The median age was 58; 51% were males. All had serum monoclonal myeloma proteins, 48 of IgG and 13 of IgA type; patients with only Bence-Jones proteins or without serum myeloma proteins were excluded from this study. All patients received intermittent courses of melphalan and prednisone at approximately constant intervals until death, according to one or several dose regimens described elsewhere.^{1,3}

In general, response to treatment could be classified according to two categories: patients whose tumor mass was reduced by therapy but whose serum M-component peak was evident at each measurement and patients whose serum peak disappeared from the electrophoresis strip. However, in order to obtain complete patterns of tumor reduction and regrowth, only patients followed continuously until death were included in the analysis.

The serum myeloma protein production rate was used as an index of changing tumor

From the University of Texas System Cancer Center M.D. Anderson Hospital and Tumor Institute, and Rice University, Houston, Texas 77030.

Supported by U. S. Public Health Service Grants CA-11430, CA-03195, and CA-05831; and ONR Grant NR-042-283.

* Department of Biomathematics, M. D. Anderson Hospital.

[†] Department of Mathematical Sciences, Rice University.

Department of Clinical Chemistry and Laboratory Medicine, M. D. Anderson Hospital.

[‡] Department of Medicine, M. D. Anderson Hospital.

§ Present address and address for reprints: Dr. James A. Hokanson, Biostatistician, Cancer Center, Room 226 Basic Science Building, The University of Texas Medical Branch, Galveston, Texas 77550.

Received for publication May 17, 1976.

mass.^{2,23} Myeloma protein production rates were calculated from clinical measurements obtained at 6-week intervals immediately prior to each treatment course. The production rate was derived as previously described from the serum myeloma protein concentration, the catabolic rate of the abnormal globulin,^{2,24} and the plasma volume. Plasma volumes were estimated from the hematocrit and body weight in 53 patients^{2,24} and were measured directly using standard radioisotope techniques in eight patients.^{2,24} Comparative studies of tumor mass change in patients with serial plasma volume measurements showed no significant differences in tumor halving or doubling times when compared to results using estimated plasma volumes; however, the magnitude of the maximum tumor reduction was probably underestimated in some patients with a markedly increased plasma volume. Values for myeloma protein production rate were expressed as a percentage of the pretreatment value and plotted against time until death. Based on specific laboratory criteria, a clinical tumor mass grade of "high", "intermediate", or "low" was assigned to each patient before the initial course of treatment.^{4,6,8}

Two mathematical functions were used to model the data and are presented in order of increasing complexity. Basic to both models was the assumption that the tumor in untreated patients was composed of two cell populations, one comparatively drug-sensitive and the other drug-resistant.⁷ A constant fractional cell kill for sensitive cells was also assumed. In order to describe the observed serial tumor mass changes in the most simple terms, a double exponential model was developed (Fig. 1a).

The double exponential model, formulated by

$$Y(t) = (1 - p) \exp(-\alpha t) + p \exp(\beta t)$$

where $Y(t)$ is the tumor mass at time t , used the sum of two independent exponential functions to describe tumor kinetic behavior during the clinical phase of the disease (Fig. 1). The model required three parameters: p , the drug-resistant fraction of the tumor at the time of the initial treatment; α , the net rate of decay of the sensitive population, which was related to the time required to reduce the sensitive population by one-half (tumor halving-time = T_h) by $\alpha = \ln 2/T_h$; and β , the net rate of growth of the resistant population, which was related to the doubling-time of the resistant tumor mass (tumor doubling-time = T_d) by $\beta = \ln 2/T_d$. According to the double exponential model, the halving time of the sensitive population corre-

sponded approximately with the initially observed tumor halving-time; the doubling-time of the resistant population corresponded approximately with the observed tumor doubling-time during relapse.

In order to evaluate the likelihood that the tumor growth rate decreased with tumor progression,^{12,20,21,23} a second function was evaluated that required an additional parameter for describing changes in tumor growth rates as a function of tumor size. This model (Fig. 1b) was formulated by

$$Y(t) = (1 - p) \exp(-\alpha t) + p \exp(K(1 - \exp(-\kappa t)))$$

and was called the exponential-Gompertzian model. This model used the sum of an exponential decay and a Gompertzian regrowth function to fit the data.²⁵ the parameters p and α were defined as before; $p(\exp(K))$ was a theoretical asymptotic maximum value of tumor mass, and $(1 - \exp(-\kappa t))$ was an expression for the changing growth rate at time t . Sensitive and resistant tumor cell populations were assumed as before, with the additional assumption that the growth rate of the resistant population decreased with time.

The data from each patient were evaluated using both models. A computer program was used that could find the values for α , β , and p that would generate the double exponential equation with the best least-squares fit to a patient's data. The tumor halving-time was obtained primarily from the regression portion of the data curve and the tumor regrowth parameters primarily from the relapse portion, while estimates of the initial fraction of resistant cells required knowledge about both portions of the data curve. The criteria for the quality of fit was the sum of the squares of deviations (SSDs) of the calculated values from the observed values. Those values producing the minimum SSD between a patient's data and the double exponential equation were used to define the calculated tumor mass curves such as those illustrated in Fig. 2. The values for the parameters of the exponential-Gompertzian model were obtained in an analogous fashion, although a fourth parameter, for growth rate inhibition, was also calculated for this equation. Tumor halving-times were also calculated for all patients on whom the M-component disappeared from the electrophoresis strip; however, since most of these patients died before the relapsing growth kinetics could be defined, their halving-times were analyzed separately. In these

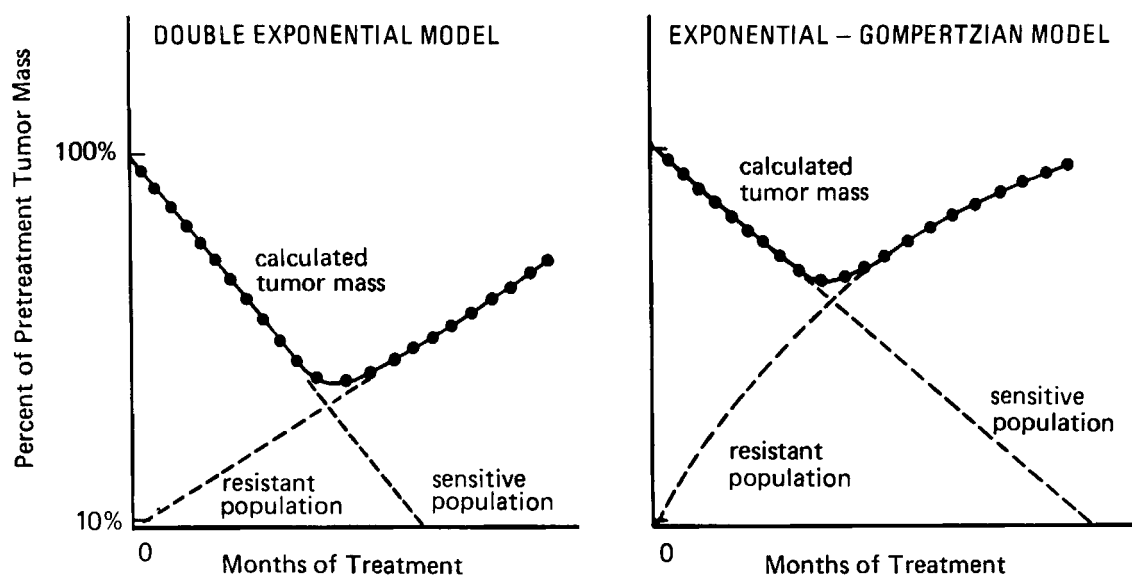


FIG. 1. Illustration of the two mathematical models used in the analysis of myeloma patient data.

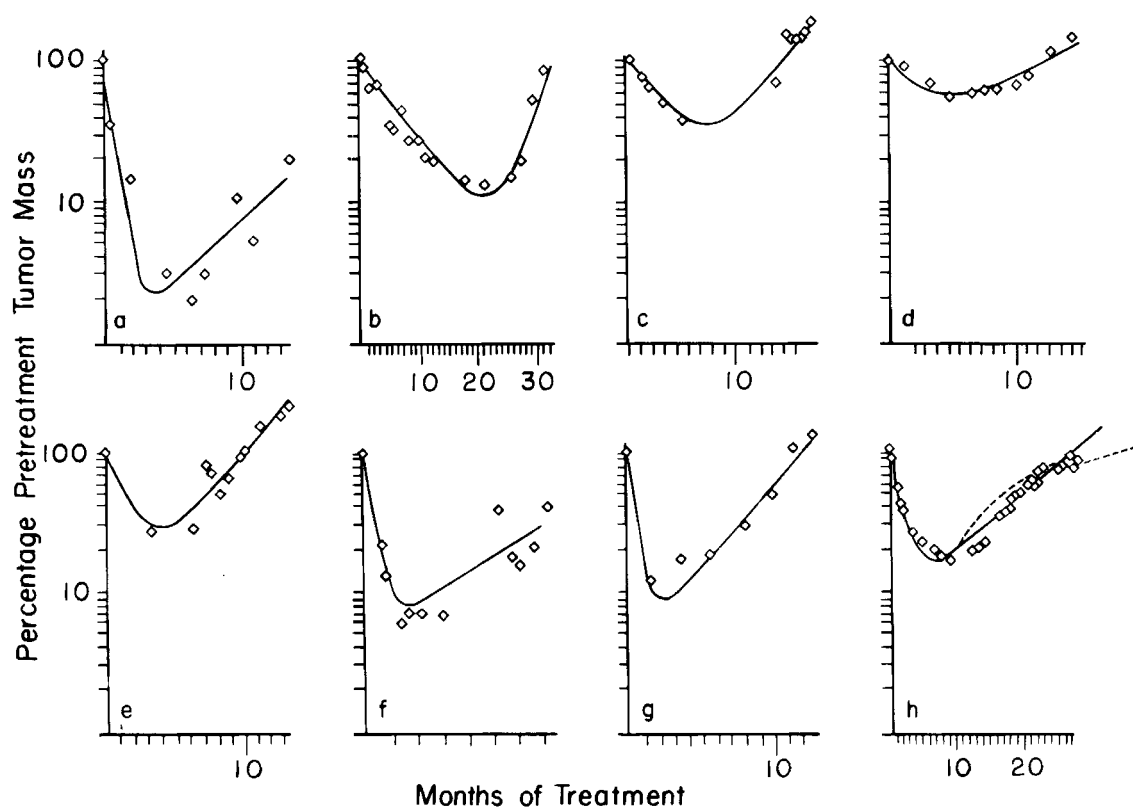


FIG. 2. Curves calculated from serial measurements of tumor mass in eight patients using the double exponential model. Fig. 2h (dotted line) illustrates the curve calculated for one patient using the exponential-Gompertzian model. Abscissa indicates months of treatment and ordinate is percentage of pretreatment tumor mass.

patients it was not possible to compute doubling-times or the initial fraction of resistant cells.

RESULTS

The usual pattern of tumor mass change was a decrease in tumor mass with therapy, followed by a brief constant level during remission before progressive relapse with recurrent tumor growth. Forty of the 61 patients were considered responsive because they achieved a reduction of myeloma protein production rate to less than 25% of the pretreatment values;¹⁻³ the remaining 21 were considered unresponsive. The median tumor halving-time was 1.2 months for responders and 3.8 for unresponsive patients. By the Mann-Whitney U test, this difference was statistically significant ($p < 0.01$). During relapse, the median tumor doubling-time for responders was 2.9 months; for unresponsive patients, the median tumor doubling-time was 6.9 months. This difference was also statistically significant ($p < 0.01$). Table 1 summarizes the findings calculated from our models.

In responding patients, the duration of a constant tumor mass during remission was defined as the period after maximum reduction that the serum myeloma protein production rates rose

from the lowest value by less than an amount equal to 10% of the pretreatment value. In only 11 of the 33 responding patients with both a regression and relapse phase was the tumor mass constant for longer than 6 months. The period of constant tumor mass for the seven patients who died in remission could not be determined. In all of the remaining patients, the myeloma protein production rates increased by more than 10% of the pretreatment value within 6 months of the lowest tumor mass measurement. For non-responders, a steady-state tumor protein production rate was encountered more frequently. Ten of the 21 non-responding patients had a period of 6 months or longer where there was no apparent change in tumor mass.

Both mathematical models conformed well with the data. There were no statistically significant differences between the results obtained with either model. However, in 51 of 54 patients with both a regression and relapse phase, the double exponential model gave a smaller error. In the remaining three patients, the exponential-Gompertzian model was superior. Figure 2 exhibits calculated curves using the double exponential model for eight representative patients. In addition, Fig. 2h shows the curve

TABLE 1. Kinetic Parameters Calculated for Patients with Multiple Myeloma

Protein type	Tumor mass grade	Tumor halving time (months)		Tumor doubling time (months)		Percent resistant cells	
		Median	Range	Median	Range	Median	Range
Responding patients with both regression and relapse phases N = 33	H	0.811	0.3-3.8	2.7	0.5-5.4	0.2	0.00001-5.0
	G I	1.5	0.3-5.2	6.9	0.8-10.5	1.2	0.0001-10.0
	L	1.1	0.4-5.2	2.19	1.4-9.9	0.08	0.00001-11.0
	TOTAL G	1.3	0.3-5.2	3.01	0.5-10.5	0.28	0.00001-11.0
	A	0.60	0.39-2.8	3.0	0.5-35.0	0.28	0.0001-34.0
Responding but with disappearing peaks N = 7	I	—	—	—	—	—	—
	L	—	—	—	—	—	—
	TOTAL A	0.60	0.39-2.8	3.0	0.5-35.0	0.28	0.0001-34.0
	TOTAL G and A	1.2	0.3-5.2	2.9	0.5-35.0	1.3	0.00001-34.0
		1.9	0.9-2.8	—	—	—	—
Non-responding patients N = 21	Total responding N = 40	1.3	0.3-5.2	2.9	0.5-35.0	1.3	0.00001-34.0
	H	3.8	1.2-17.0	6.3	0.7-37.0	7.8	0.8-35.0
	G I	2.8	1.3-11.8	13.0	1.4-50.0	4.0	0.05-48.0
	L	8.0	1.2-17.3	3.0	0.7-50.0	5.0	0.1-48.0
	TOTAL G	3.8	1.2-17.3	6.0	0.7-50.0	5.0	0.05-48.0
	A	2.3	1.2-6.9	6.4	4.6-7.0	1.6	0.1-3.0
	I	4.6	—	46.0	—	.25	—
	L	—	—	—	—	—	—
	TOTAL A	3.1	1.2-6.9	10.0	4.6-46.0	1.4	.1-3.0
	TOTAL G and A	2.8	1.2-17.3	7.0	4.6-46.0	0.329	.1-3.0
N = 61	Total non-responding	3.8	1.2-17.3	6.92	0.7-50.0	4.0	0.1-48.0
	Total for all patients	1.92	0.3-17.3	4.0	0.5-50.0	2.98	0.00001-48.0

obtained from the exponential-Gompertzian model (dotted line) for a patient with an apparent slowing of tumor growth rate during relapse.

Further analyses were conducted of the relationship between the calculated tumor-halving times, the tumor doubling-times, and the initial fraction of tumor mass considered resistant to chemotherapy. Using either model, the higher the pretreatment percentage of resistant cells, the longer the tumor doubling-time. (Bivariate Pearson correlation coefficient $\rho = 0.67$, $p < 0.01$ for the exponential-Gompertzian model). There were no statistically significant correlations between the tumor mass halving-times and either the doubling times or the initial fraction of resistant cells, using either model. There were no statistical associations between protein type (IgG or IgA) and the kinetics of tumor reduction or regrowth. There were no significant differences in the halving-time between those responding patients whose M-component disappeared and those responding patients whose tumor mass was followed continuously throughout the course of the disease. However, the halving-times in patients with disappearing peaks were among the most rapid halving-times observed. Using the Myeloma Staging System proposed by Salmon,⁸ there were no statistically significant associations between the absolute tumor cell numbers and the parameters of tumor reduction and regrowth. There were no statistically significant associations between the initial clinical tumor mass grade ("high", "intermediate", or "low")⁴ and either the halving-times, the doubling-time, or the initial fraction of resistant cells. Patients with a clinically established "high" tumor mass and a rapid doubling-time or those with a clinically "low" tumor mass but a slow doubling-time indicated the extremes of growth encountered in our analyses.

DISCUSSION

This study evaluated tumor growth patterns in a large number of treated patients with multiple myeloma. Only patients who had multiple sequential determinations of myeloma protein production rates, while receiving a standard program of treatment with intermittent courses of a melphalan-prednisone combination, were included. In an attempt to obtain representative data, patients were excluded for reasons of death within 6 months, insufficient numbers of measurements, or an interruption of their initial treatment program. Thus, a consecutive series of patients were studied who had serial assess-

ments of tumor mass and were following a standard program of treatment.

The myeloma protein production rate was used to assess the changing tumor mass. The tumor mass was calculated from the serum myeloma protein concentration on electrophoresis, the assumed catabolic rate of myeloma protein, and the plasma volume.² Since the plasma volumes were estimated in many patients from the hemoglobin and body weight, an overestimate of the tumor halving-time and an underestimate of the magnitude of tumor reduction was probably calculated in some patients with a markedly elevated pretreatment plasma volume. However, the differences resulting from measured vs estimated plasma volumes were not considered large enough to affect the findings in more than a small fraction of patients, leaving the principal conclusions essentially unaltered.

We assumed that alkylating agents produced a constant fractional kill of sensitive cells regardless of the absolute cell number. Other studies in human myeloma have demonstrated similar response rates for groups of patients with different tumor loads, supporting the hypothesis of a constant fractional kill of malignant cells.¹⁻³ Extensive studies in a variety of animal tumors also justify this assumption.

The course of the disease usually observed was an initial rapid decline in myeloma tumor mass as a result of successful treatment, followed by a later relapse as an ever-increasing tumor load developed despite continued courses of therapy. Two simple mathematical functions, one assuming an exponential fall and regrowth and the other an exponential fall but a Gompertzian regrowth, fitted our data closely. More elaborate functions, such as one incorporating parameters to account for non-steady state changes in myeloma protein metabolism per the first order differential equation suggested by Sullivan and Salmon,²³ may have reduced the possible overestimation of tumor halving and doubling times in our results due to the simple exponential functions we used to describe tumor regression and regrowth. Similarly, it is possible that the use of mathematically more complex functions may have produced a smaller error term between the model and the observed data. However, our goal was to accurately describe the observed tumor regression and regrowth data using a very simple but biologically consistent model. We found the concept of summed exponential functions sufficient for this purpose.

A computer program was used that could find values for α , β , and p that would generate the

double exponential equation with the best least-squares fit to a patient's data. Values for the α , p , κ , and K of the exponential-Gompertzian model were similarly obtained. Both mathematical models described the tumor mass change with treatment by an exponential decline with a rapid halving-time (median 1 month) suggesting that in some patients a large portion of the tumor cell reduction may have resulted only from the first course of therapy. This substantial antitumor effect with the initial treatment may explain the similar response rates for patients treated with intermittent courses of melphalan,¹⁻³ in comparison with those who received an initial loading dose followed by a continuous regimen.¹⁴ Some responding patients responded very slowly, requiring up to 18 months to achieve a 75% reduction in myeloma protein production rates. Patients who required many months to achieve remission may have had a slower growth rate for their resistant cell population, an occurrence that may have contributed to the longer survival times of some slowly responding patients.^{4,11}

Indefinite treatment with a specific drug combination, after all cells sensitive to that therapy have been eliminated, may be unjustified. Assuming that about 10^{12} myeloma cells were present in a typical patient with untreated myeloma,²³ that each course of therapy removed the same proportion of susceptible cells,^{1-3,22} and using a median tumor halving-time for sensitive cells of one month, the projected maximum time for the elimination of all sensitive cells would be about 3 years. Individual measurements of tumor halving-times might contribute toward the more rational planning of the duration of alkylating agent therapy for each treated patient. Responding patients with a rapid tumor reduction may require shorter terms of melphalan-prednisone maintenance therapy than patients with longer halving-times. These observations have major implications on the development of treatment protocols with more individualized durations of alkylating agent maintenance treatment.

Salmon used the regression portion of the growth curve of human myeloma under treatment to deduce a Gompertzian model for the kinetics of this disease.^{17-19,23} Essential to this work was the concept that the tumor growth rate decreased with increasing tumor size in a manner similar to that described for some animal tumors.^{12,21} According to this model, as tumor size decreased with repeated courses of therapy, an increased tumor growth fraction de-

veloped which balanced the effects of treatment so that the tumor mass remained constant for prolonged periods (i.e., in a plateau phase).²³

We confirmed patterns of myeloma tumor mass reduction similar to those described by Salmon.²³ However, a constant tumor mass of long duration during remission was uncommon in our patients. Only 10 to 33 responding patients with both a regression and relapse phase had an unchanging tumor mass for 6 months or longer. Most of the remaining patients had unequivocal evidence of relapse within several months after achieving their lowest tumor masses.

The reduced efficacy of therapy with time could be explained by an increasing fraction of resistant cells. Our arbitrary separation of myeloma cells into two subpopulations, one resistant and one sensitive, must be considered figurative since a spectrum of cell sensitivities is more likely.⁷ Yet our simple two population model provided a reasonable approach for interpreting our data. According to our model, the tumor mass halving-time corresponded with the reduction rate of sensitive cells, and doubling-time during relapse corresponded with the growth rate of resistant cells. During the brief intervening period of nearly constant tumor mass, our model suggested that an approximately equal mixture of both cell types was present.

In many tumors in which growth kinetics have been studied, including rodent myeloma, tumor growth rates have decreased with increasing tumor size.^{3,13,15,21} In our investigation of human myeloma, only the resistant tumor cell population could be evaluated for the presence of tumor-load-dependent growth-rate inhibition. Of the 61 patients studied, only three demonstrated growth-rate retardation during relapse with the exponential-Gompertzian model providing a closer approximation to the data than the double exponential model.

If absolute tumor size accounted for the retardation of tumor cell growth, responding patients who presented with lower numbers of myeloma cells might have had a more rapid doubling-time than those with larger tumor cell numbers. Yet, there was no relation between the absolute tumor cell mass and the doubling-time. Some patients with indolent myeloma and low initial tumor mass showed no growth for extended periods, while others with more extensive disease showed rapid growth. Until chemotherapy programs are developed that are capable of producing more marked degrees of tumor reduction, along with techniques for detecting very low

levels of serum myeloma globulins,¹⁶ differences between purely exponential and growth-rate inhibition models for the clinical phase of myeloma growth will not be readily apparent. Since human myeloma is not detected until the tumor clone has grown to about 10^{12} cells, models based on data that span less than two decades of tumor growth must remain speculative in regard to kinetic behavior during the 11–12 decades of tumor expansion during the pretreatment phase.

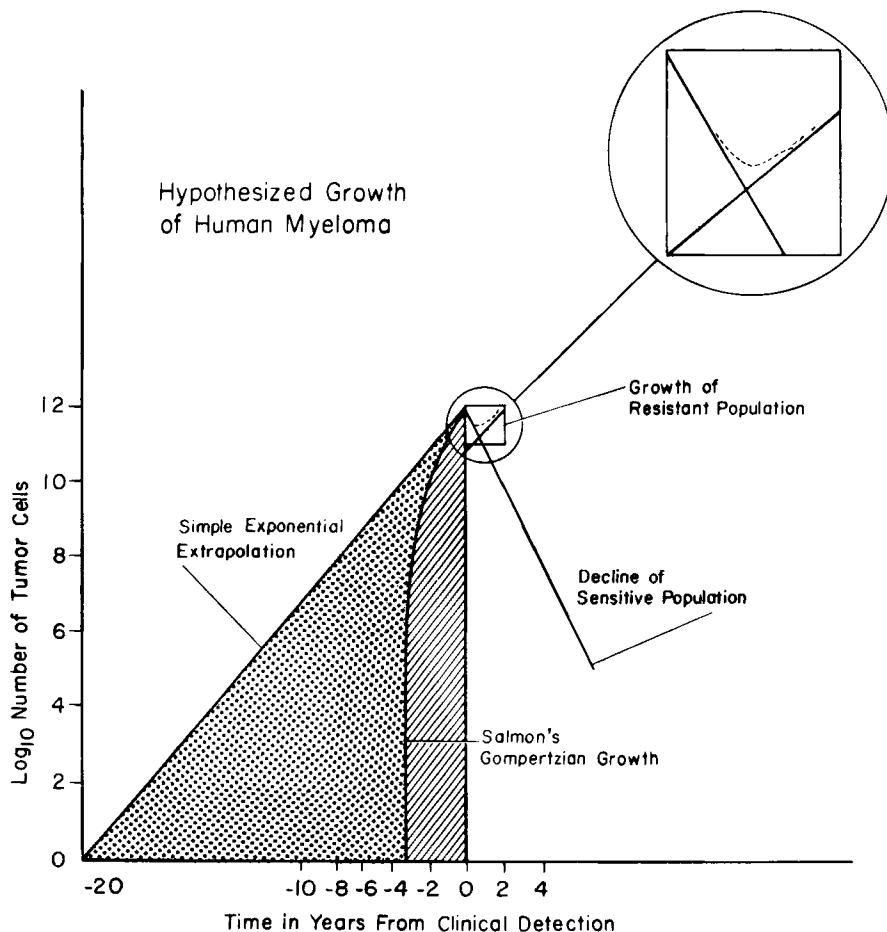
Evidenced by the longer duration of a nearly constant tumor mass in patients who did not achieve remission, our data suggested a difference in the rate of tumor growth between responding and non-responding patients that was related to the fraction of resistant tumor cells. Longer tumor doubling-times were associated with a higher pretreatment fraction of resistant cells. This association could be also explained by an inhibition of growth rate as a function of increasing size of the resistant population.¹³

However, when we utilized the exponential-Gompertzian model, which includes a term allowing for size-dependent growth-rate inhibition, this correlation between the doubling-time and fraction of resistant cells was even more pronounced.

However, as illustrated by Fig. 3, large differences between exponential and exponential-Gompertzian growth would not be readily apparent over the one decade range of tumor growth for which data are usually available. Even though exponential growth conformed with the data as well as Gompertzian growth, it is probably not an adequate model for the entire myeloma growth curve. Based on animal data, the growth kinetics of human myeloma are likely better described by a growth-rate-retardation model such as the Gompertzian model proposed by Salmon (Fig. 3).^{17–19,23}

From this we believe that the evolutionary period for human myeloma is much less than the exponential extrapolation of 20 years proposed

FIG. 3. Hypothesized growth curves of human myeloma illustrating differences in the duration of the preclinical period between pure exponential growth and Gompertzian growth. This diagram also illustrates the relative changes in tumor mass during the preclinical phase vs the clinical phase of human myeloma.



by Hobbs,⁹⁻¹¹ and closer to a 2- to 5-year period of Gompertzian growth as suggested by Salmon.¹⁷⁻²³ From a simplistic extrapolation from our tumor doubling-time of approximately 2 months, about 80 months at most would be required to produce 10^{12} cells from a single cell. More exact estimates await those refinements in myeloma treatment and detection techniques that will close the gap between hypothesized growth and measured tumor mass kinetics.

In summary, the mathematical models described in this paper closely conformed with

serial observation of myeloma tumor mass made during the clinical phase of the disease. As evidenced by concordance with observed serial tumor mass measurements, our results were compatible with the concept of "sensitive" and "resistant" tumor subpopulations in patients with multiple myeloma. Further exploitation of this approach, coupled with more sensitive electrophoretic techniques to detect low tumor mass levels, may provide a basis for future improvements in the understanding of myeloma growth kinetics.

REFERENCES

1. Alexanian, R. *et al.*: Treatment for multiple myeloma. *JAMA* 208:1680, 1969.
2. Alexanian, R., Bonnet, J., Gehan, E. *et al.*: Combination chemotherapy for multiple myeloma. *Cancer* 30:381-389, 1972.
3. Alexanian, R.: Prognostic factors in multiple myeloma. *Arch. Intern. Med.* 135:147-152, 1975.
4. Alexanian, R.: Prognostic factors in multiple myeloma. *Cancer* 36:1192-1201, 1975.
5. Aroesty, J., Lincoln, T., Shapira, N., and Boccia, G.: Tumor growth and chemotherapy-mathematical models, computer simulations, and experimental foundation. *Mathematical Biosciences* 17:243-300, 1973.
6. Conklin, R., and Alexanian, R.: Clinical classification of plasma cell myeloma. *Arch. Intern. Med.* 135:139-143, 1975.
7. Drewinko, B., and Alexanian, R.: Studies on the proliferation kinetics of plasma cell myeloma. *Proc. 17th Annual Meeting Am. Soc. Hematology* 94, 1974.
8. Durie, B. G. M., and Salmon, S. E.: Clinical staging system for multiple myeloma. *Cancer* 36:842-854, 1975.
9. Hobbs, J. R.: Monitoring myelomatosis. *Arch. Intern. Med.* 135:125-130, 1975.
10. Hobbs, J. R.: Immunochemical classes of myelomatosis. *Br. J. Haematol.* 16:599-606, 1969.
11. Hobbs, J. R.: Growth rates and responses to treatment in human myelomatosis. *Br. J. Haematol.* 16:607-617, 1969.
12. Laird, A. K.: Dynamics of growth in tumors and normal organisms. *Human Cell Kinetics* 30:15-29, 1969.
13. Mahaly, M. A., Thompson, J. R., Brown, B. W., and Alexanian, R.: A competitive model for chemotherapeutic myeloma treatment. *Biometrics* 30:562, 1974.
14. McArthur, J. R. *et al.*: Melphalan and myeloma—experience with a low dose continuous regimen. *Ann. Intern. Med.* 72:665-67, 1970.
15. Nathans, D., Fahey, J. L., and Potter, M.: The formation of myeloma protein by a mouse plasma cell tumor. *J. Exp. Med.* 108:121-126, 1958.
16. Ricks, J. *et al.*: Determination of idiotypic levels by radioimmunoassay during treatment of multiple myeloma. (In Preparation).
17. Salmon, S. E., Mackey, G., and Fudenberg, H.: Sandwich-solid-phase radioimmunoassay for the quantitative determination of human immunoglobulins. *J. Immunol.* 103:129-137, 1969.
18. Salmon, S. E., and Smith, B. A.: Immunoglobulin synthesis and total body tumor cell number in IgG multiple myeloma. *J. Clin. Invest.* 49:1114-1121, 1970.
19. Salmon, S. E.: Immunoglobulin synthesis and tumor kinetics of multiple myeloma. *Semin. Hematol.* 10:135-144, 1973.
20. Schabel, F. M.: The use of tumor growth kinetics in planning curative chemotherapy of advanced solid tumors. *Cancer Res.* 29:2384-2389, 1967.
21. Simpson-Herran, I., and Lloyd, H. H.: Kinetic parameters and growth curves for experimental tumor systems. *Cancer Chemother. Rep.* 54:143-174, 1970.
22. Skipper, H. E., Schabel, F. M., and Wilcox, W. S.: Experimental evaluation of potential anticancer agents—XIII. On the criteria and kinetics associated with "curability" of experimental leukemia. *Cancer Chemother. Rep.* 35:1-111, 1964.
23. Sullivan, P. W., and Salmon, S. E.: Kinetics of tumor growth and regression in IgG multiple myeloma. *J. Clin. Invest.* 51:1697-1708, 1972.
24. Waldman, T. A., and Strober, W.: Metabolism of immunoglobulins. *Prog. Allergy* 13:1-110, 1969.
25. Winsor, C. P.: The Gompertz curve as a growth curve. *Proc. Nat'l. Acad. Sci. USA* 18:1-8, 1932.