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Treatment of Chronic Leukemias[1,2,3]

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SYNOPSIS

Experience in the treatment of 326 consecutive cases of chronic leukemia by the method of titrated, regularly-spaced, total-body irradiation with P^{32} or x-ray has told us much about pitfalls in the analysis of survival data, the biology of leukemia, and radiobiology. It is the purpose of this paper to summarize what we have learned. However, all who plan to use the method should read all of the references cited.

The population studied includes every case of chronic lymphocytic and granulocytic leukemia referred for treatment between January 1, 1941, and June 30, 1954. The first series of 163 patients was seen prior to July 1, 1951, and has been reported (1-4). Twenty four of this series were treated with total body x-ray, all others with P^{32}. The second series of 163 patients has not been previously reported. Of the 326, 212 were lymphocytic leukemias and 114 were granulocytic leukemias. The relevant categories of the population are shown in Tables I, II, and III. The age range at onset of chronic lymphocytic leukemia is from 27 to 92, for chronic granulocytic leukemia from 3 to 81. The sex distribution is about equal in the granulocytic series, but about twice as many men as women develop lymphocytic leukemia. The distribution of leukocyte counts in these patients fits a log normal distribution with a median of 40,000 for the lymphocytic series and of 90,000 for the granulocytic series (Figs. 4 and 5 in ref. 5). Forty of the lymphocytic series were subleukemic with counts before treatment less than 15,000; only 6 of the granulocytic patients were subleukemic. Marrows in these subleukemic patients are identical to those in the leukemic patients if an ade-

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[2]Presented in part before the 10th International Congress of Radiology, Montreal, August 29, 1962.

[3]Drs. Robert H. Bigley, Robert D. Koler, Bernard Pirofsky, and Arthur J. Seaman collaborated in the care of these patients.

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quate sample is obtained but are much more difficult to aspirate, suggesting that the cells stick tightly together. The majority of patients came from within a radius of 1,000 miles of Portland, Oregon.

The private patients shown in Table II were referred by their physicians. The nonprivate were charity patients in the hospitals and clinics of the Medical School. The majority of the previously treated patients had had local x-ray therapy, but some had been treated with Urethane.

THE METHOD

The essential features of our method of treatment (1,2) are:

1. Start treatment as soon as the diagnosis is established.
2. Explain the disease and treatment to the patient and warn against pregnancy, tooth extraction, or elective surgery in infected areas at the first visit. Psychotherapy at this visit is responsible for our 100 per cent follow up.
3. The recommended initial doses of P^{32} are given in Table IV. The patients herein reported received smaller initial doses.

TABLE I.

AGE AND SEX DISTRIBUTION OF THE POPULATION AT ONSET

	Age at Last Birthday									
	3-19	*20-29*	*30-39*	*40-49*	*50-59*	*60-69*	*70-79*	*80-92*	*Total*	*Median Age*
Lymphocytic Leukemias										
Male										
#	0	1	7	13	37	54	24	8	144	62
%		0.7	4.9	9.0	25.7	37.5	16.7	5.6	100	
Female										
#	0	1	6	8	16	22	12	3	68	61
%		1.5	8.8	11.8	23.5	32.3	17.6	4.4	100	
Total										
#	0	2	13	21	53	76	36	11	212	62
%		0.9	6.1	9.9	25.0	35.9	17.0	5.2	100	
Granulocytic Leukemias										
Male										
#	3	2	9	9	11	18	7	1	60	57
%	5.0	3.3	15.0	15.0	18.4	30.1	11.7	1.7	100	
Female										
#	1	9	14	6	10	9	3	2	54	42
%	1.9	16.7	25.9	11.1	18.5	16.7	5.6	3.7	100	
Total										
#	4	11	23	15	21	27	10	3	114	52
%	3.5	9.7	20.2	13.2	18.4	23.7	8.8	2.6	100	

TABLE II

FRACTION ALIVE

	Leukemic						*Subleukemic*			*All*		
	Previously Untreated			*Previously Treated*								
	*P**	*I***	*Total*	*P*	*I*	*Total*	*P*	*I*	*Total*	*P*	*I*	*Total*
Lymphocytic	18/105	7/33	25/138	3/23	0/11	3/34	3/29	0/11	3/40	24/157	7/55	31/212
% Alive	17.1	21.2	18.1	13.0	0	8.8	10.3	0	7.5	15.3	12.7	14.6
Granulocytic	1/65	0/11	1/76	1/26	0/6	1/32	0/2	0/4	0/6	2/93	0/21	2/114
% Alive	1.5	0	1.3	3.9	0	3.1	0	0	0	2.2	0	1.8
Total	19/170	7/44	26/214	4/49	0/17	4/66	3/31	0/15	3/46	26/250	7/76	33/326
% Alive	11.2	15.9	12.2	8.2	0	6.1	9.7	0	6.5	10.4	9.2	10.1

*Patients referred by private physicians.
**Indigent patients from Medical School Hospitals and Clinic.

TABLE III

PERCENTAGE OVER 65 AT ONSET OF LEUKEMIA BY SEX AND TYPE OF LEUKEMIA

	Lymphocytic			*Granulocytic*		
Age	*F*	*M*	*Total*	*F*	*M*	*Total*
65+	23	52	75	9	17	26
%	10.8	24.5	35.4	7.9	14.9	22.8
<65	45	92	137	45	43	88
%	21.2	43.4	64.6	39.5	37.7	77.2
Total	68	144	212	54	60	114
%	32.0	67.9	100	47.4	52.6	100

4. All subsequent doses should be based on the response of that particular patient, since doses vary by a factor of at least 10 in persons of the same weight and leukocyte count (5). Until a patient's leukocyte count is between 10,000 and 20,000, he should be seen once a week. In subleukemic patients with initial counts below 15,000, the leukocyte count should never be used as a guide to therapy, and such may be seen at two week intervals initially since the lymph nodes, spleen, hemoglobin, and capacity for normal work and recreation which are the guides for this group change more gradually than do the leukocyte counts. The period during which these factors are brought under control is usually six to twelve weeks and is called "the period to control" (Fig. 1 in ref. 5).

5. During this period and all subsequent time, all associated diseases and complications should be treated.

6. In the leukemic cases, the best guide to control and maintenance is the direction of change in the leukocyte count with the objective to keep it between 10,000 and 20,000. The direction of change in all other abnormalities is also used as a guide and must be used alone in the subleukemic cases. Use absent clot retraction at 1 hour, not thrombocyte count, for evidence of risk of thrombocytopenic bleeding; and recognize that thrombocytopenia is due to too little P^{32} unless leukemic cells are scarce in the marrow.

7. The objective of therapy during the period of maintenance (Fig. 2 in ref. 5) is to keep the leukocyte count between 10,000 and 20,000 in the leukemic cases and the spleen at or above the costal margin, lymph nodes not over 1+, and the patient at his usual work and recreation. This is accomplished by gradually prolonging the interval and decreasing the dose until that level is found which maintains a completely steady optimal state. This determines for each patient the threshold dose rate for these effects (5).

8. The dose and interval are not interchangeable. If the leukocyte count drops significantly and then rises again, the dose is too large and the interval is too short. If it steadily rises, the dose is too small. If it remains constant for most of the interval and then rises, the interval is too long. Actually, the determination of the proper dose and interval is as simple as adjusting the dose of insulin in a diabetic. In most cases, the interval for maintenance is between 4 and 12 weeks and in adults the intravenous dose of P^{32} is between 0.3 mc and 10.0 mc. With any therapeutic agent, the method of administration is as important as the agent used. With any agent, including water, one can kill every patient if the dose rate is not correct. The dose rate is far more important than the total dose.

PITFALLS IN EVALUATION OF SURVIVAL DATA

If every case seen between fixed dates is not reported, results are not comparable with the data for the same age and sex in the general population, and an assumption is made as to how long it takes for a therapy to have an effect, thus losing this information. Leukemias, all other malignancies, and many other conditions follow a log normal, not a normal, distribution of survival times (1-4,

TABLE IV

RECOMMENDED INITIAL DOSE OF P^{32} FOR ADULTS*, MC., I.V.

Type of Chronic Leukemia	*Initial Leukocyte Count*		
	<40,000	40,000-100,000	>100,000
Lymphocytic	1.5	2.0	2.5
Granulocytic	3.0	4.0	5.0

*For children multiply by wt./150 lb. or wt./70 kg.

6). In other words, the logarithm of the survival time is normally distributed. There are great advantages in plotting the data on log normal probability paper[1], since significant differences can be due to differences in the population (Fig. 1), in which case the straight lines start apart and move together, or to differences in the treatment, in which case the straight lines start together and move apart (Fig. 2). Series should be closed and not analyzed until at least the estimated median survival time has elapsed; since if there is a better treatment, during the

[1]Codex Book Company, Inc., Norwood, Mass., No. 31.376 and 3128.

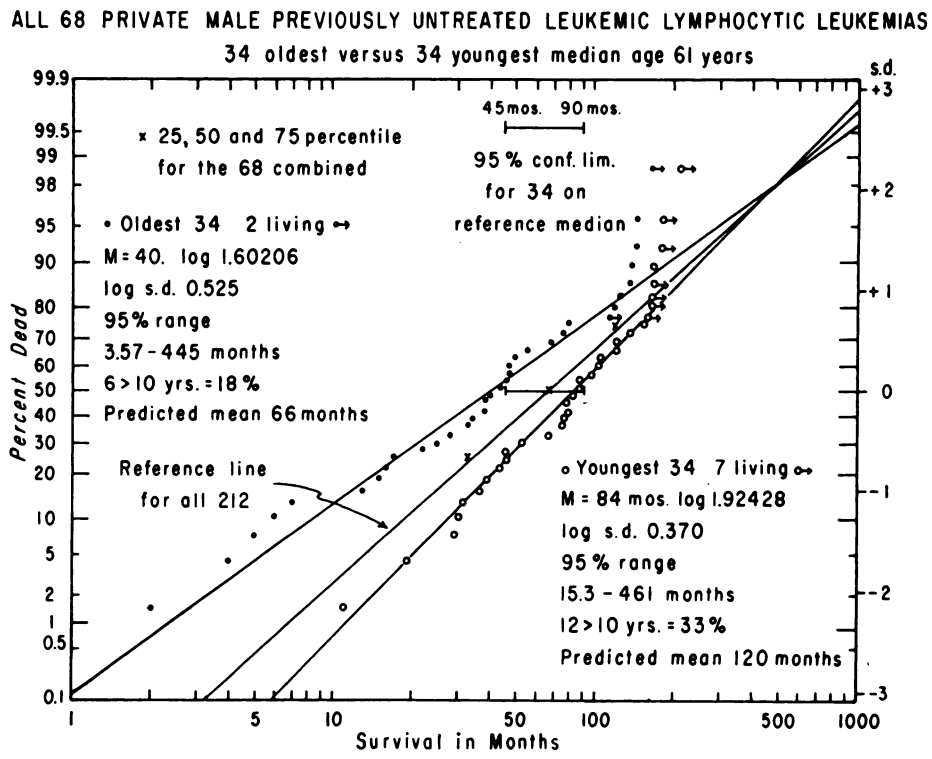

Fig. 1.

first part of the time period patients are moving from the control reference line to the final line characteristic of the treatment. The initial dashed line in Figure 2 shows that it required about 27 months for the improved treatment to have its full effect. Note how erroneous would be the prediction if this initial period were projected. Figure 3 shows that the same answer is derived if only previously untreated patients are plotted for survival after first therapy. In other words, both time and numbers are necessary for valid data. Furthermore, most of the early deaths are due to the diseases of old age, to patients who were already in the acute terminal phase, and to persons who had other major illnesses.

Any sorting on nonobjective criteria tends to invalidate the statistical method. For example, miliary tuberculosis has a much higher incidence in patients with leukemia. Would it have occurred had the patient not had leukemia, or would a cerebral vascular accident have occurred at the same time in a patient with hypertension if the patient had not had leukemia?

Graphic analysis has the further advantage that a mistake in plotting is instantly apparent, whereas an error in the computed analysis is not easily detected. For small numbers with some patients living, the random number or matched pair sign test as described elsewhere (7-9) is probably the most convenient and safe method of analysis.

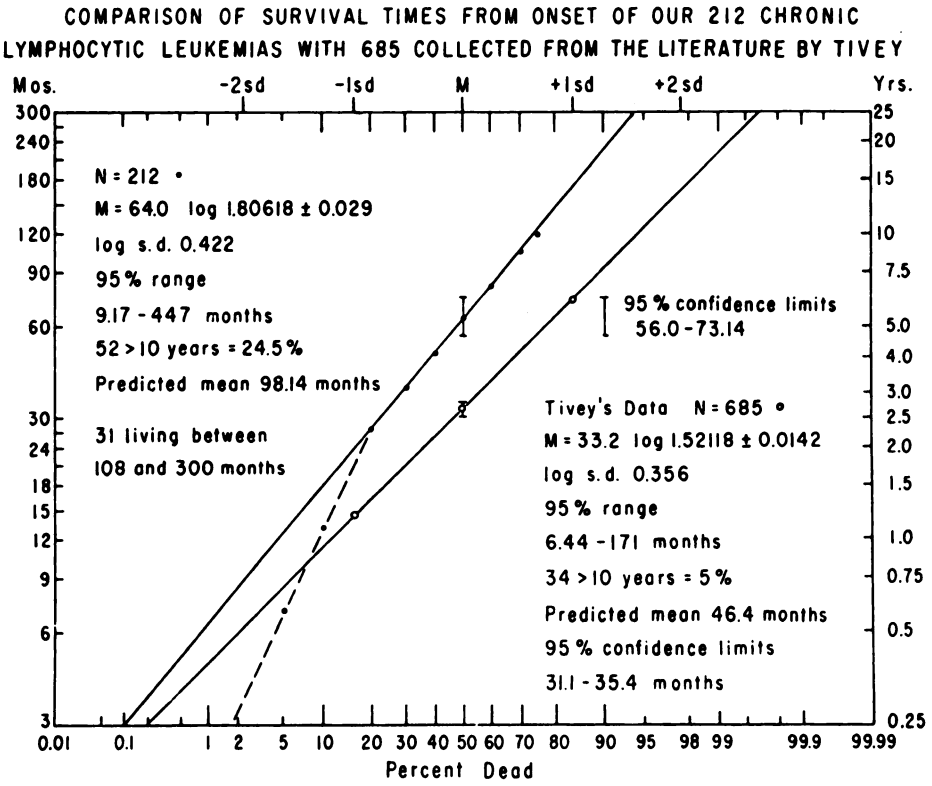

Fig. 2.

RESULTS OF THERAPY

As may be seen from Figures 2 to 5 and Tables V and VI, the results of this treatment are significantly better than those for any other published series treated by other methods[1], at least for the total series and chronic lymphocytic leukemias. Furthermore, they confirm Tivey's predictions for this therapy. The results for chronic granulocytic leukemia are not significantly different from Tivey's summarized series (1-4, 6). It is our impression, however, that others were not as rigid as we have been in including all cases, even in the acute terminal stage if at one time chronic, all early deaths from any disease, and all aged patients.

Of the 212 lymphocytic leukemias, 63 have lived more than 10 years since onset and 32 more than 10 years after first treatment, and 93 have attained the age of 70. Of the 114 granulocytic leukemias, 11 have lived more than 10 years since onset and 5 have lived more than 10 years since first treatment. Twenty three have attained the age of 70 years. There is no living patient in either series who has been followed less than 90 months, or 7½ years, after our first treatment.

The range of survival time in these patients varies from less than 4 hours after first therapy to patients living more than 25 years after first therapy. Yet,

[1]John Lawrence of the Donner Radiation Laboratory and Col. Wm. Crosby at Walter Reed are among those using our method.

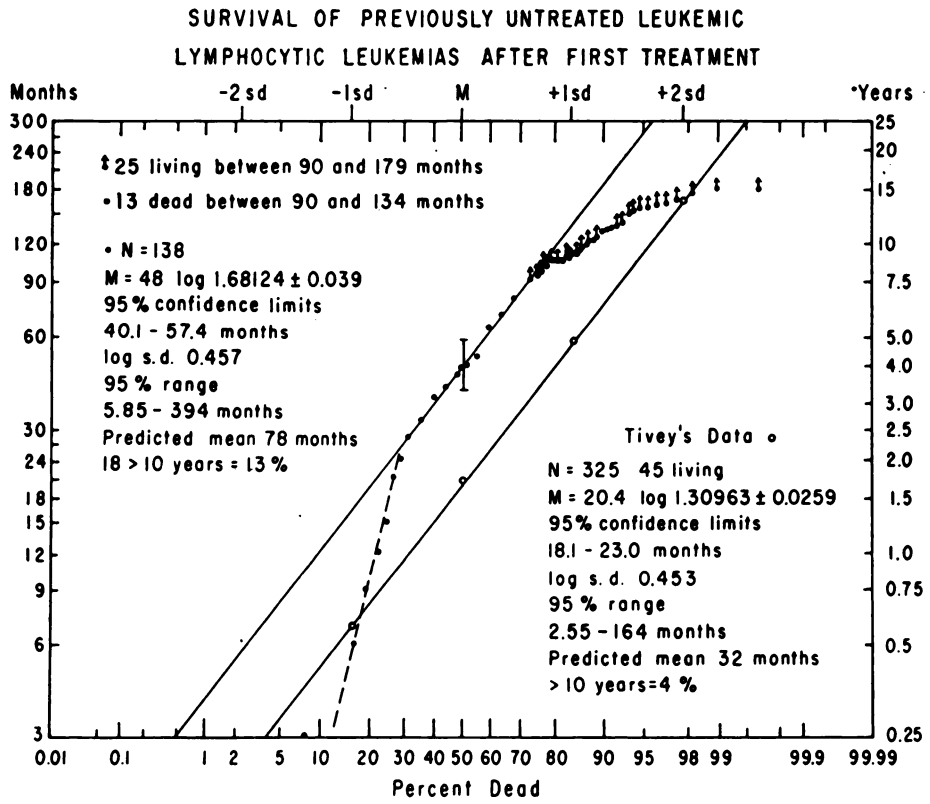

Fig. 3.

TABLE V

LOGARITHMIC PROBABILITY COMPARISONS OF SURVIVAL TIMES

	Alive/N	*% Alive*	*% > 10 Years*	*% > 5 Years*	*Median Months*	*Log s.d.*	*Predicted Mean Months*
			From Onset of Leukemia				
A Control series, Tivey*	176/1978	8.9	5	22	31.8	0.363	59
B Our leukemias	33/326	10.1	20	42	48	0.473	78
C Control lymphocytics	66/685	9.6	6	22	33.2	0.356	60
D Our lymphocytics	31/212	14.1	25	52	64	0.422	98
E Control granulocytics	110/1090	10.0	4	20	32.4	0.332	56
F Our granulocytics	2/114	1.8	10	25	34	0.370	49
			After First Specific Therapy				
A Control series, Tivey	93/651	14.3	4	14	18.7	0.438	29
B Our leukemias	33/326	10.1	13	29	31	0.536	53
C Control lymphocytics	45/325	13.8	4	14	20.4	0.453	32
D Our lymphocytics	31/212	14.1	18	37	41	0.516	69
E Control granulocytics	48/228	21.1	3	13	19.8	0.439	31
F Our granulocytics	2/114	1.8	4	15	21.5	0.430	33

*Significant differences, $P < 5\%$: A,B; C,D; D,F. *Control series includes patients treated with P^{32} by others.

TABLE VI

MATCHED SIGN TESTS OF SURVIVAL IN LEUKEMIA

Categories 1st Item Better and +	*Matched in order listed for*				*Pairs*	*After Onset r/N*	*After Onset P%*	*After 1st Rx r/N*	*After 1st Rx P%*
F vs. M	L	age	series	prev. Rx ±	68	18−/62	< 0.4*	24−/66	1.8*
F vs. M	G	age	series	prev. Rx ±	54	18−/54	1.4*	18−/54	1.4*
Youngest vs. oldest 50%	L	sex	series	prev. Rx ±	105	38−/102	< 1.0*	43−104	< 5.0*
Youngest vs. oldest 50%	G	sex	series	prev. Rx ±	54	22−/54	11.0	20−/54	3.8*
L vs. G	sex	age	prev. Rx ±	series	83	23−/81	< 0.4*	23−/84	< 0.3*
P^{32} vs. spray x-ray	L or G	sex	age	prev. Rx ±	24	11−/24	>15.4	6−/22	2.6*
Highest vs. lowest WBC	L	sex	series	prev. Rx ±	105	48−/102	>25	49+/103	>25
Highest vs. lowest WBC	G	sex	series	prev. Rx ±	54	22+/52	16.6	23−/53	>13.6

*Significant differences.

some of the patients who were expected to die within 24 hours actually lived over 5 years and some of those who were expected to live long died early. The mean survival time of the entire 326 as of April 30, 1962, is 66 months; for the 212 lymphocytics, 76 months; and for the 114 granulocytics, 47 months. But with 33 living, the predicted means shown in Table V, which may be read at the 67 per cent point from the log probability curve, are more accurate since mean survival varies greatly with the fraction living and cannot be computed until all are dead.

PROGNOSTIC FACTORS

The important variables affecting prognosis proved to be sex, and age at onset of the disease, as shown in Figure 1 and Table VI. Contrary to current opinion, younger patients survive longer than older ones and females longer than males. These are population differences, not differences due to therapy. The differences between our first and second series and between the private and indigent patients (3) proved to be due to a higher proportion of aged patients in the second series and in the indigent. The differences (3,4) due to sex and age were clearly demonstrated by the matched pairs sign test (7,8). The introduction of antibiotics has apparently led to a progressive increase in the mean and median age of patients with leukemia; and with this treatment, at least, age is a major factor in survival time.

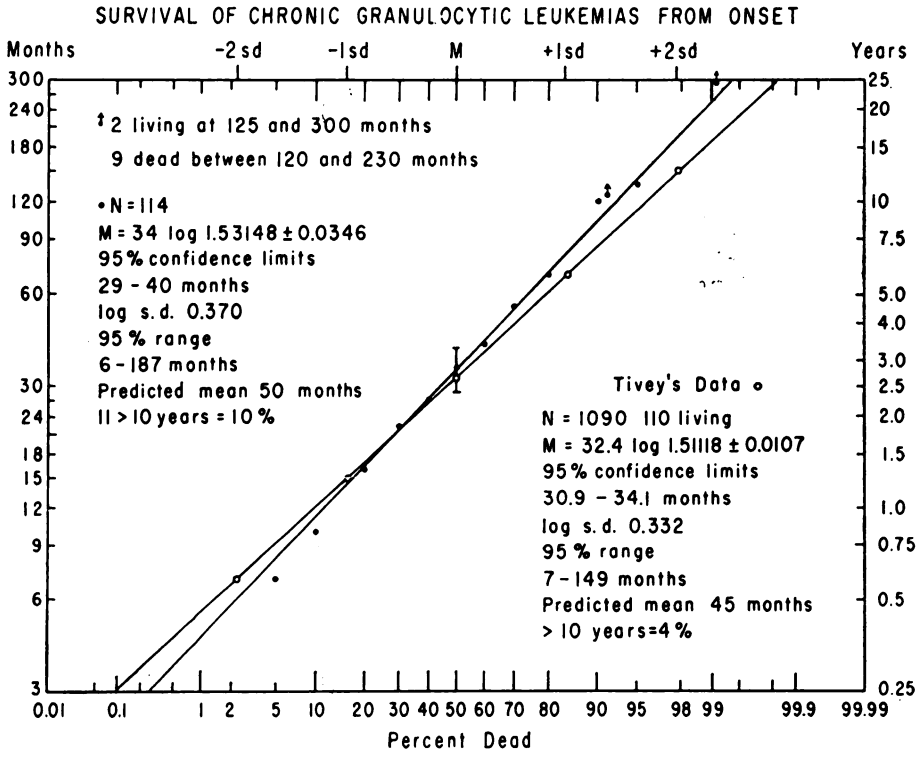

Fig. 4.

Also, contrary to current opinion, the initial level of the leukocyte count was not of prognostic value. This is perhaps due to the fact that either a rapid rate of cell division or a long life span of the cell tends to give high leukocyte counts.

The other factor tested which showed nonsignificant differences when effects of sex and age were eliminated were previously untreated versus previously treated. Here again, two opposing factors interact—the early deaths in the perviously treated have been eliminated but the genetic change to the acute terminal phase may have already occurred before the patient is referred. The longest survivors are in the previously treated group because our program was not started until 1941, but the fraction surviving is much lower in this group.

RADIOBIOLOGIC OBSERVATIONS

These have been reported elsewhere[5,10-12], but they can be summarized here. To understand them, it is first necessary to clearly grasp my concept of the fundamental nature of cell division and malignancy (13-15). The alpha cell of any series is capable of division and remains immature to divide again. It is the only cell that can start a culture or a transplant. It is potentially im-

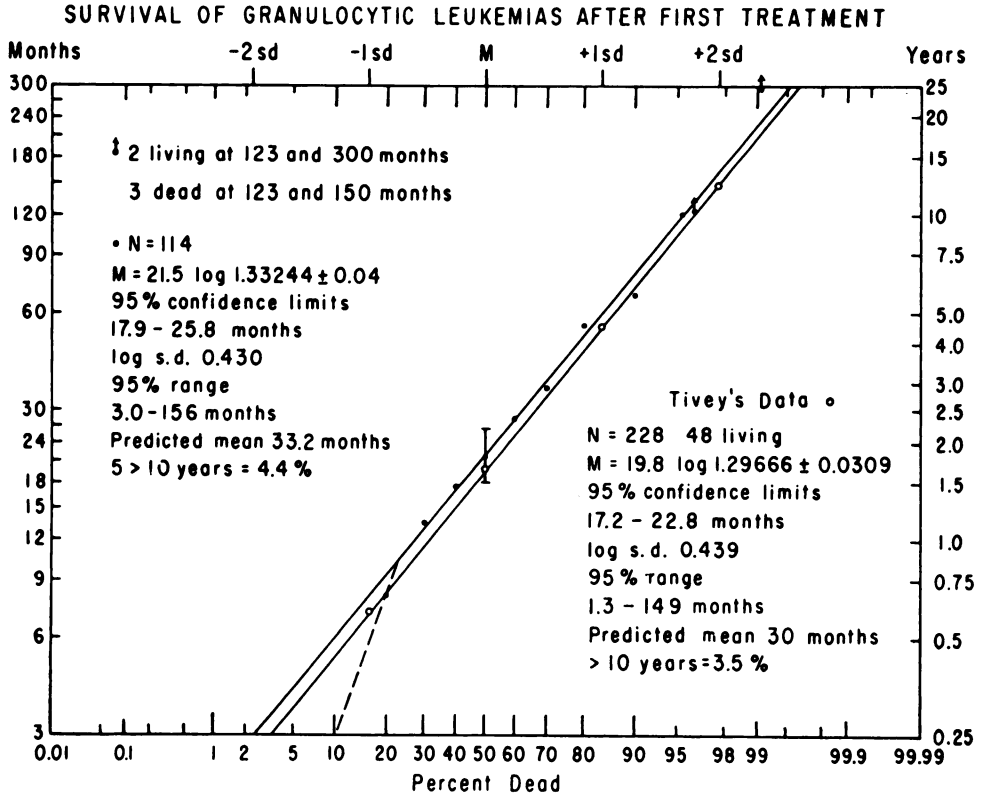

Fig. 5.

mortal. The alpha cell may undergo 2 types of division: alpha-2 alpha that eventually doubles the population, or alpha-n that maintains a constant ratio of alpha to n cells. The n cells mature, function, and die in a time that is short relative to the life span of the species; they may or may not undergo n-2n division, but these are all lost to genetic continuity. Only the alpha cell maintains somatic genetic continuity.

To regulate the rate of these two types of cell division, there are two inhibitors; one produced early in the life of the n cell inhibiting the alpha-2 alpha division and one produced late in the life of the n cell inhibiting the alpha-n cell divisions. Each is a specific feedback mechanism from the n cell of that series to the alpha cell of the same series.

Granted these postulates, all one needs for a benign tumor is any change in the genetic material of a somatic alpha cell leading to death of the corresponding n cell before it produces the inhibitor of the alpha-n division and all one needs for malignancy is any change in the genetic material of a somatic alpha cell which leads to death of the corresponding n cell during or before it produces the inhibitor of the alpha-2 alpha division.

The action of ionizing radiation is to decrease the rate of cell division of the somatic alpha cell. The effect is instantaneous and persists far longer than the life span of the corresponding n cell. Therapy with P^{32} or chemotherapeutic agents simply substitutes for the normal inhibitor of alpha-2 alpha division, thus decreasing the likelihood of further genetic change to a still shorter life span of the n cell and more acute progression of the disease. This could be determined only by trial, since both ionizing radiation and all the chemotherapeutic agents may produce somatic genetic change.

Sudden genetic changes may occur with any of these agents leading to the development of either greater (Fig. 2 in ref. 5) or lesser radiation sensitivity as evidenced by a sudden great increase in dose requirement or great decrease in dose requirement (Fig. 1A in ref. 1) and also by the sudden development of the capacity to produce an abnormal protein leading to erythrocyte agglutination and thus to hemolytic anemias (16) in the lymphocytic leukemias. Other evidences of somatic genetic change are the development of the acute terminal stage of the disease, which we interpret as being due to any genetic change which leads to a shorter life span of the n cell, and the development of acute leukemias of an entirely different type, which we interpret as due to genetic change in the alpha cell of that series. We have seen acute lymphocytic leukemia develop in patients with chronic granulocytic leukemia. It is of course theoretically possible that any agent capable of producing somatic genetic change could lead to earlier death of the n cell, and only actual trial will determine whether these agents reduce the risk more by decreasing the total number of cell divisions during the patient's life span or increase it more by themselves producing genetic change. Data from the Western Cooperative Cancer Chemotherapy Group suggest that mitotic inhibitors such as desacetylmethyl colchicine (Colcemide®) give better long term results (N = 30, median = 30 months) than agents that kill cells, such as 1,4-dimethanesulfonyloxybutane

(Myleran®) (N = 39, median = 18 months). The killing agents theoretically may eliminate the sensitive population, while mitotic inhibitors such as radiation and Colcemide preserve the sensitive population. Certainly none of these agents will ever cure a case of leukemia, even though our 5 year survival for this total series is 42 per cent, for the lymphocytic series is 52 per cent, and for the granulocytic series is 25 per cent, which might be considered good 5 year survivals in any malignant process. Yet, we know we have not cured a single case. These 5 year survivals may be compared with the data collected by Shimkin for the Third National Cancer Conference of 104/522 = 19.9 per cent for chronic lymphocytic leukemia and 15/327 = 4.6 per cent for chronic granulocytic leukemia.

The leukemic cells are far more sensitive than the corresponding normal cells as evidenced by the fact that normal granulocytic series increase in number when lymphocytic leukemias are treated and the lymphocytic series increase in number when the granulocytic leukemias are treated. The granulocytic series requires approximately twice the dose (5) either to control or maintain a constant leukocyte count as is required by the lymphocytic series. The sequence from the most radiation-sensitive to the least sensitive of the hemic cells of man is: leukemic series: lymphocytic > granulocytic > monocytic > plasmocytic > polycythemic erythrocytic > normal: lymphocytic > granulocytic > thrombocytic > erythrocytic > monocytic > plasmocytic.

Plotting log total dose against log post therapy survival time gives us the factor of 15 r = 1 mc P^{32} I.V. in an adult[1] as the roentgen equivalent man for either leukemic cells of the lymphocytic or granulocytic series. P^{32} is preferred because doses above 25 r of x-ray produce nausea which we have never encountered with P^{32}. Two of the 13 granulocytic leukemias and one of the 11 lymphoclytic leukemias treated predominantly with total body x-ray had to be transferred to P^{32} therapy late in their course because of radiation sickness as their dose requirement increased.

TREATMENT OF COMPLICATIONS

The common complications of the lymphocytic leukemias are antiglobulin-positive type hemolytic anemias (16) and chronic bronchitis with bronchiectasis. The most common complication in the granulocytic leukemias is the development of the acute terminal phase of the disease. In all cases at the initial visit, there is likely to be an anxiety-tension state which requires psychotherapy because of the fact that few people recognize that there are some 70 different kinds of leukemia with widely different prognoses.

Treatment recommended for the hemolytic anemias of lymphocytic leukemia is 11-oxycorticoids (16). Treatment recommended for the chronic bronchitis with bronchietasis is an initial course of 10 days of procaine penicillin with strep-

[1]Since weight in adults rarely varies by more than a factor of two while dose requirement in patients of the same weight and leukocyte count varied by a factor of at least 10, to calculate dose in μc/kg/year seems an unnecessary refinement.

tomycin followed by 1 Gm of a soluble sulfonamide daily for life. Other antibiotics do not kill bacteria and resistance in this disease is low. This treatment does not cure the condition but does prevent the otherwise frequent hospital admission for bronchopneumonia.

The treatment for the acute terminal phase is to decrease the interval and increase the dose of P^{32} as necessary to control the leukocyte count and other factors, using fresh blood transfusions to keep some clot retraction at one hour and packed red cells or sedimented red cells for a hemoglobin level below 7 Gm. We have tried other chemotherapeutic agents (Fig. 3 in ref. 5) in this terminal phase but find they are no more effective than the P^{32} and often involve much more hospitalization.

The psychotherapy[1] given at the first visit, we feel, is largely responsible for our 100 per cent follow up and the fact that a large proportion of these patients keep their appointments.

Experience with more than 1000 patients with leukemias or lymphomas has convinced me that the unknown is man's greatest fear. The method developed for explaining incurable disease and its treatment to the patient and his relatives has resulted in almost 100 per cent continuation of treatment, in some cases for more than 20 years.

The method includes full explanation of disease and treatment in words understood by the patient, anticipation of questions about danger to others, removal of unwarranted fears or guilt feelings, teaching a philosophy of living, making no promises that cannot be kept, and demonstrating a genuine interest in the happiness as well as health of the patient and his loved ones. Each patient must know that somebody cares.

Explaining that the disease is neither hereditary nor contagious may save much mental anxiety and expense for unnecessary examinations. Explanation of probable complications, such as purpura, leads the patient to conclude that you understand the disease when otherwise he might decide these symptoms were due to treatment and fail to return.

The parents of a child with leukemia, after explanation of the disease, can be reassured that had the ablest physician seen the child daily, the disease would still have occurred. A mother may grieve for years because she believes her child's leukemia was due to her omission of prescribed medication. Adults may regard disease as a punishment for sin.

Teaching relatives and patients three principles can greatly simplify living: Only *one* decision need be made, namely "What is the most important thing to do next?" Forget the past. Choose *only* major goals for the future. Specific analogies are helpful: if you drive a car, it is easy to decide each turn of the wheel at the time, but it is impossible and frustrating to try to make such decisions before starting. Mathematics may seem too difficult examining a text-

[1]This section of this paper was presented at the 8th International Cancer Congress in Moscow, July 24, 1962.

book, but solving the first problem is simple. No one can solve two problems simultaneously. All treatment merely prolongs life; no one lives forever; and no one knows how long he will live.

To preserve hope, I explain that it is human to err, so a possibility exists that the diagnosis is incorrect, also that a cure may be found in time.

To understand that relatives often suffer more than the patients, it is only necessary to consider the question whether you would rather have cancer or know one you love has it. A young husband whose wife had not been told she had leukemia took her on a vacation, doing everything to add to her happiness, but was only upbraided for his extravagance. How different, if she had known! Sometimes, a question reveals information that spares much anguish. Parents had purchased a toy train for their leukemic son. The suggestion that Christmas be celebrated early enabled them to see him enjoy it. How different, had the gift been unopened on Christmas after the boy's death!

Trust is won only by truth and understanding. The science and art of medicine must be combined.

In conclusion, the results reported should not be interpreted as representing the results to be expected if all the recommendations in this paper are followed. Much of this information was developed during the course of this study, and we are certain that the granulocytic leukemias here reported were undertreated initially. Many of the patients who developed hemolytic anemia developed it before corticoids were available and before we had developed skill in their use. We have been randomizing P^{32} against Colcemide and Myleran in the chronic granulocytic leukemias and P^{32} against Leukeran and TEM in the chronic lymphocytic leukemias since November 1, 1956, but as yet the time elapsed and number of patients treated is not sufficient to draw firm conclusions. Our preliminary data on these agents would suggest that P^{32} is at least as good as Colcemide in the granulocytic leukemias and far superior to Myleran and that it is at least as good as either TEM or Leukeran in the chronic lymphocytic leukemias and is much easier to titrate than any of the other agents and less expensive for the patient since it requires far fewer visits and seems much less likely to cause toxic complications.

SUMMARY

Results of treatment of 212 chronic lymphocytic leukemias and 114 chronic granulocytic leukemias with the method of titrated, regularly-spaced total-body irradiation are presented, with data on survival time, comparative effectivness of P^{32} and x-ray, radiobiologic observations, complications of the disease and therapy, and prognostic factors. The reason why this group of patients has had a better survival than any other published series of leukemias treated by other methods is now apparent in the light of my unifying concept of the fundamental nature of malignancies. The action of ionizing radiation is to decrease the rate of cell division and thus to decrease the risk of further genetic change to a still shorter life span of the involved somatic n cell. In other words, the ionizing radiation substitutes for the alpha-2 alpha and alpha-n division

inhibitors. The effect on cell division does have a threshold. The roentgen equivalent man for either cells of the lymphocytic series or granulocytic series is 1.0 mc of P^{32} intravenously in the adult equals about 15 r of total body irradiation.

The important variable influencing prognosis appears to be age and sex, with the female patients and the younger patients doing far better than the male patients and the patients over 61 at onset of the disease. The common complications and their treatment are outlined.

REFERENCES

1. Osgood, E. E., and Seaman, A. J.: Treatment of the Chronic Leukemias: Results of Therapy of 163 Patients by Titrated, Regularly Spaced Total Body Radioactive Phosphorus or Roentgen Irradiation, *J.A.M.A.* **150**:1372, 1952.
2. Osgood, E. E.: Treatment of the Leukemias and Polycythemia Vera with Radioactive Phosphorus, *in* Hahn, P. F.: Therapeutic Use of Artificial Radioisotopes, New York, John Wiley & Sons, 1956, chap. 7.
3. Osgood, E. E.; Seaman, A. J., and Koler, R. D.: Natural History and Course of the Leukemias, *in* Proceedings of the Third National Cancer Conference, Philadelphia, Lippincott, 1957, pp. 366-382.
4. Osgood, E. E.; Seaman, A. J., and Koler, R. D.: The Results of a 15-Year Program of Treatment of the Chronic Leukemias with Titrated Regularly Spaced Total Body Irradiation with P^{32} or X-ray, *in* Proceedings of the Sixth International Congress of the International Society of Hematology, New York, Grune & Stratton, 1958, pp. 44-55.
5. Osgood, E. E.: The Threshold Dose of P^{32} for Leukemic Cells of the Lymphocytic and Granulocytic Series, *Blood* **16**:1104, 1960.
6. Tivey, H.: The Prognosis for Survival in Chronic Granulocytic and Lymphocytic Leukemia, *Am. J. Roentgenol.* **72**:68, 1954.
7. Osgood, E. E.: Methods for Analyzing Survival Data, Illustrated by Hodgkin's Disease, *Am. J. Med.* **24**:40, 1958.
8. Osgood, E. E.: The Survival Time of Patients with Plasmocytic Myeloma, *Cancer Chemotherapy Reports* **9**:1, 1960.
9. Dixon, W. J., and Massey, F. J., Jr.: Introduction to Statistical Analysis, 2nd ed., New York, McGraw-Hill Book Company, 1957.
10. Osgood, E. E.: Radiobiologic Observations on Human Hemic Cells *in Vivo* and *in Vitro*, *Ann. N. Y. Acad. Sc.* **95**:828, 1961.
11. Osgood, E. E.; Seaman, A. J., and Tivey, H.: Etudes Radiobiologiques Sur Les Cellules du Sang Chez l'Homme, *Rev. d'Hemat.* **8**:403, 1953.
12. Osgood, E. E.; Seaman, A. J, and Tivey, H.: Comparative Survival Times of X-ray Treated Versus P^{32} Treated Patients with Chronic Leukemias Under the Program of Titrated, Regularly Spaced Total-Body Irradiation, *Radiology* **64**:373, 1955.
13. Osgood, E. E.: A Unifying Concept of the Etiology of the Leukemias, Lymphomas, and Cancers, *J. Nat. Cancer Inst.* **18**:155, 1957.
14. Osgood, E. E.: Regulation of Cell Proliferation, *in* Stohlman, F., Jr.: The Kinetics of Cellular Proliferation, New York, Grune & Stratton, 1959, pp. 282-289.
15. Osgood, E. E.: Leukemia as a Disturbance of Growth Regulation, *in* Hammond, D.: Current Concepts in Leukemia, Report of the Thirty-fourth Ross Conference on Pediatric Research, Columbus, Ross Laboratories, 1960, pp. 61-69.
16. Osgood, E. E.: The Antiglobulin Positive Hemolytic Anemias, *Arch. Int. Med.* **107**:313, 1961.
17. Osgood, E. E.: Psychologic Factors in the Care of Incurable Cancer. *Acta Union Inter. contre le Cancer* **19** (#5), 1963.