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(TID-4500)HEMATOLOGIC AND THERAPEUTIC EFFECTS OF TOTAL-BODY IRRADIATION
(50 R-100 R) IN PATIENTS WITH MALIGNANT LYMPHOMA, CHRONIC
LYMPHOCYTIC AND GRANULOCYTIC LEUKEMIAS, AND POLYCYTHEMIA VERA*G. A. Andrews, F. V. Comas, C. L. Edwards, R. M. Kniseley,
C. C. Lushbaugh, and Helen Vodopick

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TOTAL-BODY IRRADIATION (50 R TO 100 R) IN
PATIENTS WITH MALIGNANT LYMPHOMA, CHRONIC
LYMPHOCYTIC AND GRANULOCYTIC LEUKEMIAS,
AND POLYCYTHEMIA VERA

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Hematologic and Therapeutic Effects of Total-Body Irradiation
(50 R - 100 R) in Patients with Malignant Lymphoma, Chronic
Lymphocytic and Granulocytic Leukemias, and Polycythemia Vera*

G. A. Andrews, F. V. Comas, C. L. Edwards,
R. M. Kniseley, C. C. Lushbaugh, and Helen
Vodopick

Introduction

Since 1957 the staff of the Medical Division of Oak Ridge Associated Universities has been studying the hematologic and clinical courses of patients receiving total-body irradiation. In an early experiment the radiation therapy was done in connection with attempts to graft bone marrow (1). We also have studied intensively the hematologic courses of victims of accidental exposure to radiation (2-7). The present report covers the therapeutic and hematologic results of a ten-year study — 1959 through 1968 — of single exposures of 50 R and 100 R given at approximately 1.5 R/min in a specially designed facility for total-body radiation therapy. Some of the data from this series have been published previously in brief form (8).

This study was initiated with two principal objectives; the first was to seek information that might lead to improved radiation therapy for disseminated malignant disease, especially leukemia and lymphoma, by determining the best criteria for selection of patients, radiation dose, and dose rate. For many years radiotherapists have been able to control progression of certain hematologic disorders by giving "spray X-irradiation" and have obtained similar effects using internally administered radiation, in particular phosphorus-32 (9). Fractionation and dose protraction quite logically have been used to reduce the incidence of undesirable side effects and are believed also to decrease the damage to normal tissues more than to malignant ones. However, differences in fractionation, energy of the beams, and uniformity of exposures to different parts of the body make it difficult to evaluate and compare the effects of various radiation-exposure patterns used in such therapy.

The second objective was to acquire radiobiologic information. The radiobiologic aspects of total-body irradiation on man have been studied clinically

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since Walsh (10) first described radiation sickness in 1897. The dose-response relationships, however, are still poorly known and present estimates are based largely on conjectures and extrapolations from animal experiments, or from experience with accident victims, atom bomb casualties, and patients treated by irradiation. Because patients in the past ordinarily have been treated with divided doses, it has been difficult to compare biologic effects in the many clinical series with each other, or with the effects seen after radiation accidents.

We decided to obtain baseline data by giving individual doses of 50 or 100 R and then observing the patients long enough to evaluate effects. These single doses of radiation, somewhat higher than individual doses in a fractionated regimen, would provide a response that could be measured with a clear temporal relation to the date of irradiation. In contrast, an effect gradually induced by two or more variably spaced small doses would be more difficult to analyze and compare among groups of patients. Single exposures also would permit us to compare the hematologic responses with those of accident victims who usually receive single rapid exposures. Careful definitions of the effects of 50 R and 100 R, as attempted in this paper, are a necessary basis for later evaluating the effect of fractionation.

It was not our plan to evaluate the long-range effectiveness of these relatively large individual doses of total-body irradiation as a repetitive and sole therapy. This would have required establishing a total treatment plan with this technique, which we were not prepared to do. The larger doses provide a less continuous control, a possible disadvantage emphasized by Osgood. We wanted to be able to add or substitute other forms of treatment when specific clinical considerations seemed to indicate them. One should not infer from this study that we expected these individual or infrequently given exposures to produce better clinical results than fractionated total-body or portal irradiation. At present we feel that some pattern of fractionated exposure, such as that of R. E. Johnson (11), probably offers a preferable approach for total-body radiotherapy. The data reported here, by defining the range of clinical and hematologic effects that single exposures of 50 and 100 R can be expected to produce in these diseases, should provide a yardstick for comparisons in future total-body irradiation trials using different exposure patterns.

Such information, even though obtained in the abnormal conditions of disease, is helpful for assessing levels of accidental gamma and neutron irradiation injury and guiding therapeutic efforts. During the course of the study the urgent need arose for information on hematologic effects in man, since the National Aeronautics and Space Administration was faced with potentially high levels of radiation exposures in space exploration. The principal answers we sought were the pattern of responses for leukocytes, red blood cells, and platelets in chronic lymphocytic leukemia, lymphoma, chronic granulocytic leukemia, and polycythemia rubra vera. What differences occurred in response to 50-R and 100-R exposures? Did normal blood cells differ in radiosensitivity from their counterparts in proliferative disorders? For example, do platelets have a different radiosensitivity in chronic lymphocytic leukemia or lymphoma compared with polycythemia rubra vera? Or, do "normal" lymphocytes of polycythemia rubra vera have the same sensitivity as lymphocytes of chronic lymphocytic leukemia? We also wanted to observe

the degree and length of clinical improvement as manifested by relief of general symptoms, and regression of masses, lymph nodes, liver, and spleen. In addition, we wanted to determine the incidence and analyze the nature of the unpleasant symptoms of acute radiation exposure which are included in another study (12).

This report completes one phase of our total-body irradiation study program. In brief this study will: 1) provide baselines for the study of fractionation effects, 2) be simpler to analyze than more complex regimens, 3) provide information relevant to radiation injury in "normal" humans. It will not: 1) demonstrate that 50 or 100 R is better than the currently accepted fractionation modes, or 2) analyze the long-range therapeutic effectiveness of these doses.

Materials and Methods

Patients - A total of 89 treatments were given. This report covers information on 29 exposures to 50 R, and 55 to 100 R. The remaining five were dropped from the protocols because of an urgent need for additional or different therapy before the study was finished, or because of the patient's inability to meet the appointments for follow-up outpatient visits during the study period. The number exposed and their disease categories are listed in Table 1, along with the abbreviations used in the text.

All patients with these diseases admitted to the Medical Division hospital during this period were considered for this therapeutic program. The diagnoses were established by clinical history, physical examination, and microscopic study of surgical biopsies, bone marrow, and peripheral blood samples. The urgency for treatment was assessed, and those patients whose condition required some other kind of therapy, or no therapy at all, were omitted. If the clinical status was changing rapidly and we anticipated that other additional treatment might be needed during the postirradiation observation period, these patients were also excluded. If no clearly superior therapy was available for a particular patient and the total-body radiation treatment was regarded as an acceptable way of management, the patient was offered this form of treatment, following an explanation of the research protocol. Informed consent was obtained in accordance with ethical practice to protect the rights of the individual as a research subject. We recognize some bias in the selection of one of the two doses. In a concern for the patient's safety early in the study we evaluated only the results of 50-R exposures before using the higher dose. Later, some of the patients selected for the 100-R exposure were those with more pronounced symptoms, or in lymphoma, had tumor masses that were judged to need the more vigorous treatment. On reviewing histories and clinical status,* however, we believe that these biases are not sufficiently great to prevent us from comparing a 50-R group with a 100-R group. Other forms of treatment for the disease were discontinued before the irradiation, except that

* Summaries of clinical histories and status changes of the individual patients have been collated and included in the Appendix of this report.

in a few patients who required it, maintenance steroid therapy was kept up (see Tables D and E in Appendix). Of the patients with chronic lymphocytic leukemia, blood transfusions were given during the six-week posttreatment period (Table 2) to three exposed to 50 R and four patients exposed to 100 R. No other treatments were given during this time.

Table 1

Patients Exposed to Total-Body Radiation in Each of the Disease Categories

	50 R			100 R		
	1st R _x	2nd R _x	Total R _x	1st R _x	2nd R _x	Total
Chronic Lymphocytic Leukemia (CLL)	12	3	15	16	4	20
Malignant Lymphoma	5	0	5	17	5	22
Hodgkin's Disease	1	0	1	1	0	1
Chronic Granulocytic Leukemia (CGL)	6	2	8	4	0	4
Polycythemia Rubra Vera (PRV)	0	0	0	7*	1	8
Total			29			55

*One patient had primary hemorrhagic thrombocythemia rather than PRV.

Hodgkin's disease was originally included in the study but was eliminated early because we believed that a larger dose is needed to control the malignant process than we could safely give to the whole body at one time. The most effective modern therapy for this disease is irradiation of lymphatic tissues, sometimes involving large fields, but allowing some hematopoietic tissue to remain unirradiated. The lesions of this disease are generally less radio-sensitive and less intimately involved in hematopoietic tissue than those that can be helped by total-body irradiation.

Study Protocol - A uniform study protocol was devised to collect laboratory data on specified days during the six-week study period (Table 3). The six-week period of data collection was adopted as the most reasonable compromise between clinical research objectives and patient's needs; a longer period would

Table 2

The Requirement for Blood Transfusions in Patients with Chronic Lymphocytic Leukemia Before and After Radiotherapy with 50 R and 100 R TBI

Radiation Dose	No. Patients	Transfusions during 6 weeks pretreatment		Transfusions during 6 weeks posttreatment	
		No. Patients	No. Trans.	No. Patients	No. Trans.
50 R	13	3	18	3	15
100 R	8	3	15	4	31

have been clinically more desirable, and most of the patients continued under our care and had further observations. Because of the enormous spread of initial blood values, all results were normalized by using the immediate pretreatment values for each patient as 100%. In most instances, this value consisted of the average of day minus three and day zero (pretreatment) counts; in a few only day zero values were available. Table 4 gives the ranges and geometric means of the pretreatment data from which the normalized curves were derived.

Table 3

Protocol for Blood and Bone-Marrow Sampling Times Used in 50 R and 100 R TBI Study for All Patients

Radiation Day	-7	-3	0	+1	+2	+3	+4	+7	+14	+21	+28	+35	+42
Bone Marrow		x					x				x		
WBC, RBC, Platelets Blood Film, Hgb., Hct.	x	x	x	x	x		x	x	x	x	x	x	x
Uric Acid		x	x	x			x	x	x	x	x		

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Table 4

Range of Pretreatment Blood Values Among Patients in Each Category
(Average of Day -3 and Day 0)

Diagnostic Group	No. of Exposures	Leukocytes $\text{mm}^3 \times 10^3$			Absolute Lymphocytes/ $\text{mm}^3 \times 10^3$			Platelets/ $\text{mm}^3 \times 10^3$			Hemoglobin gm/100 ml		
		Range		Geom. Mean	Range		Geom. Mean	Range		Geom. Mean	Range		Geom. Mean
		High	Low		High	Low		High	Low		High	Low	
Polycythemia Vera 100 R	8	41.6	10.0	25.3	4.2	1.2	2.1	1,619	289	806.1	15.9	11.6	13.6
Chronic Lymphocytic Leukemia - 50 R	15	304.0	9.8	83.5	294.9	9.4	76.9	337	40	131.9	16.8	8.3	12.5
Chronic Lymphocytic Leukemia - 100 R	20	396.2	6.2	69.8	388.6	4.3	61.4	412	13	113.1	14.8	6.9	11.4
Chronic Granulocytic Leukemia - 50 R	8	463.9	52.1	114.5	9.8	1.4	3.5	1,061	211	446.5	14.2	9.0	11.3
Chronic Granulocytic Leukemia - 100 R	4	246.3	103.8	148.5	4.2	0.9	2.1	1,326	392	707.5	12.0	9.0	10.4
Malignant Lymphoma 50 R	5	14.2	6.5	9.6	9.9	1.6	4.5	23 ^R	50	134.1	16.2	9.7	13.5
Malignant Lymphoma 100 R	22	28.3	2.3	7.7	26.9	1.1	3.4	444	45	205.0	15.8	8.5	12.4
Hodgkins - 50 R	1			10.0			2.9			310			11.0
Hodgkins - 100 R	2	11.5	9.0		10.3	2.0		521.2	481.2	10.2	8.2		

Bone-marrow aspirations were performed according to the protocol described; we have decided not to present the findings in the present report.

Laboratory Methods

The hematologic studies were performed on venous blood samples using well established laboratory methods. The hemoglobin value was determined by the cyanmethemoglobin method and hematocrit percent by the Wintrobe method. Leukocytes and erythrocytes were counted electronically. Platelets were enumerated by the method of Brecher and Cronkite using phase microscopy (13). When platelet counts were low, dilutions of 1:20 were used rather than 1:100. The number of small squares counted in the chamber was increased to 10, 25, or 50 until more than 100 platelets were counted, or all platelets in 50 squares counted. In determining absolute lymphocyte values for patients with PRV, we performed differential counts on 400 leukocytes for greater statistical confidence.

The Radiation Facility and Dosimetry

The irradiation room, designated the medium-exposure-rate total-body irradiator (METBI), was completed in 1959; it is an eight-foot cube, concrete shielded, with a 385-curie source of cesium-137 in each of the eight corners. A maze connects the treatment room to its control room where a nurse or operator is in visual contact with the patient by a series of mirrors. The patient lies on an aluminum bed suspended in the center of a homogenous 2 x 2 x 6 foot radiation field. The beams from the eight sources are shaped so that the exposure rate is uniform to within $\pm 5\%$ within the treatment volume. The exposure rate can be varied by a series of attenuating filters and values from 0.64 to 1.52 R/min have been used; but most treatments were given at 1.50 R/min. This facility has been described in detail by Brucer (14) and a detailed description of the radiation field has been published (15).

We made two independent dosimetry studies to determine the dose received by patients. We filled three compartmentalized phantoms with Fricke chemical dosimeter and determined spectrophotometrically the average dose to each of the 13 compartments. In addition, we measured the midplane isodose lines by an ionization probe; details are given by Hayes et al (16). In the second study,* with a tissue-equivalent plastic phantom containing an implanted skeleton and density-adjusted lung spaces, we measured the dose to various organs using LiF thermoluminescent dosimeters in the volumes representative of these organs. Except for the bone marrow, the average rad response of the dosimeters in an organ was defined as the average organ dose. We calculated the marrow dose as a weighted average since this tissue, located at variable depths beneath the

* W. L. Beck and T. R. Stokes performed the thermoluminescent dosimetric measurements as part of our continuing total-body irradiation program.

Table 5

Variations in Average Dose to Body Compartments According to Body Size

Compartment	Average Compartment Dose in Rads Per 100 R		
	Adult*	Adolescent*	Child*
Head	78	81	79
Neck	76	83	84
Chest	63	66	70
Abdomen	66	69	71
Pelvis	65	70	71
Arms	76	78	75
Thighs	75	78	82
Legs	86	88	87
Feet	76	78	81
Whole Body	70	74	75

*Hayes Water Phantoms

surface, is not placed uniformly in a single, well defined site. The assumed marrow distribution used for the dose estimates was that suggested by R. E. Ellis (17) for a normal man. It is well known that its volume and location varies widely in patients with the diseases studied here.

The average tissue dose to the total torso of a standardized normal adult was estimated by each of the dosimetry studies to be 65 rads/100-R exposure by the compartmentalized phantom study and 68 rads/100 R by the heterogeneous phantom. The minimal bone-marrow dose occurs in the pelvic region and is only 53 rads/100 R. Variations in dose due to difference in body size and configuration are shown in Table 5. Table 6 lists the absorbed dose in various organs.

OBSERVATIONS

Chronic Lymphocytic Leukemia

During the first six weeks after therapy in 35 patient treatments with either 50 R or 100 R, palpable lymph nodes shrank in 20 and remained unchanged in 12.

Table 6

Anatomical Organ Doses in Cesium-137 Total-Body Irradiation Facility

Organ	Total Organ Dose (Rads/100 R)		
	Average	Ranges	
Bone Marrow	64	53-86	(137)*
Cerebellum	77	74-81	(9)
Cerebrum	75	70-79	(21)
Heart	66	58-70	(16)
Intestines	67	54-76	(107)
Kidneys	66	62-70	(6)
Lenses of Eyes	87	85-90	(2)
Liver	67	61-78	(42)
Lungs	67	58-77	(185)
Skin (above sternum)	73	72-75	(2)
Skin (front waist)	74	72-75	(2)
Spleen	69	64-73	(7)
Stomach	64	59-69	(34)
Thyroid	76	75-77	(2)

*Figures in parentheses indicate the number of bodily locations where dose was measured with LiF dosimeters.

Of the palpable spleens, ten were smaller after treatment, seven remained unchanged, but palpable, and seven enlarged during the same interval. There was no clear pattern of change in liver size.

Twelve patients gained weight, 13 lost, and eight had no change. (The others are unrecorded.) The general feeling of well-being improved to some degree in 21, remained unchanged in 12, and decreased in two. We could not demonstrate with any of these clinical responses that the effect of 100 R was greater than that of 50 R, although the small numbers of patients is a deterrent to comparisons.

Figure 1 shows the WBC responses of individual patients to 50 R and Fig. 2 those to 100 R. Radiosensitivity differed considerably from patient to patient. In both groups of patients (50- and 100-R exposures) there was a subgroup of "resistant" patients whose response was significantly less pronounced. There was no trend of climbing toward pretreatment values by day 42 in either dose or sensitivity subgroup.

Figure 3 shows the changes in mean blood lymphocyte numbers following 50-R and 100-R exposures in the resistant and sensitive patients. We saw no statistically significant differences in the degree of lymphocyte depression caused by these two doses. Although the most rapid fall occurred in the first week, a nadir was not reached until three or four weeks after exposure.

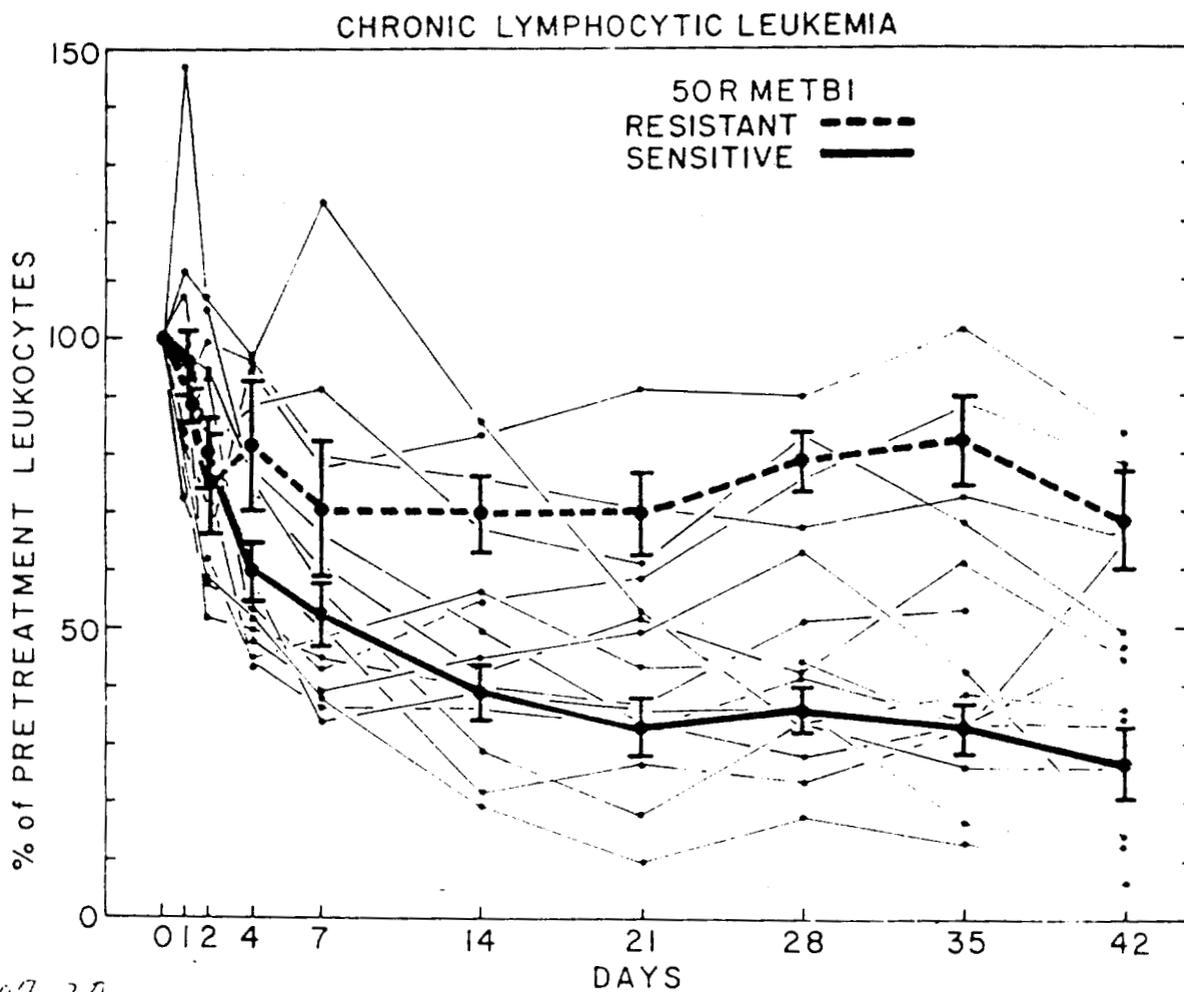


Fig. 1. Changes in the white blood levels in 15 patients with chronic lymphocytic leukemia after 50 R. The leukocyte counts have been normalized to the individual patient's pretreatment values. Two geometric means with their standard errors are shown; one (solid line) is that for the leukocyte levels in the 11 more responsive patients and the other (dotted line) is that for the four patients whose course seems more resistant. The two computed means (after seven days) are statistically different at the 95% confidence level.

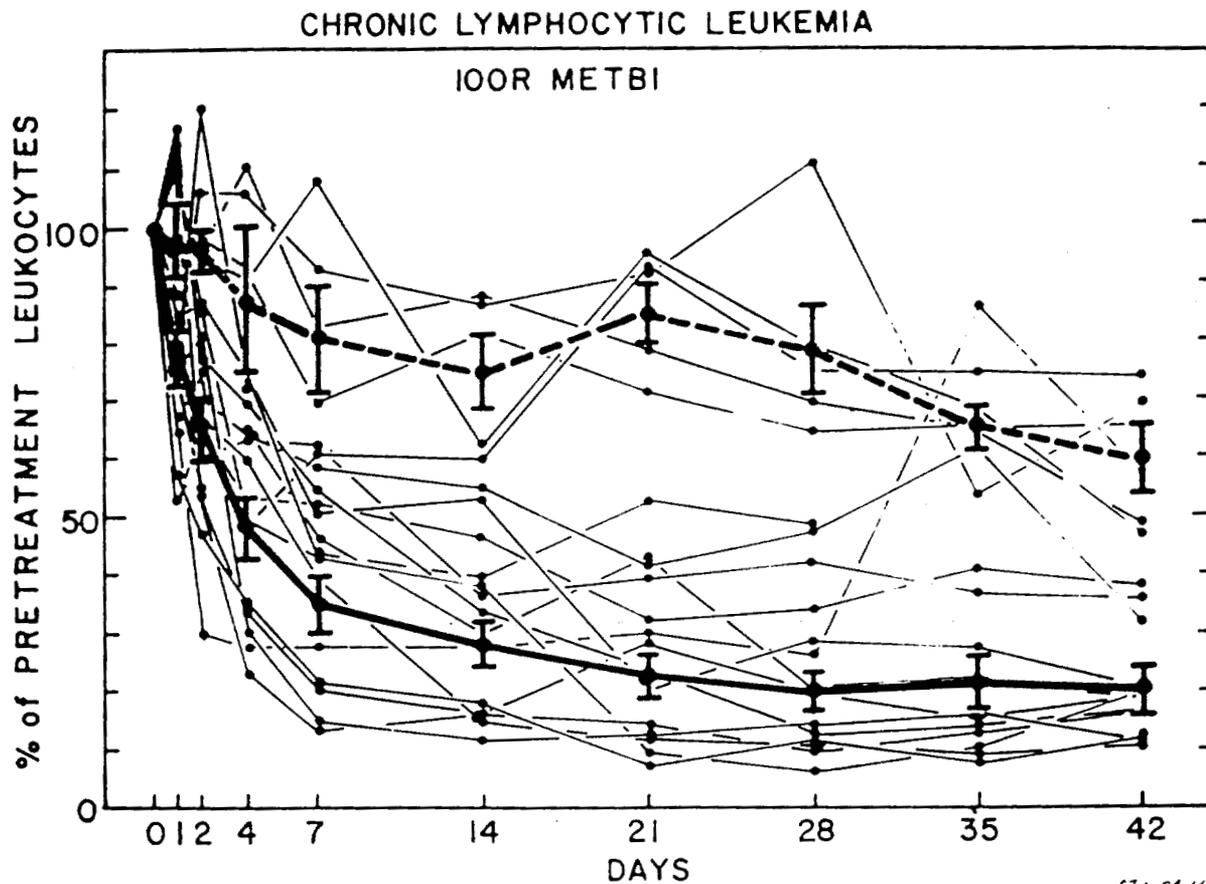


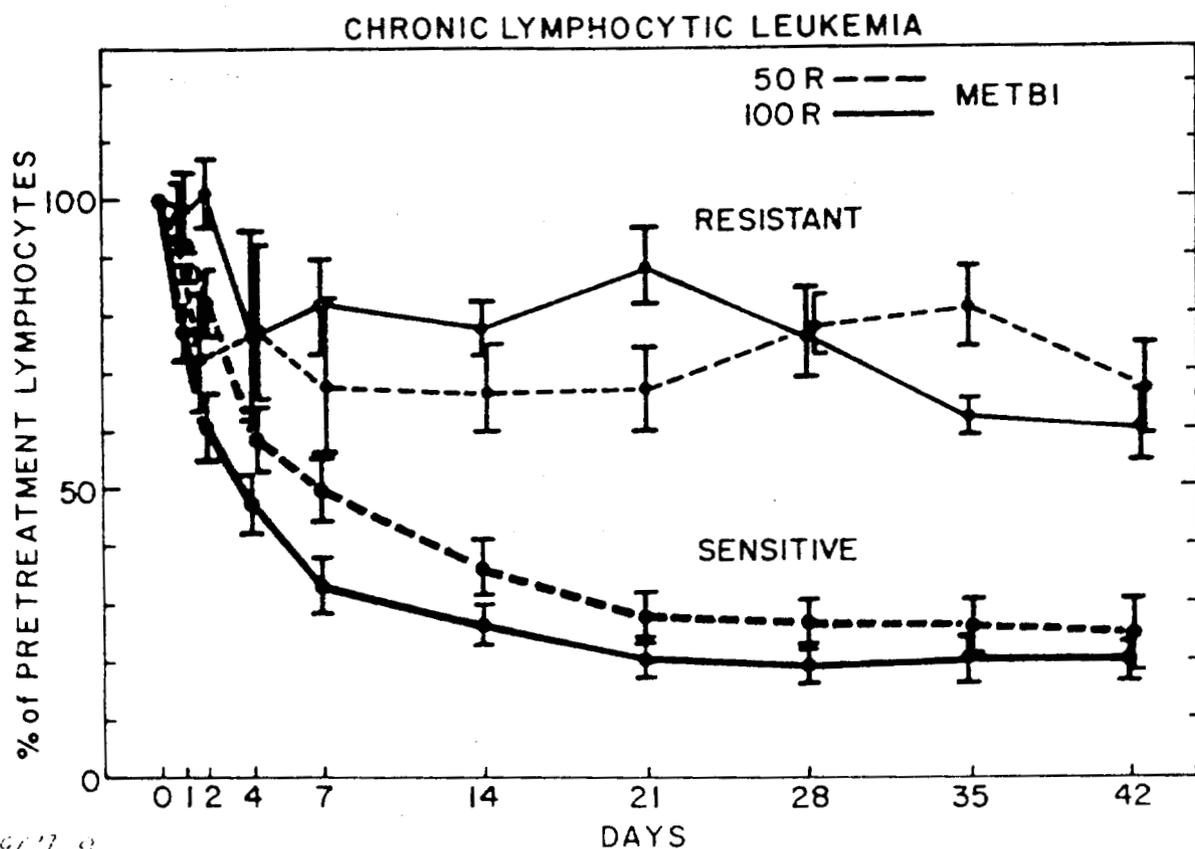
Fig. 2. Changes in the white blood counts (shown in Fig. 1) of 19 patients with chronic lymphocytic leukemia after 100 R. As in Fig. 1, the two geometric means are those for the 14 "sensitive" and five "resistant" patients and are significantly different at the 95% level from the second day onward.

The response of leukemic lymphocytes to 100 R was unrelated to the level of the pretreatment leukocyte counts, nor did it correlate with lymphocyte size, notching of nuclei, or tendency to smudge. The degree of marrow infiltration as judged by histologic examination of marrow aspirated did not tell us why some patients had "radioresistant" lymphocytes. Furthermore, we found no correlation between the lymphocyte response and the clinical response or length of "remission"; eight patients required no other treatment for seven and a half or more months, while nine patients needed additional treatment for leukemia shortly after the study period, less than three months from the irradiation.

While the leukemic lymphocytes responded similarly to 50 R and 100 R, the effect of these two doses on the platelet levels differed strikingly as shown in Figs. 4 and 5. These graphs show also that the responses of patients given 50 R vary more than those of patients given 100 R, suggesting that recovery may be manifested more variably with the lower dose. A trend toward recovery

is definitely established during the fifth and sixth weeks after exposure. As can be seen in Fig. 6, the recovery in numbers of circulating platelets after 50 R occurs earlier and more rapidly on the average than after 100 R. The standard errors of these geometric means are also larger with the lower dose indicating the greater variability of the response to the lower dose.

Hemoglobin values remained stable in the 10 patients not anemic before treatment; those that were anemic usually had no rise in their hemoglobin levels or became more anemic during the six weeks following irradiation. In a few patients who had been requiring transfusions before treatment, the 100-R exposure increased the number of transfusions needed while 50 R did not (see Table 2).



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Fig. 3. Changes in the geometric-mean blood lymphocyte values (shown as normalized percentages of pretreatment differential lymphocyte counts) for the patients with chronic lymphocytic leukemia whose changes in white blood cell values are shown in Figs. 1 and 2. There is no statistical difference between the computed mean changes after 50-R and 100-R exposures in either the "sensitive" or "resistant" groups but the statistically valid difference between the mean responses of the two groups is obvious.

Malignant Lymphoma

This group of 20 patients included five who were given 50 R, two of whom subsequently received 100-R treatments. Of the 17 patients who received 100 R,

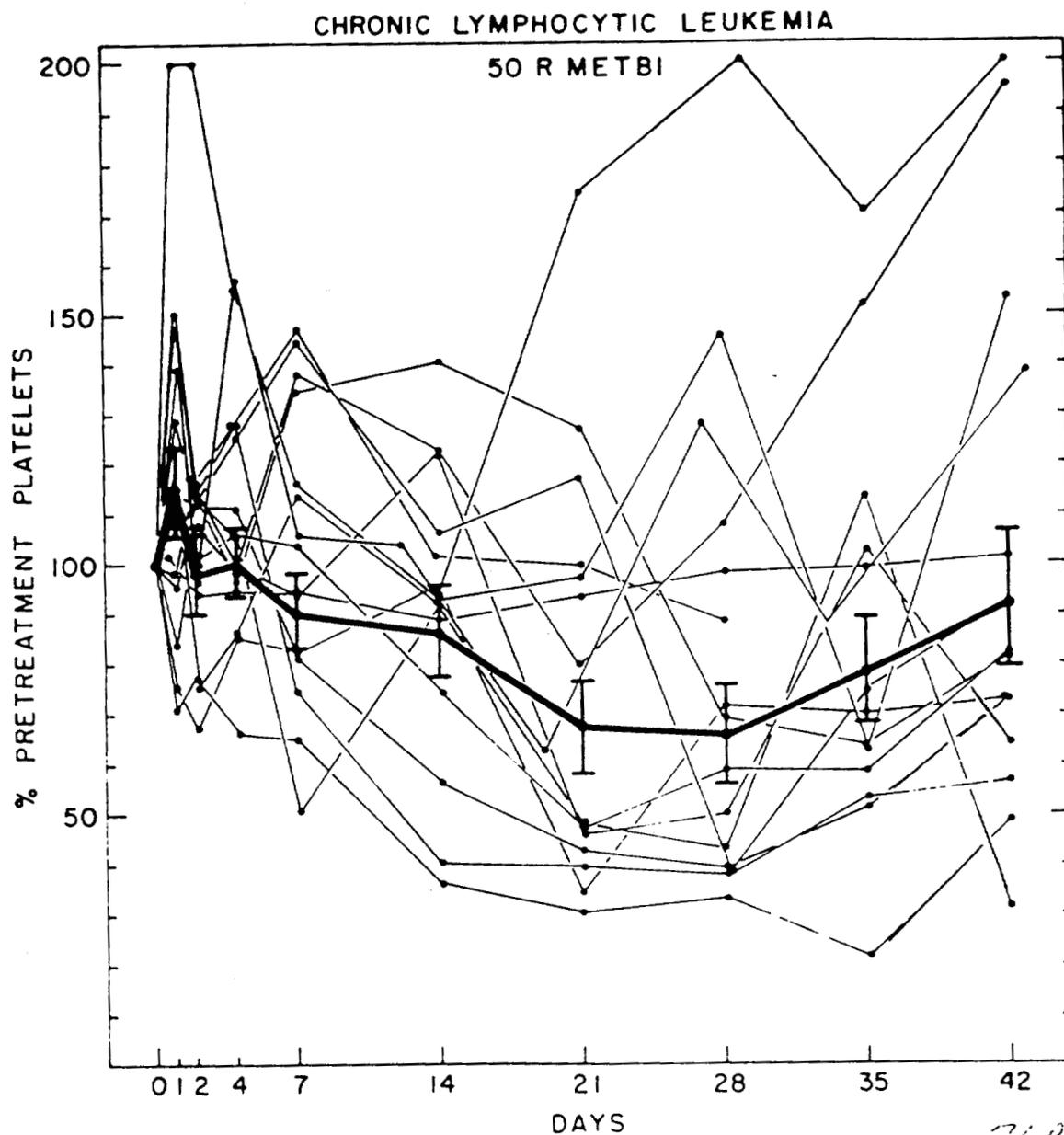


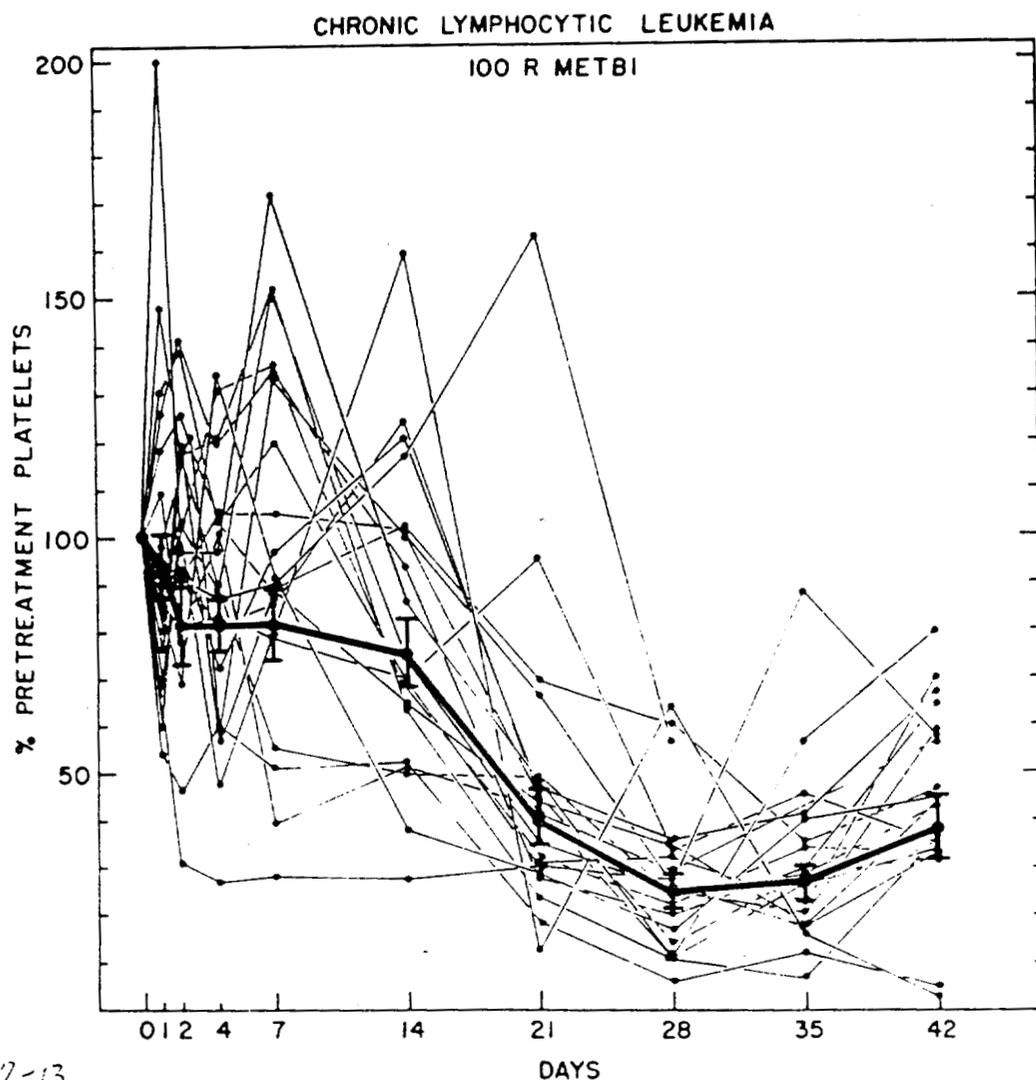
Fig. 4. Changes in the individual and geometric mean percent of pretreatment platelet levels in 15 patients with chronic lymphocytic leukemia after 50 R.

five were given a second 100-R treatment. There were 27 exposures in all.

During the first six weeks after treatment there was no clear difference in clinical responses between the 50-R and 100-R groups. In the 27 treatments, 23 of the 27 patients showed at least some degree of shrinkage of lymph nodes; 17 responded moderately or substantially, while in three the nodes remained unchanged and in one they enlarged after therapy. In the eight patients with palpable spleens, only two spleens definitely regressed, while five others

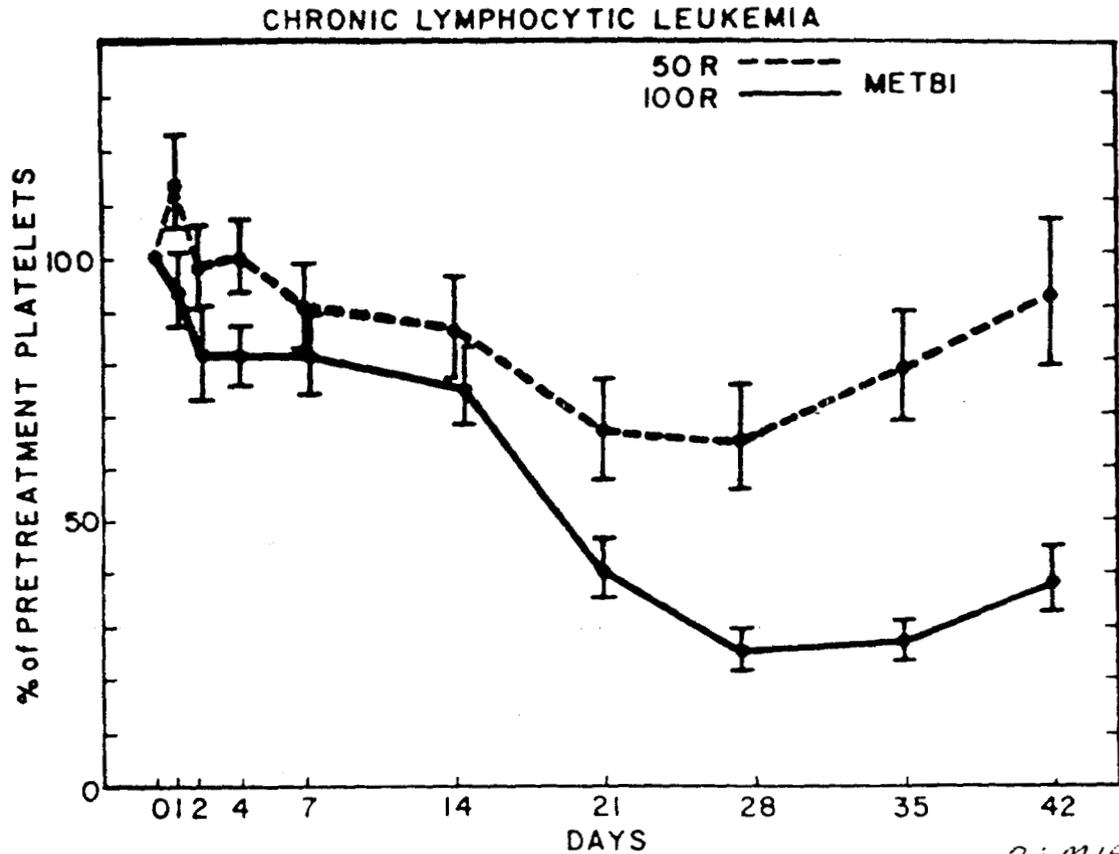
remained large and one was questionably changed. Nine palpable livers regressed while eight remained unchanged or enlarged. There was no consistent pattern of change in body weight. The subjective general feeling of well-being remained poor or unchanged in 17 patients, while 10 expressed some degree of improvement.

Most of these patients had at least a few atypical lymphocytes in the blood, and we were unable to separate definitely those that should be considered as having a "leukemic" stage of lymphosarcoma, except for two who had larger numbers of abnormal cells. These two patients described in a later paragraph responded



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Fig. 5. Changes in the individual and geometric mean percent of pretreatment platelet levels in 20 patients with chronic lymphocytic leukemia after 100 R. Comparison of the geometric means and their standard errors in this figure and in Fig. 4 shows that the degree of response in the two dosage groups differs significantly from 21 days on. Five individual patients who received 50 R, however, reacted as the 100-R group, while three in the 100-R group responded similarly to the 50-R patients.

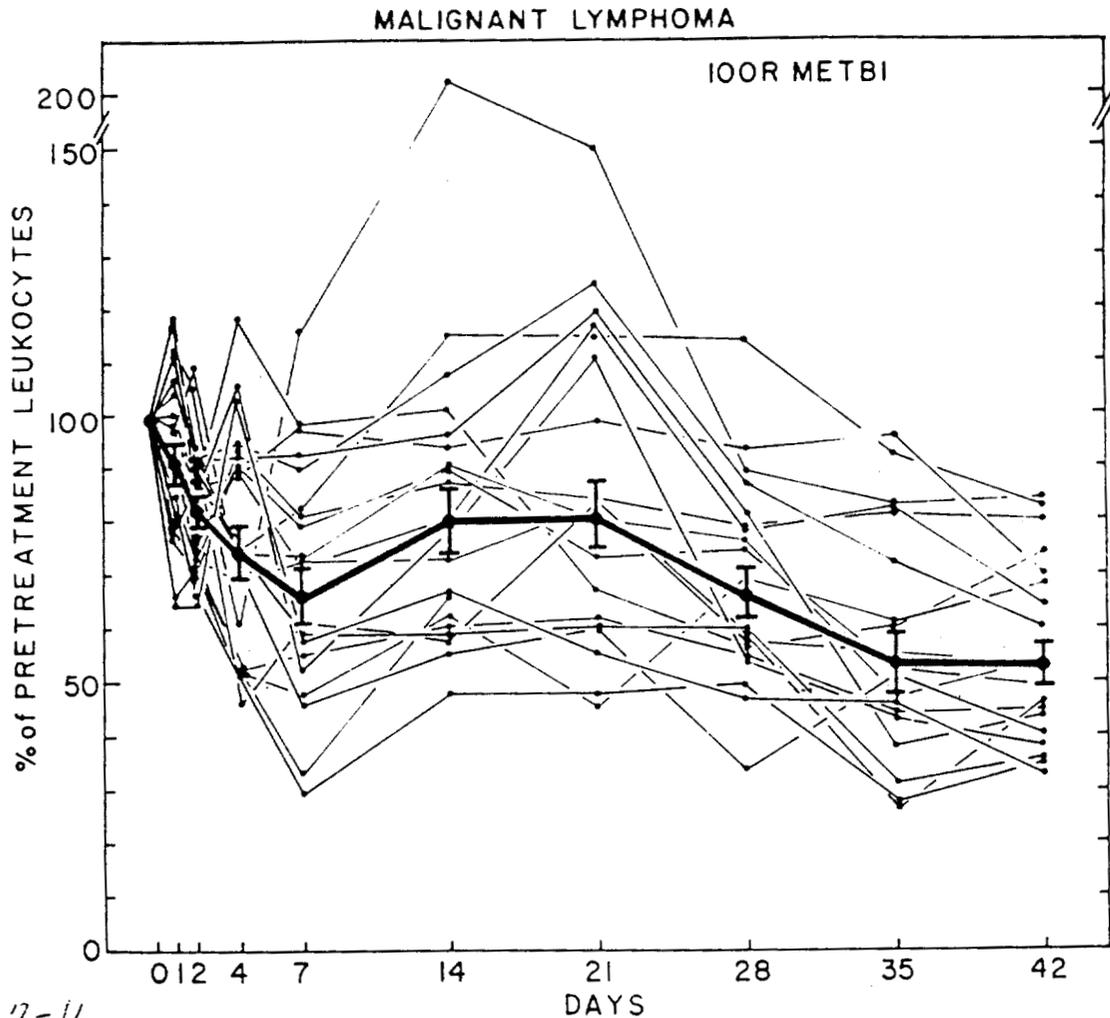


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Fig. 6. Comparison of the geometric means for blood platelet levels in patients with chronic lymphocytic leukemia after 50 and 100 R. The curves become statistically different only after 21 days.

quite differently from the rest of the group. All the others had pretreatment leukocyte counts of less than $15,000/\text{mm}^3$; the numbers of lymphoid cells were less than $11,000/\text{mm}^3$. The subsequent decrease in lymphocytes was not great (the lowest value was about 50% of pretreatment level, reached at seven days). In the majority of the patients (11/17) lymphocyte levels began to recover from this decrease by 14 days; this was unlike the response in CLL. In Fig. 7 the geometric means for the leukocytes of the main groups of patients with malignant lymphoma who received 100 R are plotted, along with one standard error of the mean. The changes in total leukocytes after 100 R in patients with malignant lymphoma have been graphed in Fig. 7 for comparison with later graphs in this study and with those of other investigators who have not differentiated the hematologic response of the various white blood cell types. In Fig. 8 the sequential changes in lymphocyte counts in individual patients can be seen varying widely.

By contrast, in the two "leukemic" patients with high numbers of abnormal lymphoid cells in the blood before irradiation ($16,000$ and $26,000/\text{mm}^3$) these cells decreased profoundly and rapidly after 100 R. Their course differed



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Fig. 7. Changes in blood leukocyte values in 20 patients with malignant lymphoma after 100 R. The actual WBC counts have been normalized to individual pretreatment levels and the geometric mean and its standard error computed on this basis.

considerably from that of the other members of the lymphoma group and resembled more closely the extreme responders of the chronic lymphocytic leukemia groups. (See Figs. 1-3).

The platelet values for the 50-R group dropped only slightly on the average and varied widely from patient to patient. In the 100-R group, the platelets responded more consistently; a steep drop appeared during the third and fourth weeks and reached a nadir of 27% of the pretreatment values. This curve resembles quite closely that of the patients with chronic lymphocytic leukemia given the same dose (Fig. 4). All showed a trend toward recovery during the fifth and sixth weeks (Figs. 4 and 10). Hemoglobin values did not change significantly during the six weeks after irradiation with either 50 R or 100 R.

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Hodgkin's Disease

Only three patients with Hodgkin's disease were treated. One patient who received 50 R early in her disease failed to respond and was quickly transferred to more conventional therapeutic regimens. The second patient, who received 100 R, showed similarly no benefit, and the third one failed to return after two weeks for further follow-up studies. The platelet and lymphocyte responses for the 50-R and 100-R exposure behaved as in patients with other types of lymphomas.

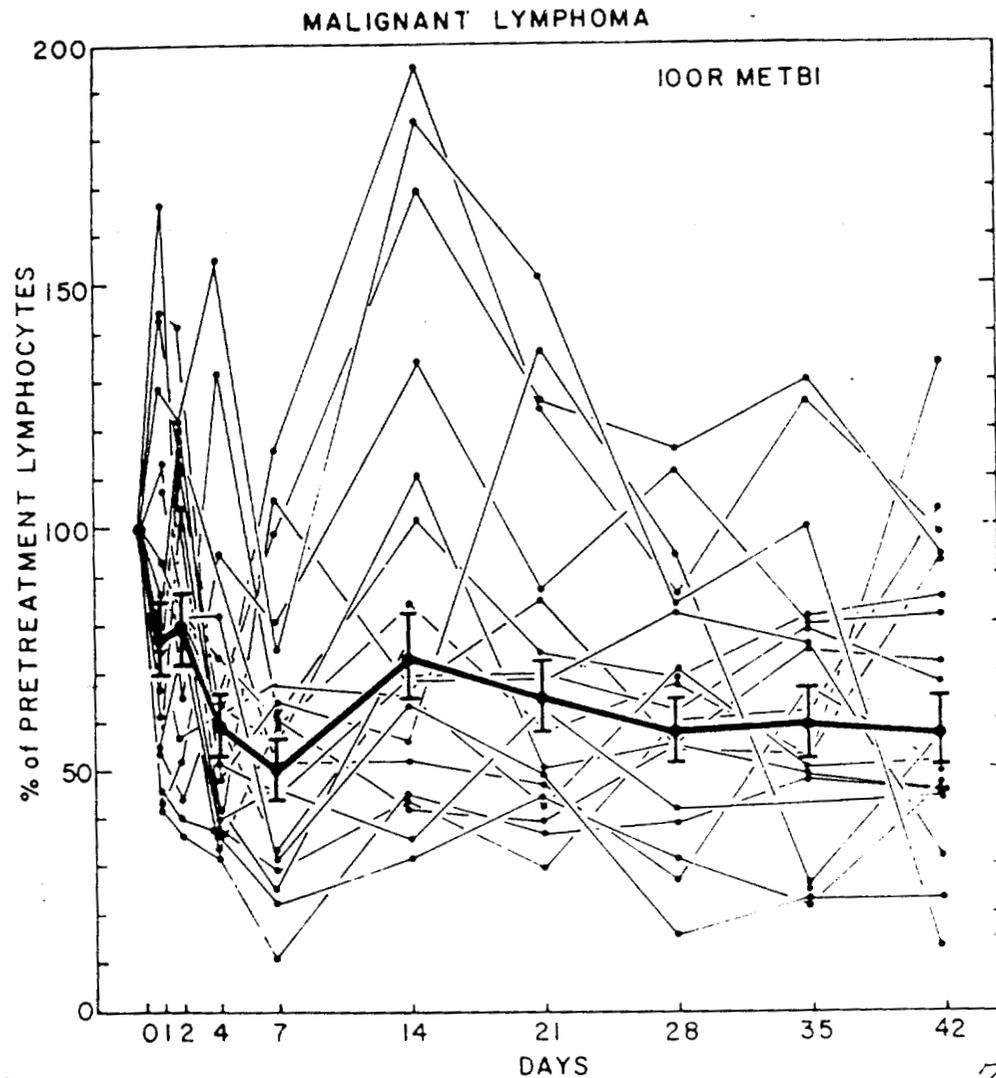


Fig. 8. The changes in Fig. 7 are shown here as changes in lymphocyte levels computed from individual absolute lymphocyte counts before and after exposure. These extremely variable responses of individual patients reduce to a geometric mean not statistically different from that of the "resistant" type of response in lymphocyte levels of patients with chronic lymphocytic leukemia treated with either 50 or 100 R (see Fig. 3). In several of these patients total-body irradiation obviously resulted in lymphocytosis in relation to pretreatment levels.

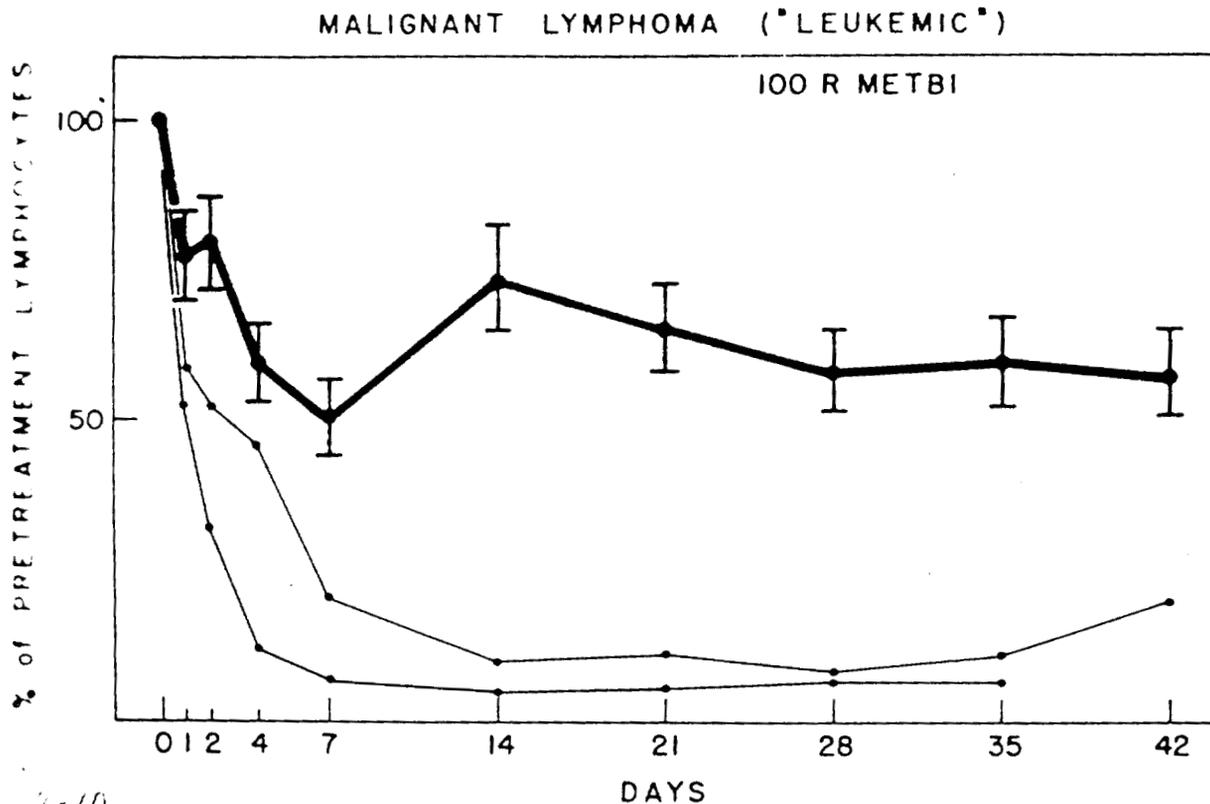


Fig. 9. The lymphocyte response curves of two patients with "leukemic" malignant lymphoma were so atypical in comparison with those of the 20 other patients with this disease (Fig. 7) that they are shown here separately along with the geometric mean of the other 20 patients. These two individual lymphocyte response curves fit within the 95% confidence limits of the "sensitive" type of lymphocyte response curves shown for chronic lymphocytic leukemia in Fig. 3.

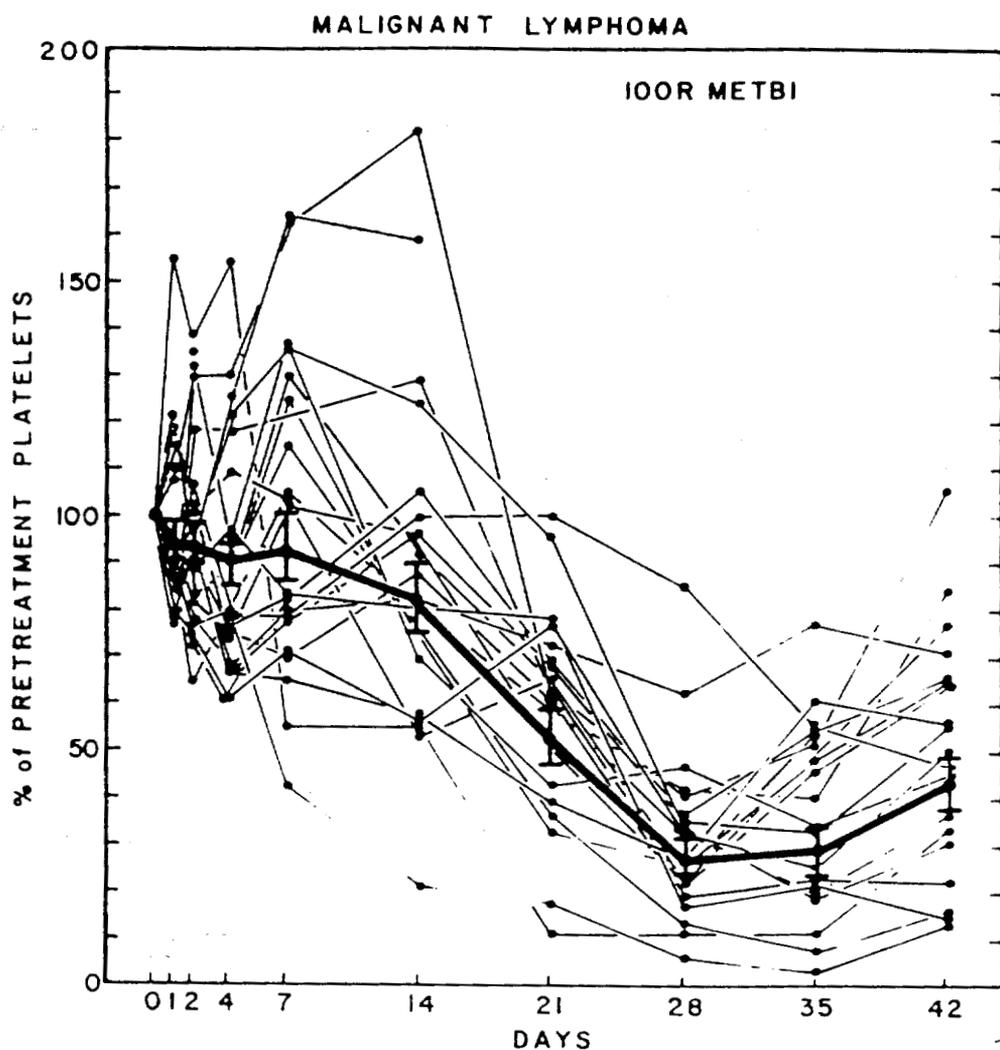
Chronic Granulocytic Leukemia

This group included eight patients exposed to 50 R and four exposed to 100 R. Their spleens remained palpable and unchanged in size in eight, became slightly smaller in one, and distinctly smaller in one. In the other two, the spleen was not palpable before or after treatment. A definite decrease in liver size was recorded in only one patient. The general feeling of well-being was improved in eight patients but unchanged in three and poorer in one.

All patients had high initial leukocyte counts consisting predominantly of mature granulocytes. Nongranulocytic elements were so few that the curves shown in Figs. 11 and 12 can be considered as representing chiefly changes in granulocytic numbers. The numbers of leukocytes began a decrease promptly after these doses and the degree of fall indicated a greater radiation sensitivity than we see in normal granulocytes (see Fig. 7). Further, this depression usually persisted longer than would a similar degree of depression produced in normal persons by a higher dose as in radiation accidents. After 50 R the decline

in values began promptly, the mean dropping to 55% on day seven, 48% by day 14, then staying in this range for the six-week period of observation (Fig. 11). The response of the four patients given 100 R (see Fig. 12) was similar to that of the 50-R group, but the degree of depression was greater: 35% on day 7, 21% on day 14. By day 21, three of the four patients had granulocyte levels below 20% of pretreatment levels; one patient showed a transient partial recovery pattern. This suppression persisted throughout the 42-day period at the end of which there was still a trend toward even lower levels.

The platelets in CGL before treatment were either in the normal range or elevated; in a few instances they were at levels over 1,000,000/mm³. After 50-R exposures, the platelet counts rose to a mean level of 136% by day 14 before declining to a nadir of 82% on day 28. The means then returned toward the pre-

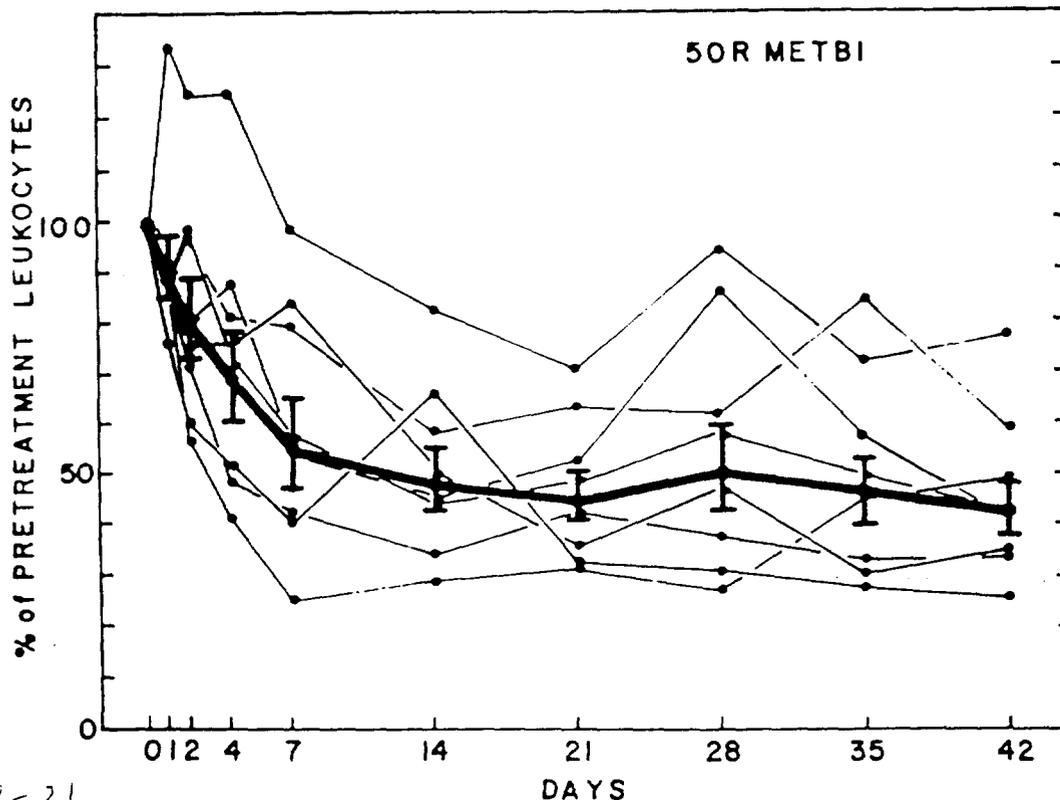


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Fig. 10. Platelet response curves in patients with malignant lymphoma exposed to 100 R. The heavy solid line represents the geometric means and their standard errors. The curve closely resembles that in Fig. 6 of chronic lymphocytic leukemia after 100 R.

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CHRONIC GRANULOCYTTIC LEUKEMIA



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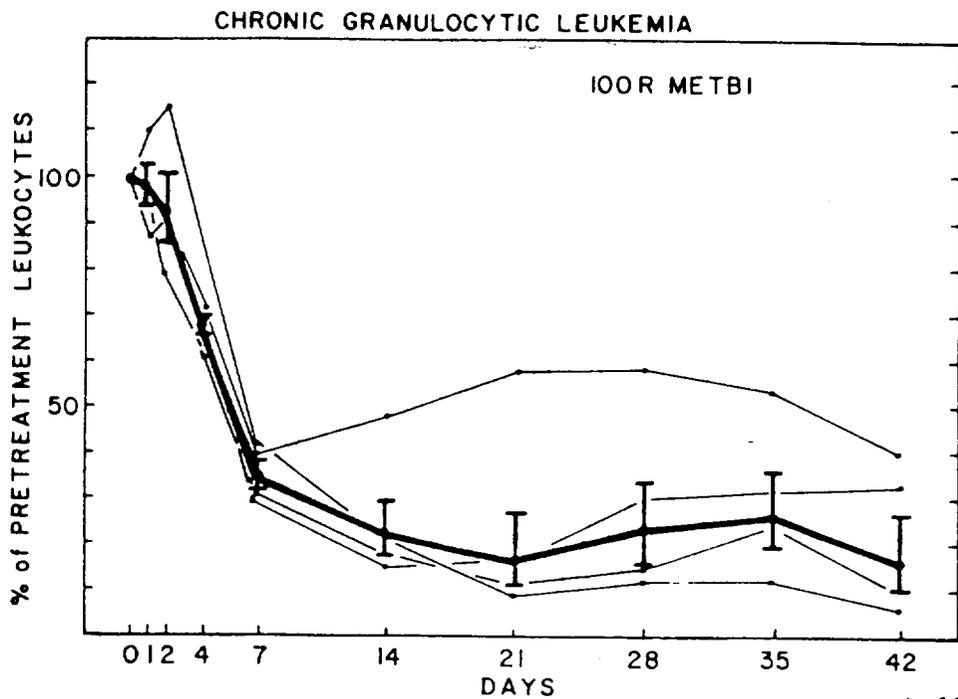
Fig. 11. Changes in blood leukocyte values, expressed in terms of individual pretreatment WBC counts, of eight patients with chronic granulocytic leukemia exposed to 50 R. The dark solid line represents the geometric means and their standard errors.

treatment range during the fifth and six weeks (Fig. 13), but the values ranged widely (53% to 191% of pretreatment values).

The platelets of the group exposed to 100 R also rose during the first two weeks but much less conspicuously (Fig. 14). The subsequent depression followed the usual temporal pattern and reached a nadir of 48% on day 42. This progressive decrease which persisted beyond 42 days is presently being observed also in our ongoing studies with fractionated and low-dose-rate exposures. A comparison of mean responses for platelets and leukocytes after 50 R and 100 R is made in Fig. 15.

The percent response (relative to pretreatment values) of the leukemic granulocyte appears from this graph (Fig. 15) to be about a factor of two greater than that of the platelets. The comparison here shows that in the occasional patients where injury to the platelet system is to be avoided because of borderline thrombocytopenia, a 50-R exposure would offer some therapeutic effect on granulocyte numbers while sparing platelet numbers.

Mean hemoglobin values were not significantly altered during this period of study. Figure 16 shows the hemoglobin values for the patients who received 100 R.



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Fig. 12. Changes in blood leukocyte values, expressed in terms of individual pretreatment WBC counts, of four patients with chronic granulocytic leukemia exposed to 100 R. The dark solid line represents the geometric means and their standard errors.

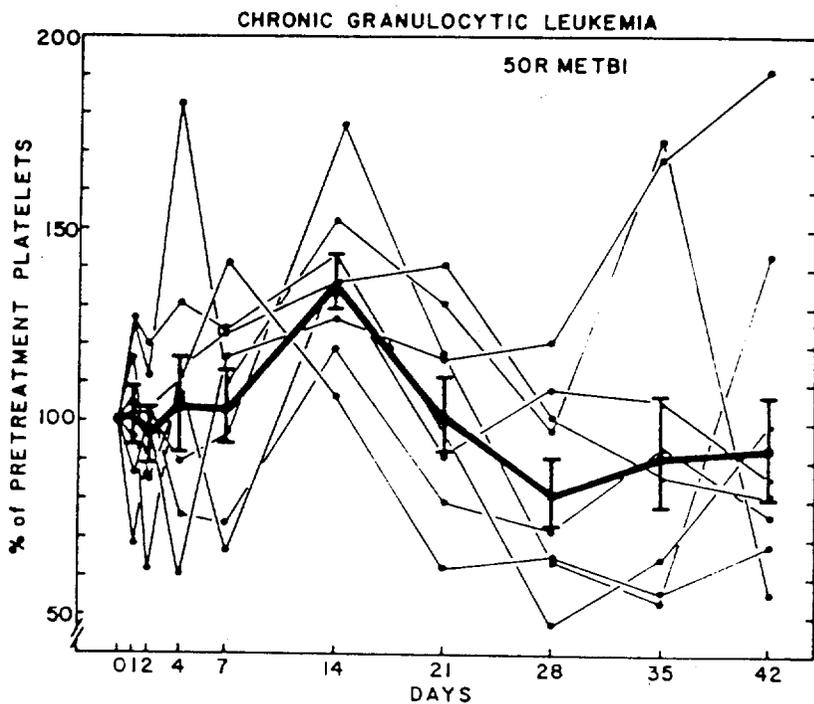
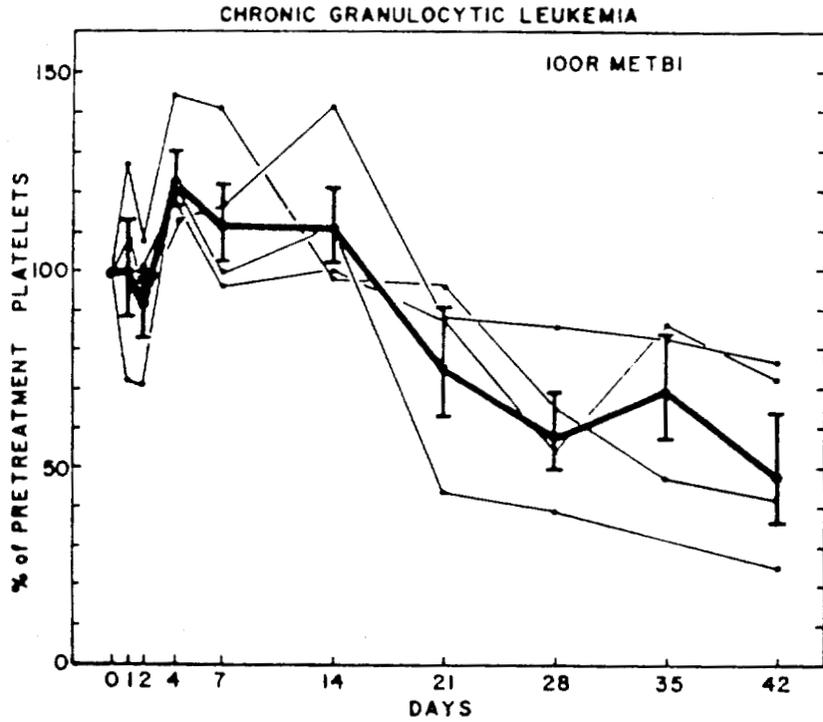


Fig. 13. Changes in platelet values expressed in terms of individual pretreatment platelet counts of eight patients with chronic granulocytic leukemia exposed to 50 R. The dark solid line represents the geometric means and their standard errors.

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Fig. 14. Changes in platelet values, expressed in terms of individual pretreatment platelet counts, of four patients with chronic granulocytic leukemia exposed to 100 R. The dark solid line represents the geometric means and their standard errors.

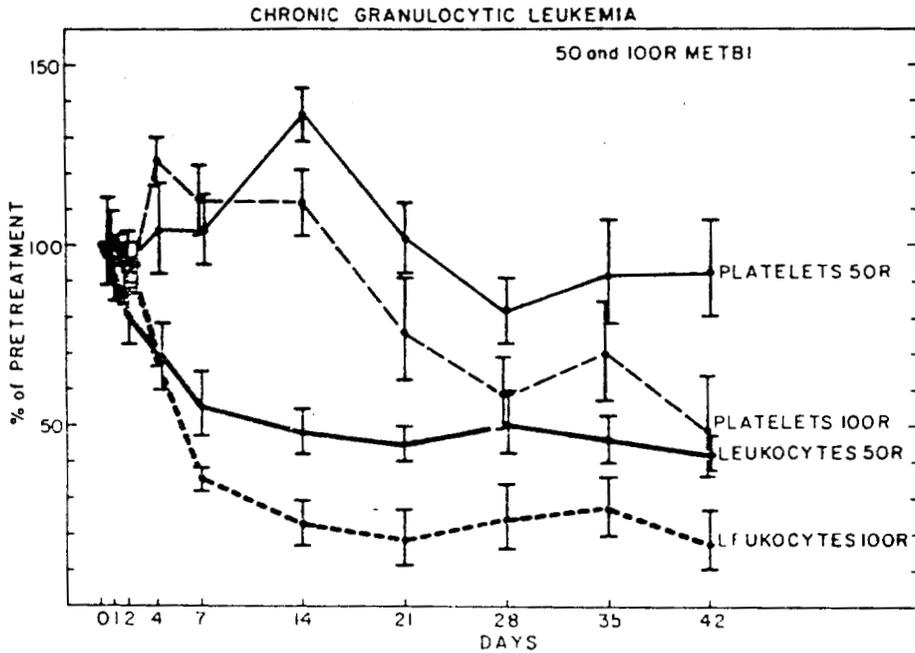


Fig. 15. Comparison of the geometric means of the leukocyte and platelet values in chronic granulocytic leukemia exposed to 50 and 100 R, shown in Figs. 13 and 14, showing the greater sensitivity of the leukocytes of these patients. In comparison with the curves for platelets (Fig. 6) in chronic lymphocytic leukemia, changes after 50 and 100 R occur earlier and are more extreme.

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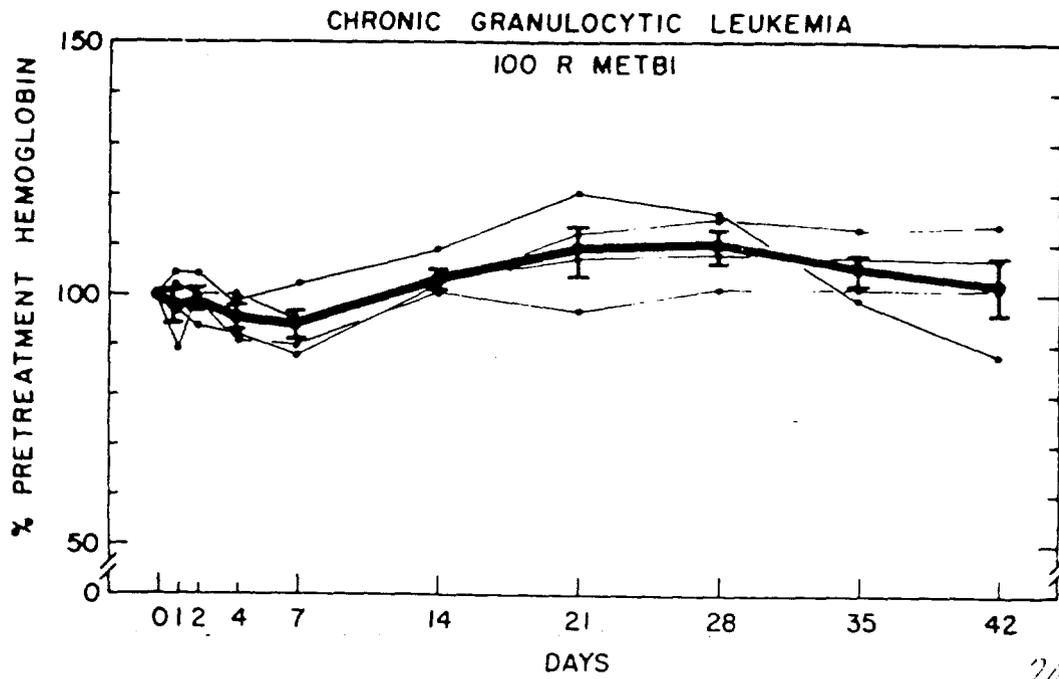


Fig. 16. Changes in blood hemoglobin values in four patients with chronic granulocytic leukemia exposed to 100 R showing a slight improvement relative to initial hemoglobin levels.

Polycythemia Rubra Vera and Primary Thrombocythemia

This group included eight patient-exposures to 100 R. Six patients had polycythemia rubra vera (PRV); one received two separate treatments (seven treatments); the seventh patient had primary thrombocythemia. In five patients there was an improvement in general feeling of well-being; in three there was no change. Of the large spleens, the size decreased in three, increased in one, and remained unchanged in two. The effects on liver size were slight and variable. In six patients a significant gain in weight was recorded.

All the PRV patients had initial leukocyte counts above 10,000/mm³. These ranged up to 41,000/mm³ pretreatment. As is shown in Fig. 17, leukocyte values began to drop after one week and reached their nadir at the six-week point, considerably later than has been observed in normals or in patients with most other diseases. As with platelet values (see below), the return of the leukocyte level toward normal was slow and was prolonged up to six months. The changes in absolute lymphocyte values in relation to pretreatment levels after 100 R (Fig. 18) were more like those after 100-R accident cases. Typically no return to normal was seen during the 42-day observation period.

Except for one patient with a normal platelet count, all had pronounced elevated platelet counts ranging from 575,000 to 1,600,000/mm³ before treatment. The qualitative platelet responses to 100 R were similar to those of accidentally irradiated normal persons and of patients without leukemic diseases in that a nadir was reached at about 30 days (Fig. 19), but characteristically the fall in

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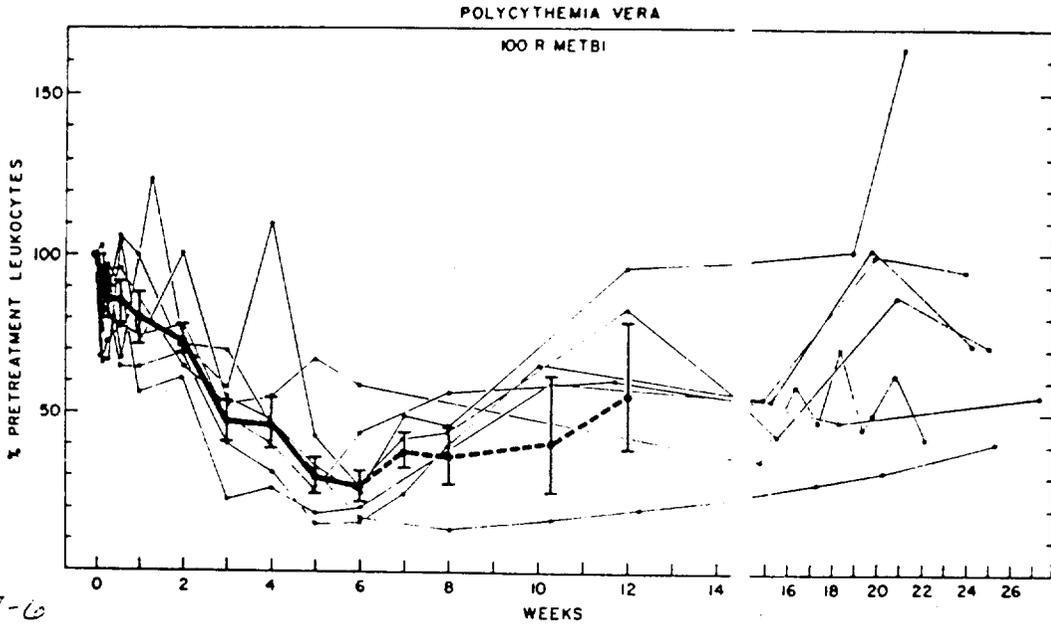


Fig. 17. Changes in blood leukocyte levels in eight patients with polycythemia rubra vera after 100 R. The solid heavy line is the geometric mean of these values through the usual 42-day postirradiation study period; the dotted line extends this mean through less regularly obtained data points over six months.

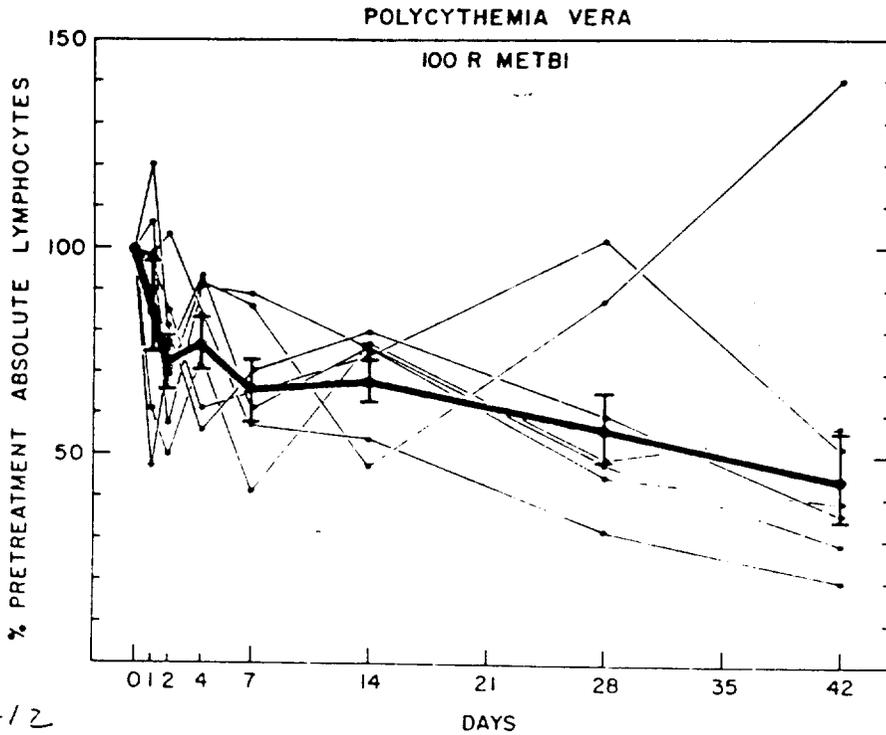


Fig. 18. Changes in blood lymphocyte values in seven patients with polycythemia rubra vera exposed to 100-R total-body irradiation. To improve statistics, 400 leukocytes were counted at each data point. One patient whose baseline values were believed to be unreliable is excluded from this figure.

count either did not begin for two weeks or was slight until that time. The return toward normal, however, was much delayed and did not reach pretreatment levels for many months. This temporal pattern differs distinctly from the response of accident victims where a return to normal (or even a rebound elevation) occurs within six weeks. It appears that some homeostatic mechanism tends to prevent platelet values from returning to abnormal pretreatment values. Figure 19 shows the platelet response during the usual six-week study period and for the following six months.

Hemoglobin values for this group were not significantly elevated at the time of treatment; excessively high platelet and leukocyte values dominated their blood picture. Evaluation of changes in red cell numbers and morphology was complicated by pretreatment phlebotomies, stage of disease, and previous marrow-depressing treatments with ^{32}P or drugs (only two of the six were new, untreated cases). Hemoglobin and hematocrit values changed little after treatment (Figs. 20, 21) with 100 R. We believe, however, that this dose suppressed the rise that usually would have occurred with therapy. The mean corpuscular hemoglobin concentration before treatment was invariably low, due to phlebotomies and intestinal bleeding. It did not change in the postirradiation period (Fig. 22).

There was a 12% decrease in numbers of RBC and 12% increase in mean corpuscular volume that offset one another so that little or no change was seen in hematocrit values. Blood volume studies, however, were not done. Generally the mean corpuscular hemoglobin concentration did not change significantly

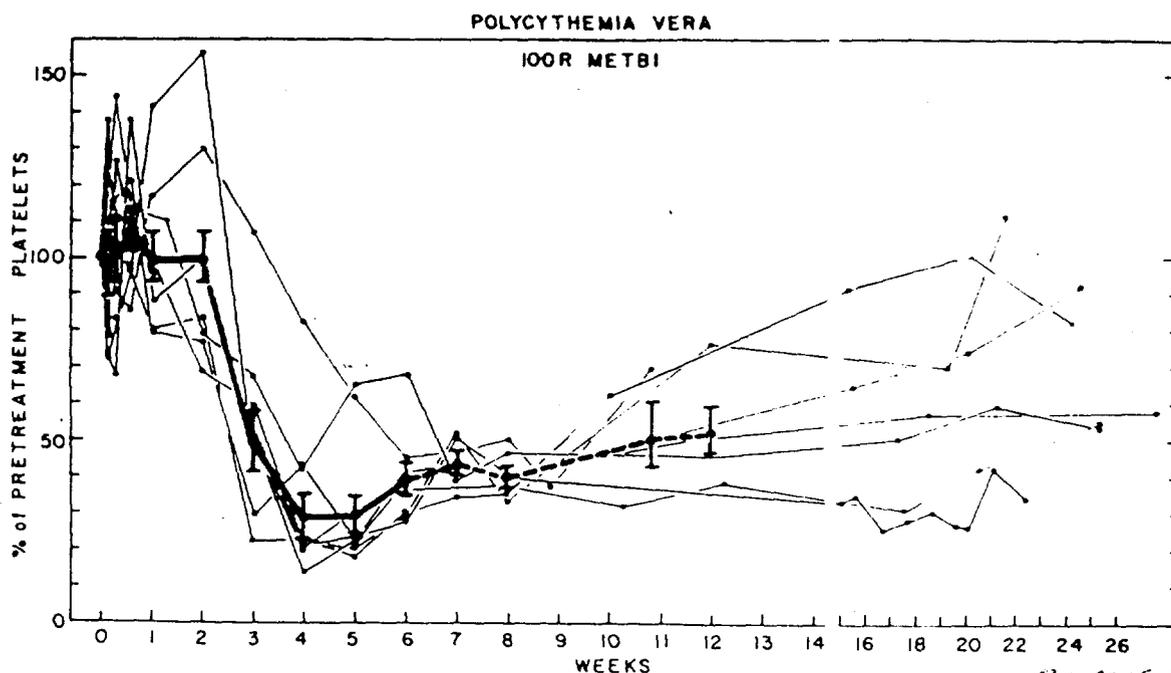
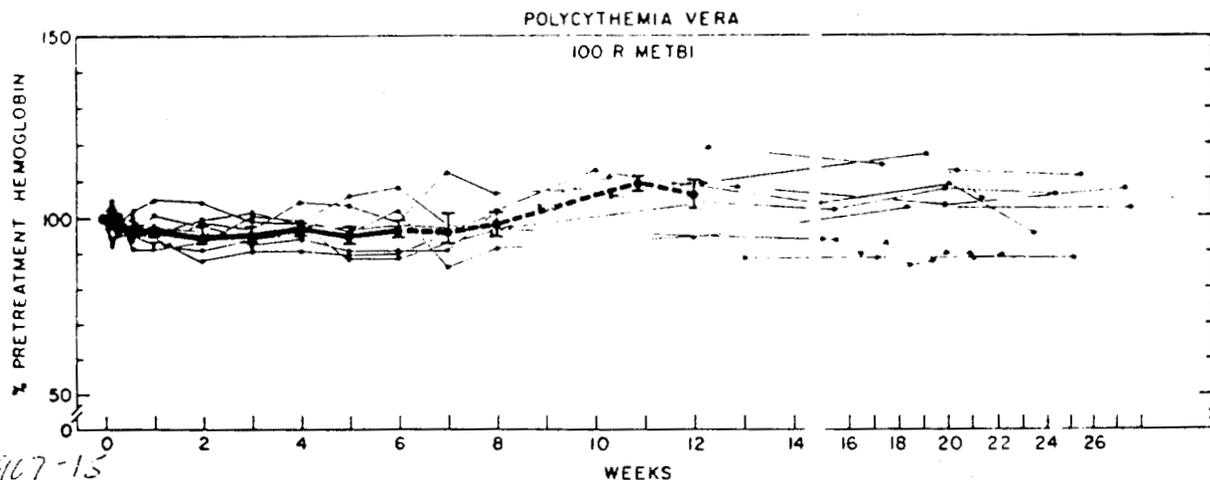
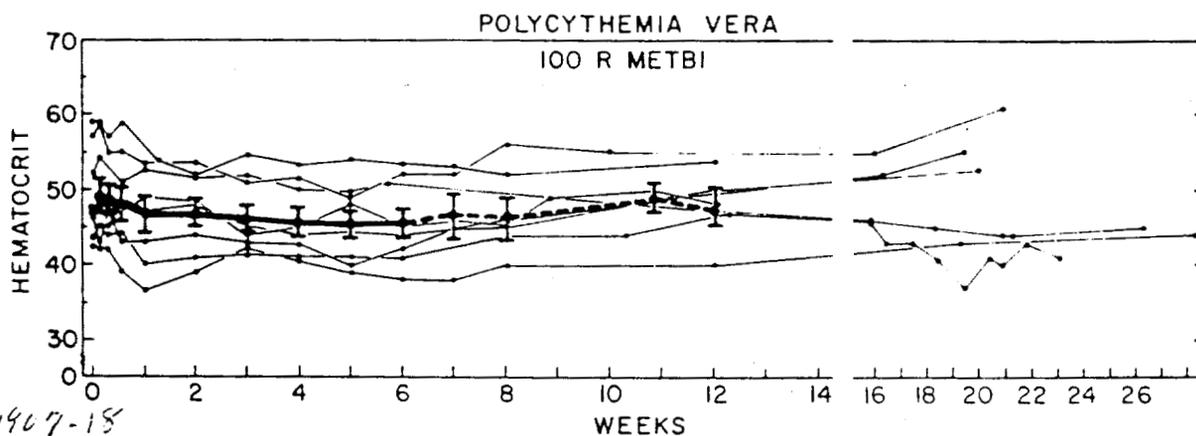


Fig. 19. Changes in blood platelet levels in eight patients with polycythemia rubra vera exposed to 100 R. Geometric mean is shown on a solid heavy line for 42 days of the protocol and as a broken line after that time when data points were less rigidly obtained.



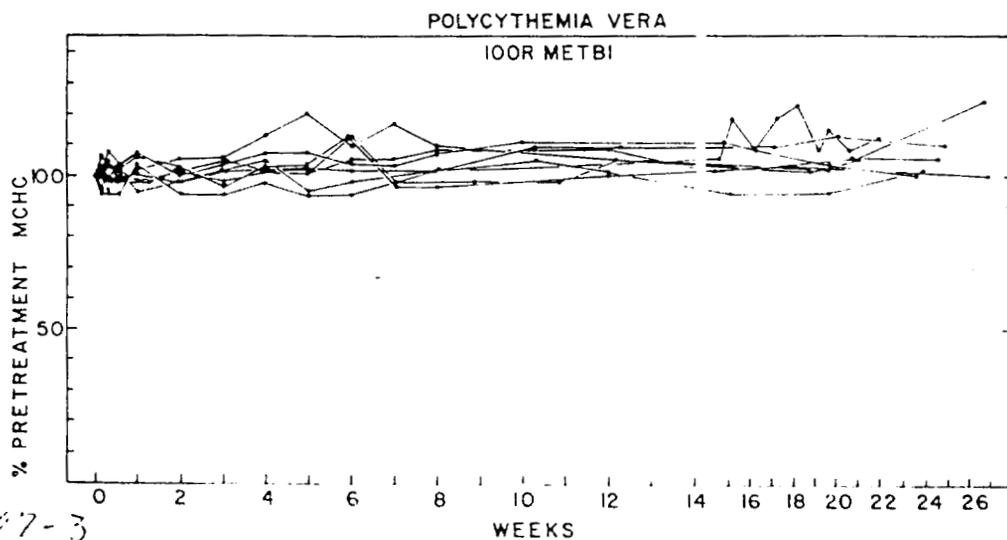
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Fig. 20. Changes in hemoglobin values of eight patients with polycythemia rubra vera over the six months after 100-R exposure.



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Fig. 21. Changes in hematocrit values (not normalized) of eight patients with polycythemia rubra vera over the six months after 100-R exposure.



70M1907-3

Fig. 22. Changes in mean corpuscular hemoglobin concentration of eight patients with polycythemia rubra vera over the six months after 100-R exposure.

but in some individuals it rose 10 to 20% (Figs. 22 and 23). * Detailed red cell values in one patient are shown for a 26-week period (Fig. 23). The principal clinical problem in this patient was her excessively high platelet count which ranged above 1,000,000/mm³ and was believed to be a factor in intestinal hemorrhage and its associated iron loss.

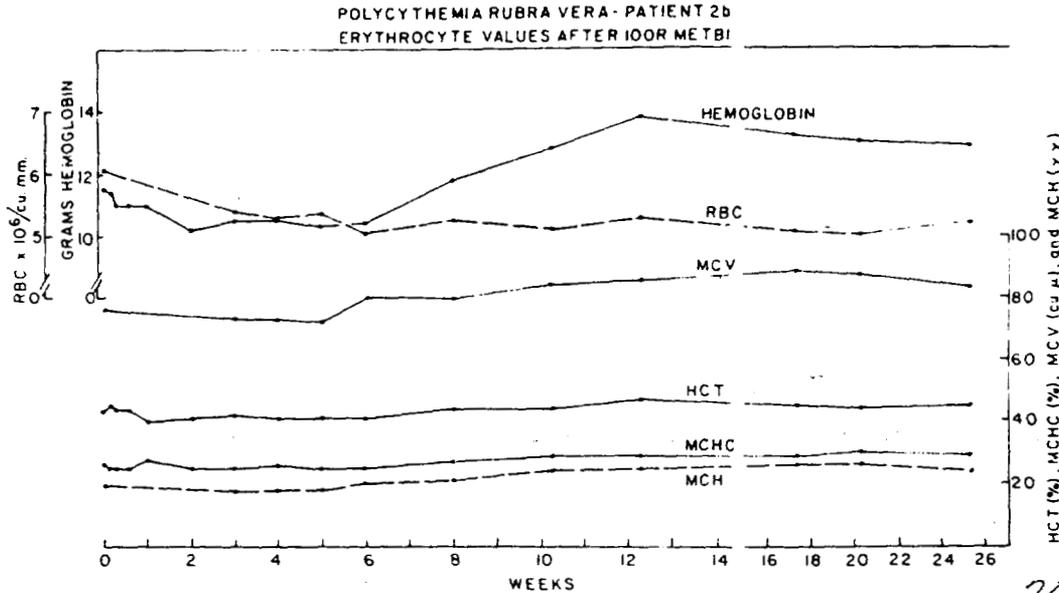


Fig. 23. Changes in actual values of blood erythrocyte parameters in one patient with polycythemia rubra vera treated with an exposure of 100 R.

Changes in Uric Acid

In all disease categories and both dose groups, we examined serum uric acid levels. After exposure, the levels changed, as might be expected from previous observations, but in this series of patients the changes were, in general, small, inconsistent, and of little clinical value. In some patients an early increase and subsequent decrease were sufficiently large to be accepted as indicative of the tissue destruction caused by the radiation exposure.

In 100-R treated lymphosarcoma and CLL, there were increased average levels on postirradiation days through four or seven (Table 7). Among the patients given 50-R exposure the CGL group showed elevated uric acids on only the second day

* In a study of RBC size distribution after low-dose-rate total-body irradiation (to be reported elsewhere; see ORAU Medical Division Research Reports 1968, 1969), we have found by electronic measurements of red cell size that irradiation produces changes in cell volume that are not demonstrated by measurements of hemoglobin, hematocrit, and cell numbers/cm³. We are finding that the erythron returns to normal within 120 days in this study only if iron stores have not been depleted by phlebotomy or hemorrhage.

Table 7

STATISTICAL SIGNIFICANCE OF OBSERVED MEAN SERUM URIC ACID LEVELS AFTER TBI

Disease Category	TBI (R)	Days							
		1	2	4	7	14	21	28	
Erythrocytopenia	50	0 (5)*	0 (5)	0 (4)	0 (5)	0 (5)	0 (4)	0 (4)	
	100	0 (15)	++ (16)	++ (17)	0 (17)	0 (17)	0 (15)	0 (11)	
Leukopenia	100	0 (7)	0 (5)	0 (7)	0 (7)	0 (7)	0 (7)	- (6)	
Granulocytopenia	50	0 (7)	+ (7)	0 (7)	0 (7)	0 (7)	0 (7)	0 (7)	
	100	0 (3)	0 (2)	0 (3)	0 (4)	0 (4)	0 (2)	- (3)	
Lymphocytopenia	50	0 (15)	0 (14)	0 (14)	+ (15)	0 (15)	0 (14)	0 (13)	
	100	0 (14)	++ (13)	++ (15)	+ (14)	0 (15)	0 (15)	0 (13)	
All Disease	50 or 100	0 (66)	++ (61)	++ (68)	0 (69)	0 (69)	0 (64)	- (57)	
Uric Acid (mg/100 ml)	pre-treatment	5.82	6.18	6.48	6.38	6.04	5.67	5.68	5.38
	± S.D.	1.75	1.73	1.82	2.02	1.99	1.75	1.60	1.71

* Figures in parentheses indicate the number of patients in each group.

No statistically significant change from pretreatment levels.

Increase $P \leq 0.05 - 0.01$; ++ $P \leq 0.001$

Decrease $P \leq 0.05 - 0.01$

and the CLL group on only the seventh day. In other disease categories and exposure groups no statistically significant early changes were found in the mean values from day to day, although some individual patients, even in these groups, showed alterations that possibly reflected increased cellular destruction. On day 28 following 100 R a decrease was seen in some disease categories and in the averaged data for all, but was not found in individual groups after 50 R.

These observations are compatible with the view that change in uric acid level is a dose-related response that is modified by at least three factors: the amount of radiosensitive tissue present at exposure, the degree of radiosensitivity, and the rate of uric acid production in relation to renal excretory capacity. Appraisal of radiation-induced perturbations in this metabolic system might be better elucidated from study of total urinary uric acid and other protein-related excretory products rather than serum levels.

DISCUSSION

This large amount of hematologic data suffers from the usual variabilities of most clinical investigations — wide range in laboratory values, many of them unexplained, and the lack of a true control population. The information derived, however, is clinically useful and meaningful for radiation biology. The differences

in response in different clinical disorders are of special interest and give some insight into the relative dependence of these disease processes on cellular survival and replication. In this discussion "sensitivity" is used to mean simply a response in cell numbers after irradiation; it is not meant to imply any specific mechanism for altered numbers.

Most of the rapid major alterations in blood values during the six-week post-treatment period were the result of irradiation. To be valid, this statement requires us to assume that all peripheral blood cell values would have remained stationary if no treatment had been given. This steady state was not always present. In fact, therapy was often indicated because certain cellular systems were changing, but the rate of change was usually slow in comparison with that induced by irradiation. Patients with chronic leukemia, polycythemia, or lymphoma were in reasonably good condition and the changes in hematologic status that would have occurred in the absence of treatment during the observation period could be predicted with some certainty. For example, most of the patients with chronic leukemia were becoming worse only gradually; white cell levels and symptoms were increasing slowly. Some with lymphocytic leukemia had falling red cell values that required transfusions. Patients with polycythemia were in need of treatment to alleviate symptoms and to lower hazardous elevations in platelet values; two had phlebotomies shortly before irradiation. A rise in red cell values might have been expected had no therapy been given.

Problems of interpreting the quantitative nature of radiation-induced hematologic response have recently been reexamined by Bergner with theoretical and stochastic mathematical models (18). He points out that all curves of blood cell counts are a composite of the effect of radiation damage and its repair, and variations introduced by data that is poor in reliability and numbers. From his theoretical viewpoint he demonstrates that an increase in dose augments the speed of "the response process" as well as the maximum response itself. He feels, however, that large numbers of patients and observations do little for quantitation of the hematologic response and that biologic variation in patients and its many causes force the development of a qualitative rather than a quantitative theory. In attempting this task he shows that the onset of repair processes and their continuance cause the "spread" of the hematologic response data to increase with time. Since larger doses more effectively suppress repair processes and thus tend to reduce one contributing cause to variability, especially later in the course of response, one would expect that larger doses would give more uniform responses. This effect is seen in most of our data but not in all of it. Bergner's analysis of the patients with chronic lymphocytic leukemia, where maximum response of lymphocytes to 50 and 100 R was the same, revealed unexpectedly that greater variability in response (evidence for greater reparative efforts) occurred with the 100-R dose rather than with the 50 R. Since this greater reparative effort after 100 R resulted in a response curve similar to that of 50 R, these observations suggest together that the expected additional cell-damaging response to 100 R was offset by the reparative processes stimulated by the 100 R, thus providing another basis for considering the 100-R dose in this disease unnecessary as well as undesirable. Further analyses, based on Bergner's "Theory of Quantitative Radiation-Response Time-Data," or on other such analytical models, are needed in radiobiology.

When examined from a cytokinetic viewpoint the mechanisms of the changes in blood cell values produced by the irradiation are, of course, complex. This problem has been well discussed by Mathé (19) and Bond et al (20). Presumably radiation-induced death of circulating cells cannot account for much of the total effect of the exposure. Alterations in patterns of tissue sequestration and release of abnormal numbers of cells may have a significant effect upon peripheral blood cell values. The basis for most of the reduction in the cells of the blood, however, is undoubtedly interference with cell proliferation brought about most likely by a radiation-induced decrease in stem cells. Therefore, it may be necessary to relate the patterns of radiation effects to a balance between cell production, release, "normal" life span or turnover rate for each cell type as it occurs in the various disease states, and cellular radiosensitivity. Table 8 lists the geometric means of the minimum blood values reached during the six-week study period in the various diseases studied after the 50-R and 100-R doses.

The patterns of hematologic response to irradiation are influenced by the dose and also by the altered cytokinetic state in each disease. We have attempted, as yet, only preliminary interpretation of our results in the light of these factors.

Lymphocytes

Patients with polycythemia rubra vera provided data on the response of presumably normal lymphocytes to 100 R. An early drop occurred by day two to 76% of pretreatment levels and a gradual decline continued to 53% at the end of the 42-day study period, so that we do not know the precise time when the lowest lymphocyte values were reached but this curve was most like that of normal men accidentally irradiated.

Table 8
Minimum Geometric Mean Values During 6 Weeks after TBI
Expressed as Percent of Pretreatment Level

	50 R	100 R
<u>Total WBC</u>		
CLL	34.8 (26.5 good response) (68.3 poor response)	29.7 (19.7 good response) (59.5 poor response)
Malignant Lymphoma	61.8	53.1
CGL	44.4	17.3
PRV	-	26.7
<u>Lymphocytes</u>		
CLL	31.9 (23.7 good response) (66.9 poor response)	26.7 (19.3 good response) (60.6 poor response)
Malignant Lymphoma	59.3	50.0
CGL	49.4	48.5
PRV	-	44.4
<u>Platelets</u>		
CLL	65.0	25.2
Malignant Lymphoma	70.9	27.3
CGL	51.5	48.5
PRV	-	28.6

Perhaps the most striking observation related to radiation sensitivity of lymphocytes is their response in chronic lymphocytic leukemia to 50 R and 100 R. The two curves are not significantly different. The two series were not entirely comparable and the stage of illness may limit the interpretation of this fact. Our data suggest, however, that if the clinical objectives can be equated with reduction of only the lymphocyte count, the lower dose may be preferable since 50 R appears to reduce lymphocyte numbers adequately with less depression of platelets. Lymphocytes in chronic lymphocytic leukemia are certainly most sensitive to 50 R, and using the lymphocyte response data of the patients with PRV (Fig. 18) as a substitute for our lack of normal control data we can say that those with leukemia are almost three times as sensitive. A comparison with the lymphocyte counts of the Marshallese normals on Rongerik Island (Group III) who were estimated to have been exposed to 78 R (21) also shows that lymphocytes of normal people are less sensitive than those patients with lymphocytic leukemia.

Schrek (22) has reported that some patients with chronic lymphocytic leukemia have radioresistant lymphocytes. In our study (Figs. 1, 2, 3) several of the patients given 50 R or 100 R showed a significantly decreased response, in contrast with the common pattern of a drop to 50% or less of initial values in four or seven days. We have been unable to discern any clear-cut clinical or hematologic correlations with this nonresponsiveness. In some of these patients the resistance of the lymphocytes is actually greater (compare Fig. 3 with Fig. 18) than that of those in PRV (considered to be "normal").

On the other hand, two cases of "leukemic" lymphosarcoma showed inordinately sensitive lymphocytes with an early precipitous drop to 10% of the pretreatment values (Fig. 9). The remainder of the patients with malignant lymphoma had depressions of the mean lymphocyte values that were less than the response in polycythemia and must be considered more resistant than normal. We wondered whether the numbers of circulating lymphosarcoma cells in the peripheral blood of these patients before treatment might be related to radiosensitivity, but when the values were graphed after sorting the patients into two groups (those with lymphocyte counts above 4,000/mm³, and those with counts less than this level) no differences in response could be detected. We found no clear relation between height of the initial lymphocyte count in CLL and the subsequent percentage fall with therapy. There is a slight suggestion that when the initial counts are low a somewhat exaggerated response may be anticipated. In general, however, from a clinical viewpoint, one cannot prescribe the amount of treatment needed on the basis of the height of the initial count.

Granulocytes

Granulocytes in chronic granulocytic leukemia begin to drop promptly and appear to be more sensitive to radiation than in other patients and in normal man. Mean values after 50 R can be superimposed on the responses of lymphocytes in lymphocytic leukemia even though we are comparing different cell types. However, the degree of change in granulocytic leukemia is related to the initial

white cell level, a relation that does not exist for lymphocytic leukemia*. As noted earlier, leukocyte values were elevated in patients with polycythemia rubra vera before treatment, in some instances to a moderately pronounced degree. The drop after 100 R was less precipitous in PRV than in patients with chronic granulocytic leukemia, with a mild decrease during the first two weeks continuing to a nadir on day 42 in contrast to the response expected in normal persons. This depression from pretreatment values persisted for a number of months, although the pattern of climb toward pretreatment values varied considerably.

Platelets

Platelets usually reach their lowest level between the 21st and 35th days. In every group, responses to 100 R were significantly greater than to 50 R, and there was little overlap: 50 R produced little change in the patients with lymphoma, lymphocytic leukemia, and with chronic granulocytic leukemia. Individual variations were rather pronounced. Patients with polycythemia rubra vera who usually have moderate or high platelet values were not rebounding toward normal by the end of the six-week study period but had leveled off, remaining for many weeks or months at values considerably below the pretreatment ones (Fig. 16). This desirable effect from the point of view of therapy perhaps indicates that a new cellular steady state has been achieved either through the establishment of normal homeostatic mechanisms or depletion of stem cells to limiting levels of cell production.

SUMMARY

Eighty-nine treatments of total-body irradiation were given in single exposures of 50 R and 100 R at 1.5 R/min to patients with lymphoma, chronic leukemia, or polycythemia rubra vera. The clinical and hematologic responses during a 42-day study period were analyzed according to disease and dose; not unexpectedly the therapeutic responses varied. In lymphoproliferative disorders measurable clinical benefit did not depend solely on the radiation dose; the majority showed some shrinkage of enlarged lymph nodes, liver, or spleen, but the larger dose was not proportionally more effective in all cellular systems. Many required additional therapy within three months but this was not surprising in view of our use of only a single exposure. In granulocytic leukemia, improvement occurred in more than half of the patients. For polycythemia, the most clinically beneficial response appeared to be a decline of the dangerously elevated platelet counts to more normal levels that were maintained for many weeks or months.

The hematologic responses to 100 R usually but not invariably exceeded those to 50 R. A notable exception was the lymphocyte response of CLL in which the mean values of the responses of two groups were statistically the same. In general the abnormal proliferating blood elements did not return to pretreatment

* This analysis is to be the subject of a separate report by J. Yuhas (ORNL), C. C. Lushbaugh, and T. Stokes (ORAU).

values in the same time sequence that is seen in recovery of normal cell lines in the acute radiation syndrome, suggesting that homeostatic mechanisms have been reestablished to hold the values within normal ranges. For example, elevated platelets in polycythemia rubra vera were depressed by the treatment but did not return toward normal by day 42, in contrast to events in lymphocytic leukemia where initial platelet levels are usually normal or low and recovery of platelet values is usually well under way by day 42.

The detailed graphs of blood cell values, together with their geometric means for each disease and exposure group form a useful reference for radiobiologic comparison with patterns in normal persons accidentally exposed, and relate the radiosensitivity of the various blood cell lines in the diseases studied.

The graphs also show the most probable or predictable response of the average patient with these diseases for 42 days after 50-R and 100-R exposure, providing a temporal course for comparing the relative effectiveness of similar total exposures of radiation given in small daily fractions at high or low dose rates. Such a comparative study of dose-rate effects upon therapeutic effectiveness is in progress.

Acknowledgements

This study represents a group effort of the clinical staff of the Medical Division with nurses, technologists, and physicians too numerous to mention. Special recognition should be given to Mary Smyser for accumulating and plotting the data, and to the Medical Illustrators, Cathy Stubbs and Jane Kimbro. The hematology technologists, Martha Clevenger, Joyce Hewins, Kathryn Lore, Shirley Colyer, and Mary Thomas performed with great care the innumerable procedures that form the backbone of the study. Dr. David White (present address: Centerville Clinic, Route 1, Fredericktown, Pa. 15333) with skill and dedication performed most of the follow-up clinical evaluations.

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TABLE A APPENDIX
RESPONSE TO 100 R METBI - POLYCYTHEMIA

Pt. No.	Sex	Age at Rx	Interval Rx to TBI Rx	Previous Ix (approx. amt.)	Interval from last Rx to TBI	Spleen Change in Size	Systemic Symptoms + = Improvement	Pruritis + = Improvement	Subsequent Major Forms of Rx	Interval from TBI to next Rx	Follow-up Interval (3)
1	F	62	3 mo.	Phlebot. 6 x	1 mo.	N	NC	NC	Phlebotomy	2 yr. 4 mo.	4 yr. 6 mo.
2 a	F	73	1 mo.	None	-	- 2	NC	N	32p 5 mc METBI 100 R Busulfan	3 mo. 23 mo. 3 yr.	4 yr.
2 b	F	75	3 yr.	METBI 100 R 32p x 1	20 mo.	- 1	+ 1	N	Busulfan	13 mo.	2 yr.
3	F	64	7½ yr.	32p x 1 Myleran Phleb. 25 x	2½ mo.	NC	+ 1	+ 1	Phlebotomy	7 mo.	4 yr.
4	M	55	15 yr	Phleb. 50 x 32p 7 x	6 mo. 6 mo.	NC	N	N	Phlebotomy	4½ mo.	4 yr.
5	M	68	6 yr. 7 mo.	Phleb. 15 x 32p 7 x	17 mo.	NC	+ 2	+ 2	None	-	D 1 yr. 7 mo.
6 (1)	M	59	1 mo.	None	-	-	+ 2	+ 2	LETBI 100 R LETBI 250 R	23 mo.	2 yr.
7 (2)	M	60	4 mo.	32p 2 x	3 mo.	N	N	N	LETBI 150 R 2 x	15 mo.	2 yr.

Change in Size:

NC = No change - abnormal before and after treatment
N = Normal or absent before and after
+ 1 or + 2 = Larger
- 1 or - 2 = Smaller

Systemic Symptoms:

NC = No change - abnormal before and after treatment
N = Normal or absent before and after
+ = Improvement
- = Worse

- (1) Splenectomy 4 yrs. earlier after abdominal trauma
(2) Primary thrombocythemia
(3) All patients alive at latest follow-up except patient 5; none with leukemia

TABLE B APPENDIX
RESPONSE TO 50 R CHRONIC GRANULOCYTIC LEUKEMIA

Pt. No.	Sex	Age at R _x	Interval Dx to TBI R _x	Previous R _x	Interval from last R _x to TBI	Change in Size		Systemic Symptoms + = Improvement	Subsequent Major Forms of R _x	Interval from TBI to Later R _x	Follow-up Interval
						Spleen	Liver				
1	M	67	3 days	None	-	NC	NC	+2	Ext. rad. to spleen Busulfan Splenectomy Hydrocortisone Prednisone Hydrocortisone	2½ mo. 5½ mo. 14 mo. 14½ mo. 15 mo.	D 15 mo.
2	M	48	3 days	None	-	-2	-1	+2	Ext. rad. to spleen Busulfan 6-MP	2½ mo. 6 mo. 2 yr., 1 mo.	D 2 yr., 3 mo.
3 a	F	52	5 days	None	-	-1	-1	+1	Busulfan METBI 50 R	1 yr. 4 yr., 4 mo.	D 6 yr., 7 mo.
3 b	F	57	4 yr., 4 mo.	METBI (50 R) Myleran	8½ mo.	NC	NC	NC	Ext. rad. to spleen Ext. rad. to liver 6-MP Prednisone Cyclophosphamide Methotrexate Hydrocortisone	9 mo. 18 mo. 23 mo. 23 mo. 2 yr., 3 mo. 2 yr., 3½ mo. 2 yr., 3½ mo.	D 2 yr., 3½ mo.
4 a	F	60	34 days	None	-	N	N	+1	Busulfan METBI 50 R	3 mo. 3 yr.	D 5 yr., 7 mo.
4 b	F	63	3 yr., 1½ mo.	METBI (50 R) Myleran	1½ mo.	NC	NC	NC	Ext. rad. to spleen Ext. rad. to liver METBI 100 R (See Table C, Case 2) Busulfan Prednisone 6-MP Hydrocortisone	2 mo. 9 mo. 11 mo. 13 mo. 2 yr., 5 mo. 2 yr., 5 mo. 2 yr., 7 mo.	D 2 yr., 7 mo.

TABLE B. APPENDIX

Pt. No.	Sex	Age at Rx	Interval Dx to TBI Rx	Previous Rx	Interval from last Rx to TBI	Change in Size		Systemic Symptoms + = Improvement	Subsequent Major Forms of Rx	Interval from TBI to Later Rx	Follow-up Interval
						Spleen	Liver				
5	M	59	1 yr. 9½ mo.	None	-	NC	NC	N	Ext. rad. to spleen Busulfan 6-MP Prednisone Hydrocortisone	2 yr. 10 mo. 3 yr. 8 mo. 3 yr. 10 mo. 3 yr. 10 mo. 3 yr. 10½ mo.	D 3 yr. 10½ mo.
6	F	53	1 mo.	None	-	NC	NC	+2	Ext. rad. to spleen (x 2) Ext. rad. to liver Ext. rad. to spleen (x 2) Hydrocortisone Prednisone 6-MP Prednisone	1½ mo. & 21 mo. 3 yr. 3 yr. 5 mo. & 4 yr. 3 mo. 4 yr. 9 mo. 4 yr. 9 mo. 4 yr. 10 mo. 4 yr. 10 mo.	D 4 yr. 10 mo.

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TABLE C APPENDIX

RESPONSE TO 100 R CHRONIC GRANULOCYTTIC LEUKEMIA

Pt. No.	Sex	Age at R _x	Interval at R _x to TBI R _x	Previous R _x	Interval from last R _x to TBI R _x	Change in Size Spleen	Change in Size Liver	Systemic Symptoms + = Improvement	Subsequent Major Forms of R _x	Interval from TBI to Later R _x	Follow-up Interval
1	F	64	4 yr	METBI 50 R (See Table B, Case 4) Myleran METBI 50 R (See Table B, Case 4) Ext. rad. to spleen Ext. rad. to liver	2½ mo.	NC	NC	+ 1	Busulfan Prednisone 6-MP Hydrocortisone	2 mo. 18 mo. 18 mo. 19 mo.	D 19½ mo.
2	M	53	16 mo.	Cytosan Ext. rad. to liver Ext. rad. to spleen Ext. rad. to spine Ext. rad. to spleen x 2	2½ mo.	NC	NC	+ 1	Ext. rad. to rt. ilium Alkeran Ext. rad. to spleen 6-MP	4½ mo. 5 mo. 16 mo. 17½ mo.	D 17½ mo.
3	M	44	4 yr., 10 mo.	Ext. rad. to spleen x 8 Ext. rad. to liver Ext. rad. to spleen	6 mo.	NC	NC	- 2 (1)	Ext. rad. to spine	24 days	D 50 days
4	F	46	20 mo.	Ext. rad. to liver Ext. rad. to spleen L.F.TBI 100 R	3 mo.	N	N	+ 2	METBI 100 R (divided dose)	5 mo.	A 13½ mo.

(1) Paraplegia - terminal blastic state

Organ Size:

NC = No change - abnormal before and after treatment

N = Normal or absent before and after

- 1 or - 2 = Smaller

+ 1 or + 2 = Larger

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TABLE D APPENDIX
RESPONSE TO 50 R CHRONIC LYMPHOCYTIC LEUKEMIA

Pt. No.	Sex	Age at R _x	Interval Dx to TBI R _x	Previous R _x	Interval from last R _x to TBI R _x	Change in Size			Systemic Symptoms + = Improvement	Subsequent Major Forms of R _x	Interval from TBI to Later R _x	Follow-up Interval
						Spleen	Liver	Lymph Nodes				
1 a	M	67	3 yr., 8 mo.	32p x 4	6½ mo.	- 2	N	- 2	+ 2	Chlorambucil Prednisone Ext. rad. to spleen 32p x 2	6½ mo. 6½ mo. 10 mo. 2 yr., 4 mo. & 3 yr., 2 mo. 4 yr., 7 mo.	A 9 yr., 3 mo.
1 b	M	72	8 yr., 3 mo.	32p x 4 METBI 50 R Chlorambucil Prednisone Ext. rad. to spleen 32p x 2	17 mo.	- 1	NC	NC	+ 1	Prednisone	5 mo.	A 4 yr., 9 mo.
2 a	M	51	23 mo.	None	-	N	N	NC	N	Prednisone Ext. rad. to neck x 2 Chlorambucil 32p x 4 Prednisone 32p Ext. rad. to axilla Ext. rad. to axilla and groin METBI 50 R	9 days 14 days & 27 days 5 mo. 12 mo. 14 mo. 16 mo. & 21 mo. 22 mo. 23 mo. 2 yr., 1 mo. 2 yr., 2 mo. 2 yr., 9 mo.	D 6 yr. 4 mo.

TABLE D APPENDIX - continued

2 b	M	54	4 yr., 8 mo.	Prednisone Ext. rad. to neck x 2 Chlorambucil 32p x 5 Prednisone Ext. rad. to axilla Ext. rad. to axilla and groin	7 mo.	+ 1	- 1	NC	+ 2	Chlorambucil Prednisone Ext. rad. to cervical nodes	3 mo., 3 mo., 3 yr., 5 mo.	D 3 yr., 8 mo.
3	M	71	3 days	None	-	NC	N	N	UD (1)	None	-	D 4 yr., 5 mo.
4	M	52	1½ mo.	None	-	NC	N	N	N	32p x 3 Prednisone METBI 100 R Hydrocortisone Prednisone METBI 100 R (See Table E, Case 4) Hydrocortisone	4½ mo., 5½ mo., 17 mo., 22 mo., 2 yr., 2 yr., 2 mo., 2 yr., 4 mo., 3 yr., 4½ mo.	D 4 yr., 2 mo.
5	F	67	3 yr., 1 mo.	Prednisone Splenectomy Chlorambucil	11 mo.	(absent)	- 2	- 2	+ 1 UD (2)	Prednisone Dexamethasone	14 d. 2½ mo.	D 2½ mo.
6	M	70	28 days	Ext. rad. to lymph nodes Chlorambucil	6 mo.	+ 1	- 1	NC	+ 1	Prednisone Hydrocortisone	1½ mo. 4 mo.	D 4½ mo.
7	M	55	6½ mo.	32p x 2	6 mo.	N	N	- 2	+ 1	32p	6 mo.	D 7 yr., 4 mo.

TABLE D APPENDIX - continued

Pt. No.	Sex	Age at R _x	Interval D _x to TBI R _x	Previous R _x	Interval from last R _x to TBI	Change in Size			Systemic Symptoms + = Improvement	Subsequent Major Forms of R _x	Interval from TBI to Later R _x	Follow-up Interval
						Spleen	Liver	Lymph Nodes				
8 a	M	68	3 days	None	-	+1	+1	-1	NC	Prednisone METBI 50 K	5 mo. 3 yr., 7 mo. 5 mo.	D 6 yr., 7 mo.
8 b	M	71	3 yr., 5 mo.	METBI 50 R Prednisone	23 mo.	+1	+1	-1	+1	Chlorambucil	15 mo.	D 3 yr., 2 mo.
9	M	74	5½ mo.	Prednisone 32p x 2	3 mo. (3)	N	N	-2	+2	Prednisone Hydrocortisone	Cont. (3) 11 mo.	D 11 mo.
10	M	82	14 days	None	-	NC	NC	-1	UD (4)	32p	2 mo.	D 1 yr., 2 mo.
11	M	63	14 days	Prednisone Hydrocortisone	(3) 7 days	-2	UD	-2	NC	Prednisone Hydrocortisone Ext. rad. to spleen	(3) Con- tinuous 28 days 1 mo.	D 3 mo.
12	M	79	23½ mo.	METBI 100 R (See Table E, Case 15) Prednisone	- 18 days	-1	NC	NC	+1	Prednisone Hydrocortisone Ext. rad. to spine Hydrocortisone Prednisone 6-MP Hydrocortisone	42 days 2½ mo. 3 mo. 5 mo. 5½ mo. 7 mo. 7½ mo.	D 7½ mo.

- (1) Hospitalized for acute meningitis days 25 - 54
- (2) Hospitalized with hemolytic anemia days 14 - 44
- (3) On Prednisone during and after treatment
- (4) Hospitalized with pneumonia days 35 - 45

TABLE E APPENDIX

RESPONSE TO 100 R CHRONIC LYMPHOCYTIC LEUKEMIA

Pt. No.	Sex	Age at R_x	Interval R_x to TBI R_x	Previous R_x	Interval from last R_x to TBI	Change in Size			Systemic Symptoms + = Improvement	Subsequent Major Forms of R_x	Interval From TBI to Later R_x	Follow-up Interval
						Spleen	Liver	Lymph Nodes				
1	F	40	2 mo.	Ext. rad. to spleen	11 days	NC	+1	-2	N	Ext. rad. to abdomen 32p Prednisone Ext. rad. to neck & chest Ext. rad. to pelvis Ext. rad. to neck & rt. axilla Dexamethasone	3 mo. 4½ mo. 7 mo. 15 mo. 2 yr., 6 mo. 2 yr., 10 mo. 5 yr.	D 5 yr., 9 mo.
2	M	49	2 yr., 1 mo.	TEM Ext. rad. to rt. axilla Ext. rad. to naso-pharynx Chlorambucil Ext. rad. to lt. axilla		NC	+1	NC	UD (1)	Prednisone 32p	2 mo. 4 mo.	D 3 mo.
3	F	49	3 days	Ext. rad. to neck and abd., axill. & ing. nodes	- 12 mo.	NC	NC	NC	NC	Prednisone Ext. rad. to liver Hydrocortisone	1½ mo. 2 mo. 4 mo.	D 4 mo.
4 a	M	54	2 yr., 2 mo.	METBI 50 R (See Table D, Case 4) 32p x 3 Prednisone	1½ mo. (2)	-1	-2	-2	NC	Hydrocortisone Prednisone METBI 100 R	2 mo. (2) 16½ mo.	D 21 mo.
4 b	M	55	3 yr., 6 mo.	METBI 50 R (See Table D, Case 4) 32p x 3 Prednisone METBI 100 R Hydrocortisone	3 days	+1	+1	NC	+1	Hydrocortisone Prednisone	11 days 1½ mo.	D 4½ mo.
5	M	88	4 yr.	Chlorambucil	1 mo.	N	N	+2	-2	32p	1½ mo.	D 1 yr., 1½ mo.

TABLE E APPENDIX - continued

Pl. No.	Sex	Age at Rx	Interval Dx to TBI Rx	Previous Rx	Interval from last Rx to TBI	Change in Size			Systemic Symptoms + = Improvement	Subsequent Major Forms of Rx	Interval From TBI to Later Rx	Follow-up Interval
						Spleen	Liver	Lymph Nodes				
6	M	57	6 days	None	-	+1	+1	NC	+1	32p Ext. rad. to neck Prednisone Hydrocortisone	3 1/2 mo. 7 mo. 9 mo. 2 yr., 5 mo.	D 3 yr., 5 mo.
7	F	54	13 days	None	-	+1?	N	-1	N	Chlorambucil Prednisone Dexamethasone Hydrocortisone Cortisone Acetate Splenectomy	2 1/2 mo. 4 mo. 2 yr., 2 mo. 3 yr., 4 1/2 mo. 3 yr., 4 1/2 mo. 3 yr., 4 1/2 mo.	A 4 yr., 9 mo.
8 a	M	61	7 days	None	-	-1	NC	NC	+2	METBI 100 R	22 mo.	D 2 yr., 2 mo.
8 b	M	63	22 mo.	METBI 100 R	22 mo.	-1	NC	-1	+1	Prednisone	2 1/2 mo.	D 4 1/2 mo.
9	F	82	1 mo.	None	-	N	N	N	NC	None	-	A 4 yr., 4 1/2 mo.
10 a	M	74	3 days	None	-	N	N	-1	N	METBI:100 R	18 mo.	D 3 yr., 9 mo.
10 b	M	75	18 mo.	METBI 100 R	18 mo.	N	N	-1	+1	Ext. rad. to lt. ear LETBI 100 R LETBI 100 R Prednisone	8 mo. 16 mo. 21 mo. 2 yr.	D 2 yr., 3 mo.

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TABLE 3 APPENDIX - continued

11	M	69	10 days	None	-	-2	-1	+1	Prednisone Hydrocortisone	9 mo. 3 yr., 4 mo.	A 4 yr., 1 mo.
12	M	76	1 mo.	Chlorambucil	18 days	NC	NC	+1	Prednisone Hydrocortisone	2 mo. 4 mo.	D 4 mo.
13 a	M	61	14 mo.	Prednisone 131I x 3 (3) 32P x 3	3½ mo.	+1	NC	+1	Ext. rad. to abd. Prednisone METBI 100 R	2½ mo. 8½ mo. 12 mo.	D 3 yr., 8 mo.
13 b	M	62	2 yr., 2 mo.	METBI 100 R Ext. rad. to abd. Prednisone	1 mo.	N	NC	+1	Ext. rad. to ing. nodes Prednisone Cyclophosphamide Ext. rad. to lt. eye	9 mo. 15 mo. 21 mo. 2 yr., 4 mo.	D 2 yr., 8 mo.
14	M	71	18 days	None	-	-1	UD	UD (4)	Prednisone Hydrocortisone	43 days 2½ mo.	D 2½ mo.
15	M	77	3 days	None	-	-1	NC	+1	Prednisone METBI 50 R (See Table D, Case 12) Hydrocortisone Ext. rad. to spine 6-MP	7½ mo. 23½ mo. 2 yr., 2 mo. 2 yr., 3½ mo. 2 yr., 6½ mo.	D 2 yr., 7 mo.
16	M	55	4 days	None	-	-1	-2	+2	Prednisone	8 mo.	A 3 yr., 1 mo.

- (1) Hospitalized 3 weeks post I₁₃₁ for thrombocytopenia
- (2) On Prednisone during and after treatment
- (3) Toxic adenoma of thyroid
- (4) At 6 weeks post I₁₃₁ admitted for transfusions and Prednisone

TABLE F APPENDIX
RESPONSE TO 50 R METBI - LYMPHIOSARCOMA

Pt. No.	Sex	Age at I _x	Interval Dx to TBI R _x	Previous I _x	Interval from last I _x to TBI	Change in Size			Systemic Symptoms + = Improvement	Subsequent Major Forms of I _x	Interval From TBI to Later R _x	Follow-up Interval
						Spleen	Liver	Lymph Nodes				
1	F	37	12 days	None	-	NC	- 1	NC	+ 1	METBI 100 R (See Table G, Case 3 a) Splenectomy METBI 100 R (See Table G, Case 3 b) Ext. rad. to pelvic and abdominal nodes Prednisone Nitrogen mustard Ext. rad. to axillae Vinblastine Ext. rad. to lower abdominal mass Hydrocortisone	3 mo. 13 mo. 16 mo. 21½ mo. 2 yr. 3 yr. 3 yr., 3 mo. 3 yr., 6 mo. 3 yr., 11 mo. 3 yr., 11½ mo.	D 4 yr.
2	M	42	19 days	None	-	?	?	- 1	N	Ext. rad. to ing. and iliac nodes METBI 100 R (See Table G, Case 13) Ext. rad. to abd. Nitrogen mustard Chlorambucil Prednisone Ext. rad. to mediastinum	2 yr., 7 mo. 3 yr., 1 mo. 3 yr., 1½ mo. 3 yr., 2½ mo. 3 yr., 4 mo. 3 yr., 4½ mo. 3 yr., 5 mo.	D 3 yr., 5 mo.

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TABLE F APPENDIX - continued

3	M	46	2 yr., 3 mo.	Ext. rad. to neck & axilla 32P x 3	5 mo.	+1	N	-1	NC	Chlorambucil	5 mo.	D 3 yr., 2½ mo.
4	M	72	17 days	None	-	N	-1	-1	NC	Prednisone 32P x 3 Chlorambucil	7 mo. 2 mo. 13½ mo.	A 4 yr., 10 mo.
5	M	45	10 mo.	Nitrogen mustard Ext. rad. to spleen Thio-Tepa	8½ mo. ?	+1	+1	+1	+1	Prednisone	2 mo.	A 2 yr., 1 mo.

TABLE G APPENDIX
RESPONSE TO 100 R METBI LYMPHOSARCOMA

Pt. No.	Sex	Age at Rx	Interval Dx to TBI Rx	Previous Rx	Interval from last Rx to TBI	Change in Size			Systemic Symptoms + = Improvement	Subsequent Major Forms of Rx	Interval from TBI to Later Rx	Follow-up Interval	
						Spleen	Liver	Lymph Nodes					Abd. Mass
1 a	F	49	2 mo.	Ext. rad. to left inguinal nodes	1 mo.	N	-1	-2	0	N	Ext. rad. to sub-mandibular nodes 32p METBI 100 R	10 min. 11 mo. 21 mo.	D 4 yr., 9 mo.
1 b	F	51	23 mo.	Ext. rad. to left inguinal nodes METBI 100 R Ext. rad. to sub-mandibular nodes 32p	10½ mo.	N	N	-2	-1	+1	Ext. rad. to abdomen Nitrogen mustard Ext. rad. to spine Ext. rad. to rt. inguinal nodes Ext. rad. to rt. cerv. nodes Prednisone Ext. rad. to rt. thigh Ext. rad. to left pelvis 32p Hydrocortisone	2 mo. 5 mo. 5½ mo. 14 mo. 14 mo. 17 mo. 20 mo.	D 2 yr., 11 mo.
2	F	48	16 yr.	Ext. rad. to right cerv. nodes Ext. rad. to nasopharynx Ext. rad. to left cervical nodes Ext. rad. to right breast and axilla Nitrogen mustard	16 yr. 11 mo.	N	-2	-2	NC	(1)	None	-	D 2½ mo.
3 a	F	36	3½ mo.	METBI 50 R (See Table F, Case 1)	3 mo.	+1	NC	-2	0	N	Splenectomy METBI 100 R	10 mo. 13 mo.	D 3 yr., 8 mo.

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TABLE G APPENDIX - continued

3 b	F	39	1 yr., 4½ mo.	METBI 50 R (See Table F, Case 1) METBI 100 R Spleneectomy	3 mo.	-	NC	- 1	0	NC	Ext. rad. to pelvic and abd. nodes Prednisone Nitrogen mustard Ext. rad. to axillae Vinblastine Ext. rad. to abd. mass Hydrocortisone	5½ mo. 7½ mo. 19½ mo. 23 mo. 2 yr., 2 mo. 2 yr., 7 mo. 2 yr. 7½ mo.	D 2 yr., 7½ mo.
4	M	80	1 mo.	None	-	N	NC	- 1	0	- 1 (2)	Ext. rad. to mediastinum 198Au to right pleural cavity Ext. rad. to mediastinum	1½ mo. 2 mo. 2½ mo.	D 6½ mo.
5 a	F	60	9 mo.	Ext. rad. to cheeks	8½ mo.	N	N	- 2	0	+ 1	METBI 100 R	12 mo.	D 4 yr., 2½ mo.
5 b	F	61	21 mo.	Ext. rad. to cheeks METBI 100 R	12 mo.	N	N	- 2	0	+ 1	Ext. rad. to rt. inguinal nodes Ext. rad. to rt. cervical nodes Ext. rad. to lt. femur & iliac nodes	3 mo. 13 mo. 2 yr., 7 mo.	D 3 yr., 2½ mo.
6	F	68	8 yr.	32p x 4 Trichthylenemelamine Ext. rad. to neck Ext. rad. to rt. axill. and inguinal nodes Ext. rad. to upper chest Ext. rad. to mediastinum	2 mo.	+ 1	NC	- 2	0	- 1 (3)	Ext. rad. to lt. axilla Ext. rad. to abd. mass Hydrocortisone	13 mo. 2 yr., 2 mo. 2 yr., 10 mo.	D 2 yr., 10 mo.
7 a	M	76	1½ mo.	None	-	N	- 1	- 1	0	N	32p METBI 100 R	10 mo. 18½ mo.	D 22½ mo.

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TABLE G APPENDIX - continued

Pt. No.	Sex	Age at R _x	Interval from Dx to TBI R _x	Previous R _x	Interval from last R _x to TBI	Change in Size			Systemic Symptoms + = Im-provement	Subsequent Major Forms of R _x	Interval from TBI to Later R _x	Follow-up Interval	
						Spleen	Liver	Lymph Nodes					
7 b	M	78	20 mo.	32p METBI 100 R	18½ mo.	UD	UD	- 2	- 1	N	Ext. rad. to abd. mass Nitrogen mustard Hydrocortisone	3½ mo. 4 mo. 4 mo.	D 4 mo.
8	M	49	10 days	None	-	N	+ 1	- 1	0	N	Ext. rad. to neck, axill. & ing. nodes Ext. rad. to rt. cervical nodes 32p Prednisone Ext. rad. to iliac and inguinal nodes Ext. rad. to left axilla Ext. rad. to cheek Ext. rad. to spine Ext. rad. to spine Ext. rad. to thorax Ext. rad. to lt. cheek Cyclophosphamide	2 mo. 9½ mo. 13½ mo. 15 mo. 17 mo. 17½ mo. 3 yr., 2 mo. 4 yr., 9 mo. 5 yr., 5½ mo. 5 yr., 7 mo. 5 yr., 8 mo. 5 yr., 8½ mo.	A 5 yr., 10 mo.
9	M	87	53 days	None	-	N	N	NC (4)	0	NC	Ext. rad. to both ing. & iliac nodes Ext. rad. to neck nodes	28 d. 5½ mo.	D 6 mo.
10 a	F	55	1 mo.	None	-	N	- 2	- 1 (5)	0	+ 1	Ext. rad. to rt. clavicle Ext. rad. to lt. axilla	2 mo. 2½ mo.	D 4 yr., 9 mo.

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TABLE G APPENDIX - continued

Pt. No.	Sex	Age at R _x	Interval D ₀ to TBI R _x	Previous R _x	Interval from last R _x to TBI	Change in Size			Systemic Symptoms + = Im-provement	Subsequent Major Forms of R _x	Interval from TBI to Later R _x	Follow-up Interval	
						Spleen	Liver	Lymph Nodes					
14	M	78	1 1/2 mo.	None	-	N	-1	-1	0	+1	Ext. rad. to sacrum Prednisone	8 mo. 20 mo.	D 21 mo
15	M	78	3 mo.	None	-	-1	-1	-1	0	+1	LETBI 100 R Chlorambucil Prednisone Cyclophosphamide Hydrocortisone	15 mo. 22 mo. 23 mo. 2 yr., 3 1/2 mo. 2 yr., 4 mo.	D 2 yr., 4 mo.
16	M	76	4 yr., 1 mo.	Ext. rad. to neck & both axillae Nitrogen mustard Ext. rad. to neck, both axillae, and mediastinum Ext. rad. to abdomen x 3 Local rad. sq. Ca cheek Methylprednisolone Triethylenemelamine Prednisone	(8)	N	NC	-1	0	UD (8)	Prednisone Ext. rad. to keratoses Cortisone Acetate	(8) 1 1/2 mo. 5 1/2 mo.	D 5 1/2 mo
17	M	68	4 mo.	None	-	-1	NC	-2	0	+1	Cyclophosphamide Ext. rad. to sq. Ca face Ext. rad. to mct. Ca pelvis	9 mo. 10 mo. 2 yr., 9 mo.	A 2 yr., 9 mo.

(1) In terminal condition at time of R_x
(2) In hospital with bilateral pleural effusion days 31-81 post R_x
(3) In hospital with pneumonia days 21-66 post R_x
(4) No regression at day 14. External radiation at day 28
(5) Maximum regression at 4 weeks, enlarging again by 6 weeks
(6) In another hospital with herpes zoster at 6 weeks
(7) External radiation to abdomen on day 16. No change at day 42
(8) On Prednisone during and after treatment

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TABLE H APPENDIX
RESPONSE TO METBI - HODGKIN'S

Pt. No.	Sex	Age at Rx	Dose	Interval Dx to TBI Rx	Previous Rx	Interval from last Rx to TBI	Change in Size			Systemic Symptoms + = Im-provement	Subsequent Major Forms of Rx	Interval From TBI to Later Rx	Follow-up Interval
							Spleen	Liver	Lymph Nodes				
1	F	21	50 R	1 mo.	None	-	N	N	- 1	N	1 1/2 mo. 17 mo. 2 yr., 2 1/2 mo. 3 yr., 1 mo. 3 yr., 9 mo. 5 yr., 1 mo. 5 yr., 3 mo. 5 yr., 8 mo. 5 yr., 9 mo. 7 yr., 1 mo. 7 yr., 7 mo. 7 yr., 11 mo. 8 yr., 3 mo. 8 yr., 5 mo. 8 yr., 5 mo. 8 yr., 6 mo.	A 8 yr., 10 mo.	
2	F	65	100 R	14 d.	None	-	N	N	- 1 (1)	NC (1)	-	1) 14 d.	

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TABLE II APPENDIX - continued

Pl. No.	Sex	Age at Rx	Dose	Interval Lx to TBI Rx	Previous Rx	Interval from last Rx to TBI	Change in Size			Systemic Symptoms + = Im-provement	Subsequent Major Forms of Rx	Interval From TBI to Later Rx	Follow-up Interval
							Spleen	Liver	Lymph Nodes				
3	F	20	100 R	21 d.	None	-	N	N	- 1	NC	Nitrogen mustard Prednisone Ext. rad. to supra-clav. nodes and mediastinum Ext. rad. to lt. axilla Ext. rad. to lt. neck Ext. rad. to rt. axill & supraclav. nodes Nitrogen Mustard Vinblastine Ext. rad. to abdominal mass Ext. rad. to left axilla & mediastinum U'racil Mustard	1½ mo. 2 mo. 2½ mo. 7½ mo. 7½ mo. 12½ mo. 14 mo. 17 mo. 2 yr. 2 yr. 2½ yr.	D 2 yr., 3½ mo.

(1) Last seen at 2 weeks after Rx

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TABLE J APPENDIX

GEOMETRIC MEANS (% PRETREATMENT)

Values of the Computed Geometric Means Used in the Hematologic Figures of this Report

Day

Disease	R	Blood Value	Day														No. Pts.	Fig. No.					
			1	2	4	7	14	21	28	35	42	49	56	62	76	84							
CLL	50	WBC (all)	94.3	79.0	65.2	56.5	45.6	39.8	44.3	41.6	34.8									15			
		WBC (good response)	96.0	80.5	60.2	52.2	39.0	32.5	35.9	32.4	26.5										11	1	
		WBC (poor response)	89.8	74.9	81.2	70.5	69.8	69.7	79.1	82.3	68.3											4	1
		Absolute Lymphs (all)	94.3	79.4	63.1	54.4	42.9	34.6	36.2	34.6	31.9											15	
		Abs. Lymphs (good response)	96.9	81.7	58.4	50.0	36.5	27.2	26.6	25.4	23.7											11	3
	Abs. Lymphs (poor response)	87.7	73.5	78.1	68.4	67.2	66.9	78.1	81.0	66.9											4	3	
	Platelets	114.1	97.9	100.4	90.5	86.3	67.0	65.0	78.2	92.0											15	4,6	
	100	WBC (all)	86.1	74.3	58.4	46.3	38.1	35.0	29.7	32.6	30.7											20	
		WBC (good response)	78.1	65.4	48.4	35.2	28.1	22.4	19.7	21.2	21.0											14	2
		WBC (poor response)	97.7	96.2	87.0	81.4	74.9	85.2	78.4	65.1	59.5											5	2
Abs. Lymphs (all)		82.2	69.3	54.2	42.3	34.9	30.0	28.2	27.7	26.7											19		
Abs. Lymphs (good response)		77.2	60.6	47.3	33.3	26.2	20.4	19.3	20.3	19.5											14	3	
Abs. Lymphs (poor response)	97.9	101.3	77.3	82.6	78.0	88.5	76.3	62.3	60.6											5	3		
Platelets	94.0	81.6	81.6	81.6	75.4	40.5	25.2	26.8	38.1											20	5,6		

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