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June 30, 1954

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HOO ADMINISTERED RESEARCH CONTRACTS IN FORCE, JULY 1, 1954

School	Division of Biology & Medicine		Division of Research		Total	
	Number of Contracts	Total Yearly Support Level	Number of Contracts	Total Yearly Support Level	Number of Contracts	Total Yearly Support Level
Reed College	2	$ 11,125	-	$ -	2	$ 11,125
Washington State	3	21,351	2	5,154	5	26,505
U. of Oregon	1	1,100	2	20,200	3	21,300
U. of Oregon Med. School	2	42,355	-	-	2	42,355
U. of Washington	7	174,401	2	107,100	9	281,501
Oregon State	4	36,830	3	23,200	7	60,030
U. of Idaho	1	6,855	-	-	1	6,855
Total	20	$294,017	9	$155,654	29	$449,671

NOTE: The total amount supplied to current and terminated contracts is $2,483,535.06.

HIGHLIGHTS OF NORTHWEST CONTRACT RESEARCH

Reed College:

1. Uses a large amount of cobalt 60 - 100 curies - to determine effects of radiation on biological compounds.
   Benefits: Establishment of radiation tolerances.
2. Found chemical atomic weight of silver is too high.
   Benefits: Resetting of chemical atomic weights of heavy elements.

U. of Oregon Medical School:

1. Using radioactive tracers has established certain metabolism rates for acetate into fatty acids and cholesterol fractions.
   Benefits: Methods for correcting malnutrition and basic science.
2. Using phosphorus^{32} to reduce white blood cells in leukemia patients - Dr. Osgood.
   Benefits: Highly effective leukemic therapy of international renown.

Oregon State:

Using radioactive tracers has found 2.4 D, a weed killer, affects plant phosphates or carbohydrate carriers.
Benefits: Ultimate-better weed killing compound or using technique.

Washington State:

Using radioactive tracers to determine pattern of element movement in plants.
Benefits: Establishment of plant mineral requirements and correction of theories of plant growth.

U. of Washington:

1. In application of radiation to fish has found tolerance limits for egg hatching. Also, temperature has been found to definitely affect egg development and hatching.
   Benefits: Establishment of temperature and radiation limits for HOO River effluent.
2. Use of the 60" cyclotron.
   Benefits: Basic nuclear research at various energy levels and with various particles.

U. of Washington Medical School:

Use of radioactive tracers has found (1) the liver to be the storehouse for excess iron, (2) extreme difficulty by orally replenishing iron. In other work, with Dr. Finch, on blood has found (1) that the normal man can give one pint every two weeks if iron is given orally and parenterally, (2) blood preservation facts.
Benefits: To blood donation.

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[1]

EDWIN E. OSGOOD, M.D., ARTHUR I. SKAMAN, M.D., and HAROLD TIVEY, M.D.
With the technical assistance of Charlotte A. Moffat, M.T., and Margret E. Hughes, M.T.

IN THE PERIOD from January 1941 to July 1951, treatment of 163 patients with chronic leukemia by the method of titrated, regularly spaced total-body irradiation (1, 2) was started. The basic principles of treatment were identical for all of these patients, but some were given spray roentgen irradiation and others internal irradiation by intravenously injected radioactive phosphorus (P^{32}). No difference between the clinical response to x-ray irradiation and to P^{32} was noted. A comparison was made of the survival times of the two groups to determine if spray irradiation by x-rays offers a better prognosis than equivalent internal irradiation by radioactive phosphorus.

Leukemia is a completely disseminated neoplasm, with infiltration of all organs and tissues. It has repeatedly been observed that the feeling of well-being of the patient with this disease is maximal when leukocytosis, hepatomegaly, splenomegaly, anemia, and lymphadenopathy are minimal. To reach all neoplastic cells, total-body irradiation should be administered at such intervals as are necessary to keep the leukemic cell population within optimal limits.

In the small doses used in this study radiation acts primarily on leukemic cells by inhibiting mitosis in the granulocytic series, but it may be capable of killing lymphocytes, as well as interfering with their proliferation (3). The life span is approximately five days for cells of the granulocytic series and something in excess of thirty days for the lymphocytes of *chronic* leukemia (4). Small alterations in the mitotic rate can rapidly change the total mass of leukemic cells in a few generations. Such changes will be most evident in the patient with a large number of leukemic cells initially present. It therefore becomes desirable to follow chronic leukemia patients at intervals consistent with the short life span of these cells to prevent the possibility of massive leukemic cell overgrowth.

The margin between doses of total-body irradiation suppressing the leukemic process and those depressing erythropoiesis is sometimes small. Since leukemic infiltration of all available marrow spaces and/or a hemolytic process frequently predisposes toward anemia, considerable caution in radiation dosage is indicated (5). The patient's most probable prognosis for total survival, 2.65 years by the usual method of treatment (6), is so modified by a skewed distribution of survival times that the recorded survivals in excess of twenty years (7) are predictable events. Unfortunately, there is no reported basis for determining those patients who are destined to have an unusually long survival (8). It then becomes evident that the smallest effective doses of radiation are least likely to produce depression of erythropoiesis or to effect over this long period a mutagenic change leading to carcinoma or other fatal complications.[2]

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[1] From the Division of Experimental Medicine, Department of Medicine, University of Oregon Medical School, Portland, Ore. Supported in part by grants-in-aid from the Division of Biology and Medicine of the U. S. Atomic Energy Commission, The National Cancer Institute of the United States Public Health Service, and the Medical Research Foundation of Oregon. The radioactive phosphorus used in this investigation was supplied by Clinton Laboratories, Knoxville, Tenn., and by Union Carbide and Carbon Corporation, Oak Ridge, Tenn., on authorization from the Isotopes Division, U. S. Atomic Energy Commission.

Presented at the Thirty-ninth Annual Meeting of the Radiological Society of North America, Chicago, Ill., Dec. 13–18, 1953.

[2] For footnote, see page 375.

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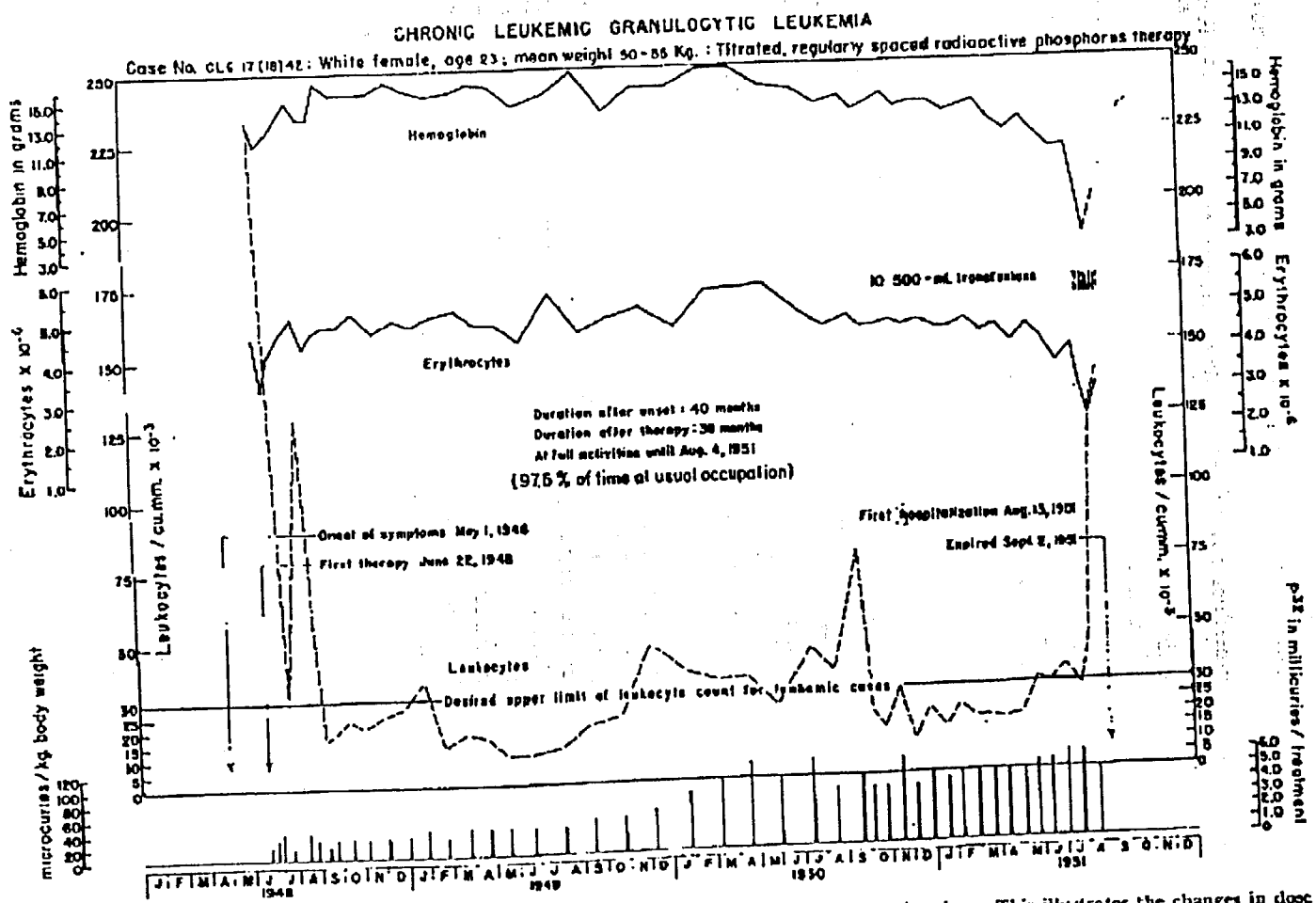

Fig. 1. Course of a case of chronic leukemic granulocytic leukemia, with unusual difficulty in titration. This illustrates the changes in dose and interval that are sometimes necessary with either radioactive phosphorus or x-ray therapy.

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TABLE I: TYPICAL (MEDIAN) TOTAL RADIATION REQUIREMENTS FOR PATIENTS WITH CHRONIC LEUKEMIA

	Granulocytic		Lymphocytic	
	P^{32}	X-ray	P^{32}	X-ray
For Control:				
r or μc./kg. P^{32} radiation	160	100	90	90
given in this number of treatments	5	9	4	6
To Maintain Control:				
r or μc./kg. P^{32} per year	280	350	100	130
given in this number of treatments per year	7	17	5	7

Radiation "to control" is progressively spaced over a period of about six to twelve weeks. Radiation "to maintain" characteristically is regularly spaced over the year. This is not a guide to therapy. See text.

Since associated diseases and complications account for an appreciable proportion of morbidity and mortality in the chronic leukemias (2), some one person should accept overall responsibility for the management of all the patient's problems from diagnosis to death. One of the more common problems, an acquired hemolytic anemia, is not limited to lymphocytic leukemias, but occurs also in both a latent and manifest form in granulocytic leukemia (11).

On the basis of the foregoing fundamental considerations, the principles of treatment by the method of titrated, regularly spaced total-body irradiation are:

(*a*) To bring the patient's disease under initial control by small doses (*ca.* 10 to 20 r or equivalent P^{32}) at intervals of one or two weeks.

(*b*) To maintain that control by minimal doses (10 to 20 r) at such appropriate regular intervals that the patient *remains* in an optimum state of health. Dosage based upon the patient's total previous response is given to prevent the leukemic process from going out of control just as the highly individualized insulin requirements of a diabetic are repeated to maintain his ideal status.

(*c*) Most important, to adjust the treatment to fit the needs of the individual, *i.e.*, *titrate* the amount of radiation given against the clinical condition. One must not treat the leukocyte count, but the entire patient. Most patients with leukemic leukemias will feel best with leukocyte counts below 25,000 per c. mm. and above 10,000 per c. mm., but rarely one may be in optimal condition with a leukocyte count as low as 5,000 or as high as 50,000. Further essential details of this program of therapy have been previously reported (1, 2).

The details of the variability of dosage and interval used in the treatment of this disease are the subject of a separate report (12). These can best be summarized by stating that any inflexible radiation schedule would probably be ineffective in at least one-third of all patients and prove definitely harmful to at least an additional third. The continuing adjustment of the treatment to the individual's needs is the most important single aspect of this method of management. With these reservations, typical values of dosage and interval are given in Table I. The clinical course of a patient treated by this method is shown in Figure 1.

The patients studied include all who were referred for treatment, even those moribund at the first visit. No patients have been lost to follow-up. Details on age, sex, and clinical characteristics of these patients have been previously presented (2).

We believe this series of patients to be representative of similar groups seen at university hospitals in other parts of the country. As far as we can determine, there is only one factor which might have influenced the selection of patients referred. When radioactive phosphorus first became available, a few unusually difficult cases may have been referred on

[1] The problem of radiation-induced mutations in patients with leukemia is of more than academic interest. In this series, 4 patients have died with a blood picture suggestive of an *acute* leukemia of *another cell type* (9). If confirmed, such changes might be attributed to the mutagenic effects of the radiation used to treat the patient's chronic leukemia. Hall (10) reported 4 cases of *acute* leukemia in 124 polycythemia vera patients treated with P^{32}. Among 90 cases of polycythemia vera treated with P^{32} during a comparable period in this Division, one definitely and a second possibly terminated in acute leukemia.

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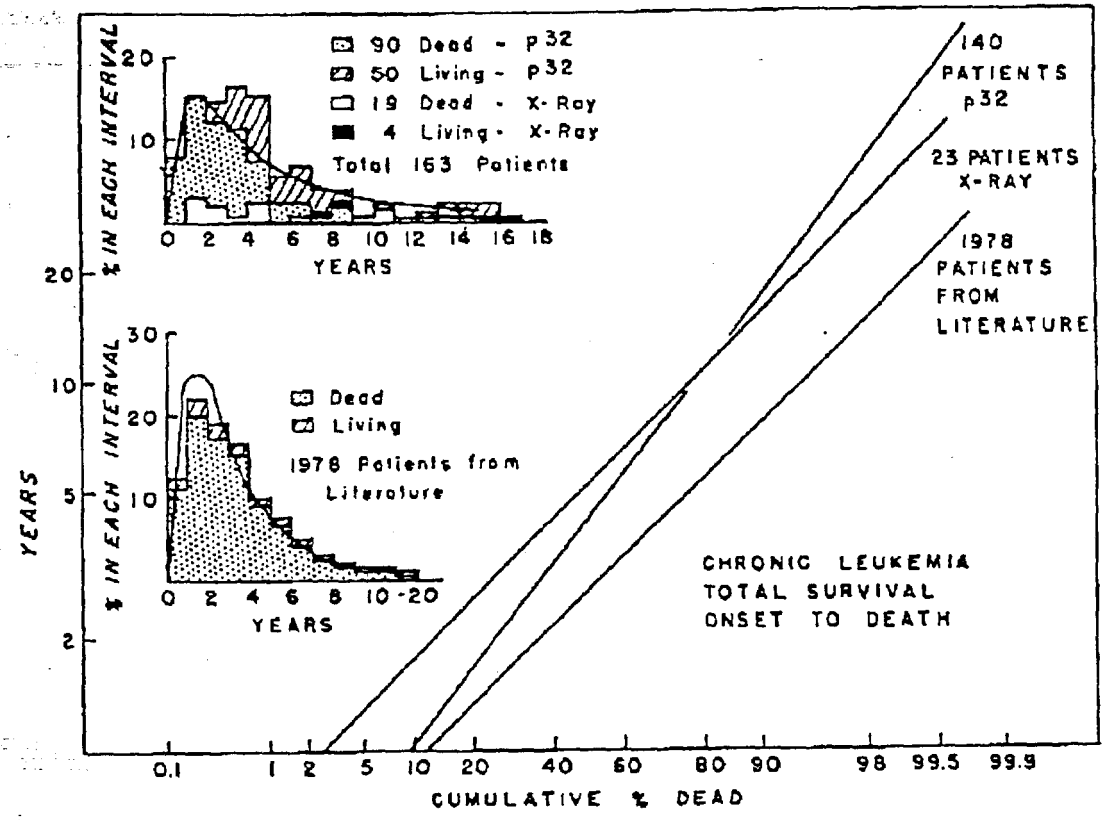

Fig. 2. Distribution of comparative survival times from onset of symptoms to death of x-ray and P^{32} treated patients with chronic leukemia. The curve superimposed on the upper histogram of the actual data represents both the x-ray and P^{32} treated cases.

the premise that P^{32} represented a new "wonder drug." We have attempted to minimize this possible source of error by larger numbers of patients in the P^{32} treated group. In all other respects we feel the x-ray and P^{32} groups are essentially identical.

Factors used in roentgen irradiation were 220 kv; 0.5 mm. Cu +1.0 mm. Al filter to give h.v.l. 1.1 mm. Cu; 60–100 cm. target-skin distance; rate, 11 r per minute. Two ports were used at each visit, the entire upper and lower halves of the body. Successive treatments were alternated front and back. Dosages were measured in air at skin level and do not include back-scatter; "10 r" means 10 r to *each* of the upper and lower ports.

It has been previously demonstrated that the logarithms of survival time in patients with chronic (6) (and acute) (13) leukemia follow normal distributions. D. E. Lea has devised a method of predicting the ultimate outcome of such a log-normal distribution of survival times before all of the patients are dead (14). The data given are the *predicted* median (logarithmic mean) survival times for the various groups studied. Significance of differences was calculated in the usual fashion, with use of the logarithmic means and standard deviations derived from Lea's methods of calculation.

We have previously shown that delay to treatment and the survival after treatment may also be represented by log-normal distributions. It has been further demonstrated that there is little correlation between the duration of symptoms before therapy and survival after therapy. The median total survival of these patients is not the sum of the median survival after

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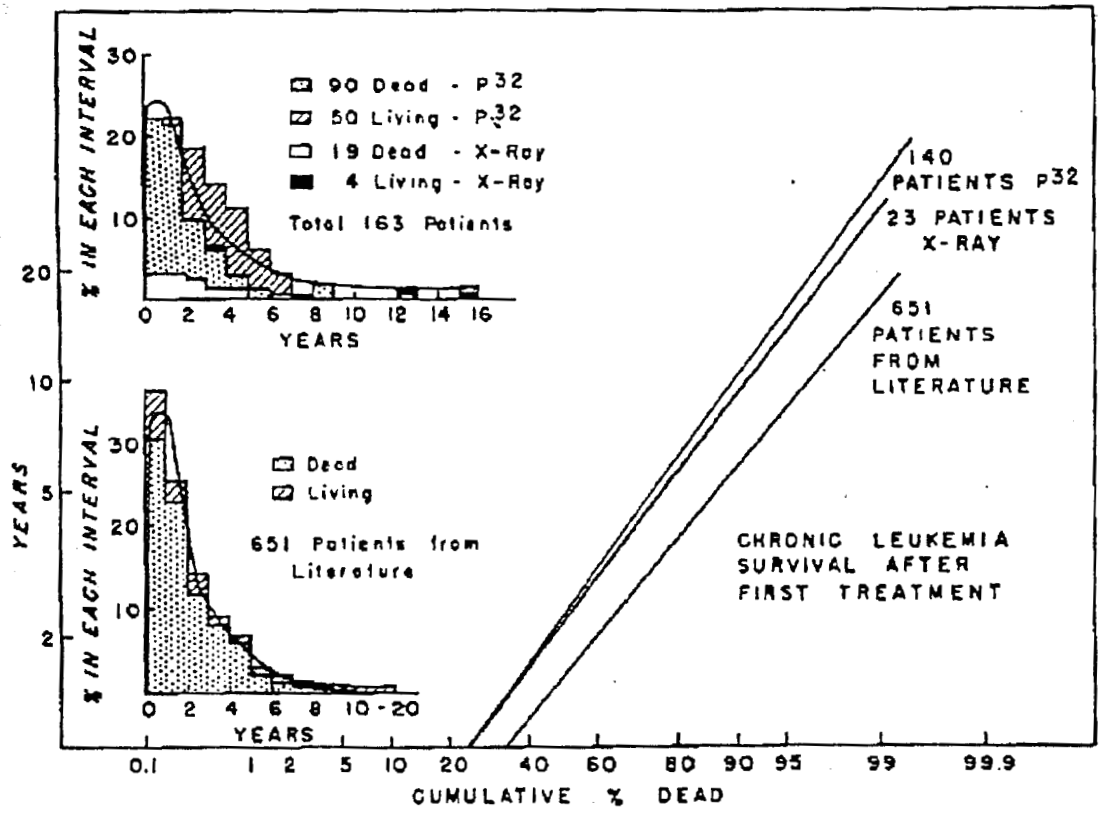

Fig. 3. Distribution of comparative survival times from first treatment to death of x-ray and P^{32} treated patients with chronic leukemia. The curve superimposed on the upper histogram of the actual data represents both the x-ray and P^{32} treated cases.

therapy and the median delay to therapy but will be represented by a somewhat larger figure than this sum (6).

RESULTS

In Figures 2 and 3 we have shown the distributions of total survival time and survival after therapy of the 23 x-ray treated patients, 140 P^{32} treated patients, and the corresponding distributions of survival time in leukemia taken from a review of the literature. Results for lymphocytic and granulocytic leukemia are combined, since no difference in prognosis is discernible (6). The parameters of the various distributions and the significance of differences between the median survival times are given in Table II. Successive predictions of the outcome of this series are given in Table III.

DISCUSSION

Reference to Table I will show that the differences in total survival time between those patients treated with spray roentgen irradiation and those treated with P^{32} are no greater than could be expected on the basis of chance alone 16 times out of 100 if additional series with similar numbers of patients in each group were studied. The difference between median survival times after therapy could arise on the basis of chance alone in 38 trials of 100. On the basis of this study, therefore, the prognosis for survival will be no different whether the patient receives total-body irradiation externally by the spray technic or internally by radioactive phosphorus.

The observed equal effectiveness of these two methods of delivering ionizing radiation to the patient is to be anticipated as

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TABLE II: COMPARISON OF SURVIVAL OF PATIENTS TREATED BY SPRAY ROENTGEN IRRADIATION AND P^{32}

Item	No. Patients	Treatment	Median Survival*	95 per cent Confidence† Limits	10 per cent Live‡ Longer Than	Probability of§ Chance Difference (%)	Between Items
		Years Total Survival					
1	23	Spray roentgen therapy: present series	5.2	3.5–7.5	15	<1 16	1, 4 1, 2
2	140	P^{32}: present series	4.2	3.6–5.0	17	<1	2, 4
3	163	Both: present series	4.2	3.5–5.0	17	<1	3, 4
4	1,978	Roentgen therapy: cases from literatures (8)	2.65	2.55–2.75	7.8		
		Years Survival After Therapy					
5	23	Spray roentgen therapy	2.2	1.8–2.7	8.8	<1 38	5, 8 5, 6
6	140	P^{32}	2.3	1.9–2.8	10	<1	6, 8
7	163	Both	2.3	1.9–2.7	9.7	<1	7, 8
8	651	Roentgen therapy: cases from literature (8)	1.56	1.44–1.70	5.7		
		Years Delay to Therapy					
9	23	Spray roentgen therapy	1.3	0.8–2.2	6.0	~1	9, 10
10	140	P^{32}	0.7	0.6–0.9	3.5		
11	163	Both	0.8	0.6–0.84	3.9		
12	...	No comparable data from literature					

* These are log-normal distributions, and at the median survival 50 per cent of the patients are dead. "Average" survival times would be much higher than the median but are not representative of this type of skewed distribution.

† A series of the size shown would have median values within the limits given in 95 of 100 trials.

‡ The skewness of the distribution is emphasized by these values.

§ The probability that differences of medians as large as those seen could arise by chance alone.

long as the method of treatment is the same. It may be noted that the results of the regularly spaced, titrated, whole-body irradiation technic are superior to those for a series of cases of leukemia treated by conventional methods which were assembled from the literature (6). It is possible that this "control series" from the literature does not represent present-day radiologic practice, but no more modern data are available for comparison.

Since the conclusions of this report are based upon comparisons of series of patients in which some are still living, one may legitimately question the reliability of prediction. It should be pointed out that the method of calculation gives the observations on the living a lesser importance than those on the dead patients. All such uncertainties are reflected in the fairly large confidence limits attached to each of the median survival times. Boag has made an elegant extension of this method of prediction to the problem of calculation of absolute cure rates in patients treated for carcinoma (15). He has found that predictions based upon an analogous method of computation are extremely reliable. A series of successive predictions of the outcome of this series is shown in Table III. It will be noted that there is no greater variation in the predicted outcome of this series than would be anticipated on the basis of chance alone. The agreement between predicted and observed median values is excellent.

For the internist, the use of radioactive phosphorus is more convenient than the use of spray roentgen irradiation. For the radiologist, there is probably little to recommend one method of treatment over the other. No radiation sickness has been encountered with either type of therapy in the usual dosage range. On the basis of the evidence at hand, the patient can be equally well treated by either. The principal contribution that this study can make is to dispel some of the "magic aura" which, in the minds of some physicians, surrounds the clinical use of radioactive isotopes.

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TABLE III: SUCCESSIVE PREDICTIONS OF MEDIAN TOTAL SURVIVAL TIME IN PATIENTS OF THIS SERIES

Patients	Composition	Predicted Median Survival Time (in Years) and [Confidence Limits]				Observed Survival Time of Median Dead Patient (July 1953)
		July 1950	July 1951	January 1952	July 1953	
58	All seen January 1941–December 1949 Per cent living	4.4 [3.1–6.1] 55	4.8 [3.4–6.9] 50		5.0 [3.0–7.0] 43	4.7
117	All followed 2 years by January 1952 Per cent living	...	...	4.1 [3.3–5.0] 37	4.2 [3.5–5.1] 30	4.4
163	All seen January 1941–July 1951 Per cent living	...	...	4.1 [3.4–5.0] 39	4.2 [3.5–5.0] 33	4.3

Note that there has been no change in the predicted values greater than that expected from chance alone over a period of three years. The first two groups of 58 and 117 patients are sub-groups of the third group.

SUMMARY

A study was made of the survival times of 163 patients with chronic leukemias by the method of titrated, regularly spaced total-body irradiation. Twenty-three received spray roentgen irradiation; 140 were given P^{32}.

The prognosis for survival was not significantly different whether the total-body irradiation was delivered externally by the spray technic or internally from radioactive phosphorus, provided all other conditions of treatment were identical.

The prognosis for survival of patients with leukemia treated by titrated, regularly spaced total-body irradiation, either with the spray technic or P^{32}, is significantly better than that for a collected series including all radiation treated cases reported in the literature in the interval 1925 to 1951.

ACKNOWLEDGMENT: Drs. Wallace Haworth, G. B. Isenhart, J. Richard Raines, and C. T. Jessell of Portland, Ore., administered the spray irradiation given most of the patients in this series in accordance with dosage and intervals prescribed by the authors. Without the careful and considerate cooperation of these radiologists, and others, this study would have been impossible.

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SUMARIO

Tiempos Comparados de Sobrevivencia de los Leucémicos Crónicos Tratados con los Rayos X y los Tratados con P^{32} Conforme al Plan de Irradiación Espaciada Regularmente y Titulada de Todo el Cuerpo

Este estudio versó sobre los tiempos de sobrevivencia de 163 enfermos que tenían leucemia crónica y fueron tratados con la técnica de irradiación titulada y espaciada regularmente de todo el cuerpo. Veintitrés recibieron irradiación roentgen dispersa; a 140 se les administró P^{32}.

El pronóstico en cuanto a sobrevivencia no varió mayor cosa, ya se entregara la irradiación total del cuerpo externamente con la técnica dispersa o internamente con P^{32} siempre que fueran idénticas las demás condiciones del tratamiento.

El pronóstico en cuanto a sobrevivencia de los leucémicos tratados con la irradiación titulada y espaciada regularmente de todo el cuerpo, ya con la técnica dispersa o el P^{32}, fué significativamente mejor que el obtenido en una serie compilada que comprende todos los casos tratados con la irradiación descritos en la literatura en el período de 1925 a 1951.

DISCUSSION

Theodore P. Eberhard, M.D. (Philadelphia, Penna.): It is unfortunate with the short period of five minutes available to me that Dr. Osgood and Dr. Tivey have given us three papers in one. We have one portion of this paper dealing with the principles of treatment, one portion dealing with the relative results of P^{32} versus total-body x-ray therapy, and a third part consisting of a most beautiful demonstration of how we all ought to present our statistics and analyze our results.

So far as the relative value of P^{32} and spray radiation is concerned, like Dr. Tivey, I am not at all surprised that the two came out together. They are both forms of total body ionizing radiation and hence should, if properly handled, give essentially the same results. The essayists are certainly to be congratulated on having done such a beautiful piece of work in proving that our anticipated conclusions were correct.

In regard to the principles of treatment, however, I think there is room for discussion. It is implied in this paper, as well as in other publications by Dr. Osgood, that the results can be attributed to what is called titration, regular spacing, and total body exposure. Let us take these three up separately.

In the first place, I object personally to the essayists' use of the word "titration." I believe the dictionary defines titration as a volumetric method of determining concentration. As used here, it simply means adjusting dosage to the individual patient. Most of us do that. I doubt if there is anybody in this room today who goes up to a leukemic patient he has never seen before and blasts him with 200 r, and to heck with it! It is essential, as we all know, that we approach these patients cautiously with small doses and determine their individual reactions. The tolerance limits vary tremendously from one to another. It is most important to avoid overdose.

Second is the matter of regular spacing. It is observed on Dr. Osgood's own chart that the treatments are not regularly spaced. They are regularly spaced to a certain extent during the asymptomatic periods, but the rest of the time they are varied, just as the rest of us vary our treatments. We come here to a matter of philosophy, particularly in regard to chronic lymphatic leukemia. The principle of treatment in the Osgood group is that every patient, when he is first seen, should receive treatment immediately. The approach of our group differs from this. We feel that a great many of the chronic lymphatic leukemia patients are actually asymptomatic. Many of them are discovered on routine blood counts for some totally different cause.

I picked out of our group of 75 cases treated since 1943, a couple of days before I came out here, 7 of chronic lymphatic leukemia that we have been following from four to nine years. None of these patients has ever received any irradiation; when required, they receive TEM, nitrogen mustard, and high vitamin therapy. They carry counts anywhere from 20,000 to 200,000; they are quite happy; and they, too, have continued at their work for 97

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per cent of their useful lives. So I think there are many patients who do not require continuous treatment. There are a few that do not require any suppressive therapy.

I think, as Dr. Tivey suggested, that one of the reasons for the apparent great improvement in this series as compared with the series which was chosen for control is the greater use of antibiotics to control infection—which was the bugbear of the leukemia patient—the greater use of transfusions, the greater realization of the importance of high vitamin therapy (particularly vitamin B complex) and a high-protein diet. It is remarkable in how many of these patients the blood count will fall and node masses disappear under no treatment except massive doses of brewer's yeast and a high protein intake. Furthermore, as Dr. Tivey suggested, we must consider the possible mutagenic effects. I am sure all of us have seen these rather disturbing and peculiar instances of development of a new type of leukemia long years after chronic exposure to radiation and similar agents.

Then we come to the problem of total-body exposure. Is it wise? Is there only a direct ionizing effect on the individual leukemic cell, or may there not be some photochemical associated effect? We are all familiar with the fact that most of us treat a very small part of the body and the lumps, if they are present, will frequently subside with the count, suggesting that perhaps it is not necessary to expose the entire body, and I think it does carry in the long term perhaps more hazard than more localized radiation. Of course, we are on the defensive because Dr. Osgood and Dr. Tivey have produced a beautiful series, beautifully controlled and beautifully analyzed, and the rest of us have not.

One thing that has impressed me is the great importance of maintaining these patients under the control of one individual. The patient, if passed around from internist to hematologist, to radiologist, working individually, is always going to suffer. He must be treated as an individual and as a total individual. He must not be treated by the book. He must be treated according to the way he responds and according to his individual requirements.

And finally, again I want to emphasize and call to the attention of all of you the beautiful analytical work of Dr. Tivey. I understand that he is now engaged on the monumental task of trying to take this very involved statistical method, which only a fellow like himself can handle, and reduce it to terms that you and I can take care of.

R. R. Newell, M.D. (San Francisco, Calif.): Dr. Tivey has shown what one can do for leukemia patients under one philosophy, or school of therapy, well persisted in. It turns out that the patients did equally well with x-rays and with P^{32}. What I want to point out is that both groups were under the same skillful handling. If a radiologist is administering the therapy, success will come according to his skill as a physician, not just by his skill in applying the radiation. Patients treated with P^{32} are some of them likely to be continuously under the care of an internist or hematologist. It remains to be seen whether such a specialist will average more skillful than radiologists in the past. The physical measurements and technics are no longer a dominant consideration. It is good to have Dr. Tivey's reassurance that we can do as adequate a job with one agent as with the other: P^{32} or total body x-ray therapy.

I'm glad to hear Dr. Eberhard speak for the patient's own powers of controlling his leukemic processes for long periods of time.

Harold Tivey, M.D. (*closing*): I want to thank Dr. Eberhard for his kind words. I have not clinical experience to evaluate the relative merits of these two types of treatment. I think that question will ultimately be answered when the experiences of the groups who utilize them are published further in detail.

In regard to the effects of antibiotics and other adjuncts, we have no method of separating these effects from those of other modes of treatment.

I should like to express my appreciation to the Society for the privilege of attending this meeting and presenting this paper. I am sure that I have learned a great deal more from this discussion and from numerous other discussions about the treatment of leukemia than we have been able to contribute.

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