JOURNAL OF NUCLEAR MEDICINE 6:421-432, 1965

The Relative Dosage Required of Total Body X-Ray Vs Intravenous ^{32}P for Equal Effectiveness Against Leukemic Cells of the Lymphocytic Series or Granulocytic Series in Chronic Leukemia[1,2]

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Search of the literature fails to reveal any published data from which the relative biological effectiveness[4] of conventional total-body x-ray and intravenous ^{32}P can be computed. It seems worthwhile, therefore, to present our accumulated data on patients with chronic leukemia, 27 of whom were treated primarily by titrated total-body x-ray and 299 primarily by intravenous ^{32}P.

The objective, in each modality of therapy, was to obtain exactly the same end point of clinical and hematological control and to maintain this status in a steady optimal state for as long as possible. In essence, the plan of treatment determined the threshold dose for each patient (see Reference 1 and the references cited therein).

The basis of comparison, therefore, was the determination for each patient of total x-ray therapy required, as contrasted with total intravenous ^{32}P therapy required, to achieve ideal status and to maintain ideal status for the time the patient survived to date of analysis. (Outlined in items 1-8 on pages 140-142 in Reference 1). In other words, for each patient the total dose was

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[1]Presented in part before the Eleventh Annual Meeting of the Society of Nuclear Medicine, Berkeley, California, June 19, 1964.

[2]This work was supported in part by grants from the U. S. Atomic Energy Commission, Contract AT(45-1)-581; the U. S. Public Health Service, National Cancer Institute, Grant CA-6109; and the Medical Research Foundation of Oregon.

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[4]Throughout this article I have used the term "relative biological effectiveness" as the most nearly equivalent term to what we have measured. Strictly speaking, this is usually limited to experiments in which dosage can be measured in rads. In this article, comparisons are made in terms of conventional methods of measuring total-body x-ray and intravenously administered ^{32}P, since these would be more clinically useful, and attempts to compute dosage in rads would probably introduce more error than they would eliminate.

determined by the sum of the individual doses necessary to attain and maintain this ideal status during the time elapsed from his first treatment according to this method until death or May 1, 1964. Individual doses were spaced far enough apart so that the effect of one dose before the next dose was given could be seen. Interval and dose were adjusted as necessary to maintain the patient in ideal status with no oscillation. Doses were given at intervals of 1 to 12 weeks, with rare exceptions. Since, obviously, total dose to maintain control is related to time of survival, total dose has been plotted against time of survival in Figs. 1-4.

The clinical results of this treatment have recently been fully summarized (1). The distribution of doses of ^{32}P to control, doses per year, and dose rate per year to maintain have been previously reported (2); as have many of our radiation biology observations on these patients (3, 4).

POPULATION STUDIED

The total population includes every patient with either chronic lymphocytic or chronic granulocytic leukemia referred for treatment between January 1, 1941 and July 1, 1954. None of the living patients, therefore, has been followed less than 118 months as of May 1, 1964, the date of analysis. The age distribution of the total population at the time of our first treatment, and other pertinent factors, have been described (1).

In the x-ray treated group, all 11 patients with chronic lymphocytic leukemia and 12 of the 16 patients with chronic granulocytic leukemia were started on therapy prior to January 1, 1947, when ^{32}P first became available to us. These first 23 patients, also subjects of an earlier report (5), were continued on x-ray therapy as long as possible. However, a few who lived into the period when ^{32}P was available and whose dose requirement increased above 25 r, were transferred to ^{32}P therapy because nausea and vomiting developed after each dose exceeding 25 r. Such nausea and vomiting were never observed following even the largest of our doses of ^{32}P.

The four patients with chronic granulocytic leukemia who were started on x-ray therapy after January 1, 1947, were initially treated by exactly the same criteria of therapy as the other x-ray treated patients and by the same radiologists who were treating the patients directly under our supervision. They were later referred to us for our direct supervision. The cumulated dose of x-ray received by these four patients is, therefore, that received while under their supervision plus that received since they were directly under our supervision.

At the time our titrated x-ray therapy was started, the lymphocytic leukemia patients ranged in age from 39 to 68 years. Ten were males and one was female. The chronic granulocytic leukemia patients ranged in age from 3 to 71 years; of these, 7 were males and 9 were females. Seven of the 11 lymphocytic and 4 of the 16 granulocytic leukemia patients had had previous treatment with local x-ray therapy to nodes or spleen. One in each series is still living. For several patients the x-ray therapy overlapped the period when new patients were started on ^{32}P.

DOSE FACTORS

All the ^{32}P was administered intravenously, and doses given before such standards for ^{32}P were available have been adjusted to Bureau of Standards equivalents. During the period when these patients were started on therapy, the initial dose for the lymphocytic leukemias was usually 1.33 mc, and for the chronic granulocytic leukemias, 2.67 mc, rather than the larger doses we now would recommend (1). All subsequent doses were adjusted up or down as necessary, by the criteria outlined in Reference 1, to bring the patient under control within 12 weeks and to maintain a steady state. All the ^{32}P was administered by our own staff.

The x-ray therapy was administered by ten different groups of competent radiotherapists with their own radiation therapy equipment and in four dif-

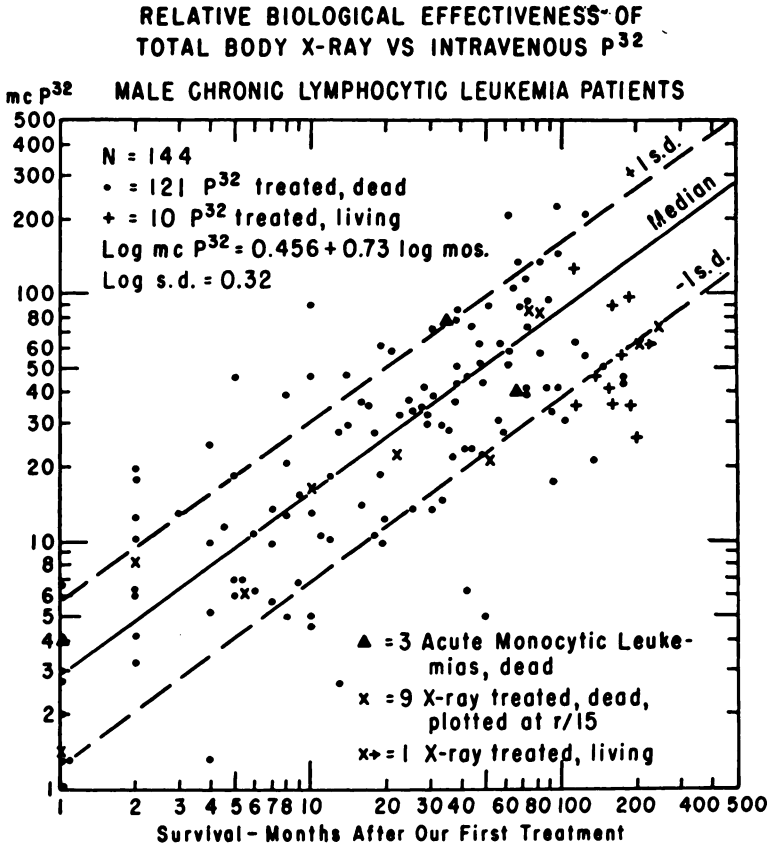

Fig. 1. Log-log plot of total ^{32}P or total-body x-ray received by male patients with chronic lymphocytic leukemia after they were first seen by us. For the x-ray treated, multiply the millicurie scale by 15 to read cumulative r received. Note that four of the 10 x-ray treated males are shown above the median and six below.

The only x-ray treated woman is shown in Fig. 2. She was well above the median in dose requirement.

This, and all other figures, were initially plotted on Keuffel and Esser log-log paper, Catalogue No. 328-120.

ferent hospital radiotherapy departments. All were located in Portland except for one in Salem, Oregon, one in Boise, Idaho, and one in Lewiston, Idaho. Therapy machines were replaced with newer equipment from time to time during the 23 years the x-ray group was treated. Details of our plan of treatment were discussed individually with each radiotherapist and, except in the cases of the four chronic granulocytic leukemia patients mentioned, we made the decision as to each dose received.

The dose factors were 200 to 250 kv, 80 to 100 cm target skin distance, filtration equivalent to a half-value layer of 1 to 2 mm of copper, average dose rate 4 to 11 r per minute. The dose rate measurement was with Victoreen ionization chambers at the target skin distance, with the patient not in place so there was no correction for back scatter.

With the exception of the 3-year-old boy who received irradiation to the entire body, front and back, on alternate visits, all patients received equal doses at the same visit, first to the upper and then to the lower half of the body, the unexposed half being protected to the umbilical level with a leaded apron. Radiation was from the front on the first visit and from the back on

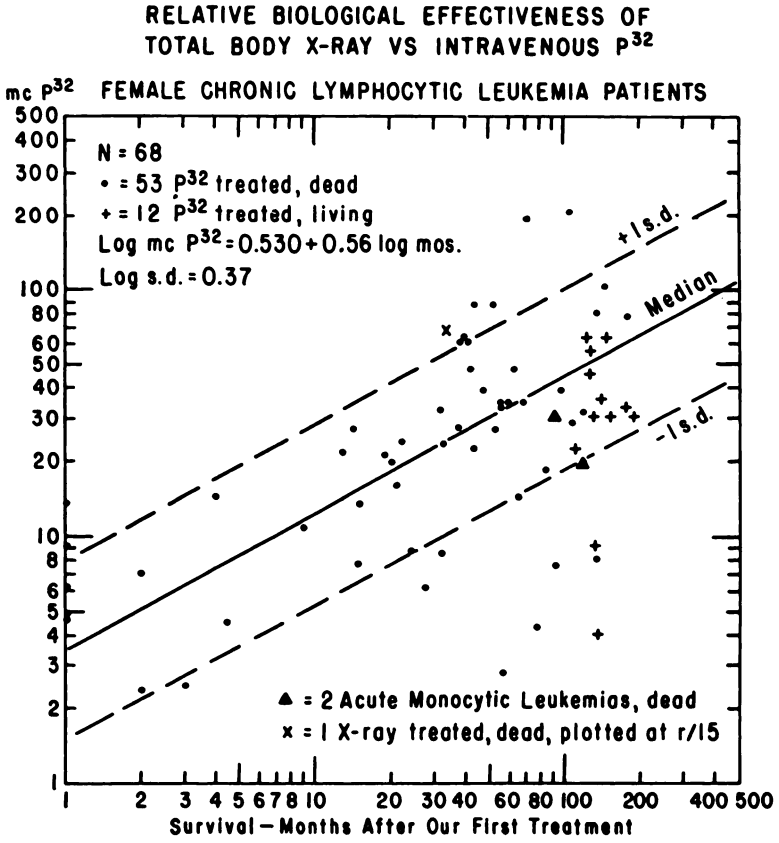

Fig. 2. Log-log plot of female patients with chronic lymphocytic leukemia. See Legend to Fig. 1 for explanation.

alternate visits throughout the period of treatment. A dose of 10 r to upper and then to the lower half of the body is cumulated as 10 r, not 20 r.

Usually, the lymphocytic leukemia patients received an initial dose, as above defined, of 10 r; the granulocytic leukemia patients, 20 r. All subsequent doses were adjusted by exactly the same criteria as were used in adjusting doses of ^{32}P. Doses were ordered as either 10, 15, 20, or 25 r. A few of 30 r were prescribed, but since this produced nausea, when ^{32}P became available and the disease could no longer be maintained under control by 25 r every 2 weeks, ^{32}P therapy was substituted. With three of the men and the one woman with lymphocytic leukemia this did become necessary, as it did with two of the men and four of the women with chronic granulocytic leukemia. In these cases, where ^{32}P was substituted for x-ray, the x-ray dose was divided by the factor under investigation (15 in the final figures) to get mc equivalents, and this amount was added to the mc ^{32}P received. Since the ^{32}P in these cases was given only during the terminal phase of their disease, these patients are all included with the x-ray treated group and are indicated by "x's" in the figures.

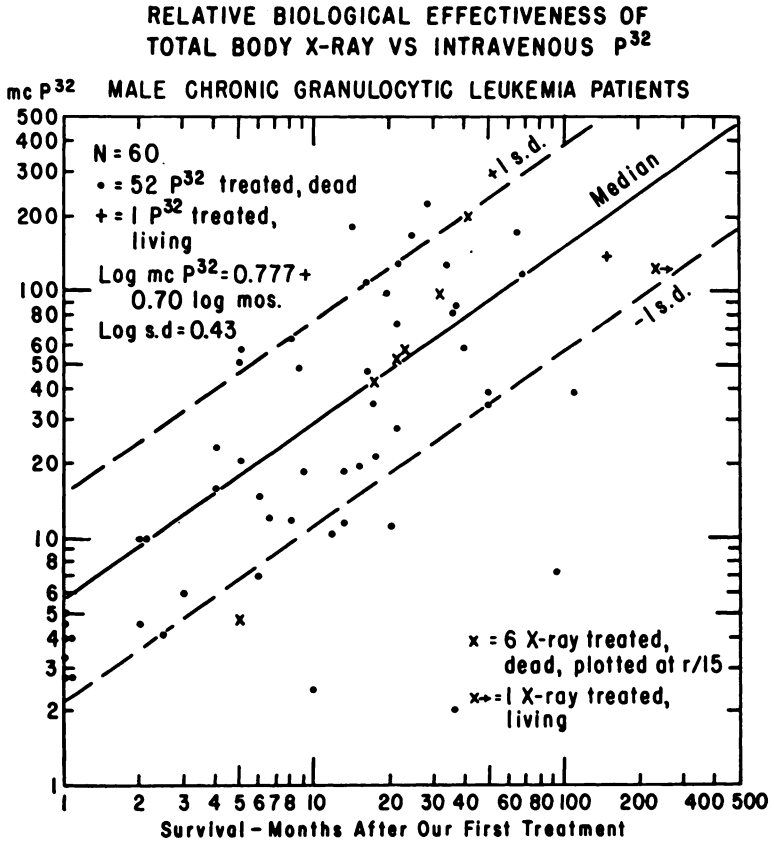

Fig. 3. Log-log plot of male patients with chronic granulocytic leukemia. See Legend to Fig. 1 for explanation. Note that 4 of the 7 x-ray treated patients are above the median and that, by comparison with Fig. 4, male patients required more ^{32}P and more x-ray to maintain control than did the female patients.

In nearly all the cases, x-ray therapy had to be given at more frequent intervals after the first 12 weeks than was required for ^{32}P therapy. The median number of doses per year, for the lymphocytic leukemia patients, was, for x-ray therapy, 6.33; for ^{32}P therapy (2), 5.4. For the granulocytic patients, the corresponding figures were 24 and 7.8. After the initial period of control the range of interval was from once a week to once in 12 weeks. The interval of 12 weeks was arbitrary because, with few exceptions, it was found patients began to miss appointments if the interval between visits was any longer.

The major exception was the patient with chronic granulocytic leukemia who had had 7.8 years of local radiation to spleen and long bones before we saw him, and who has had 235 months of x-ray treatment under our supervi-

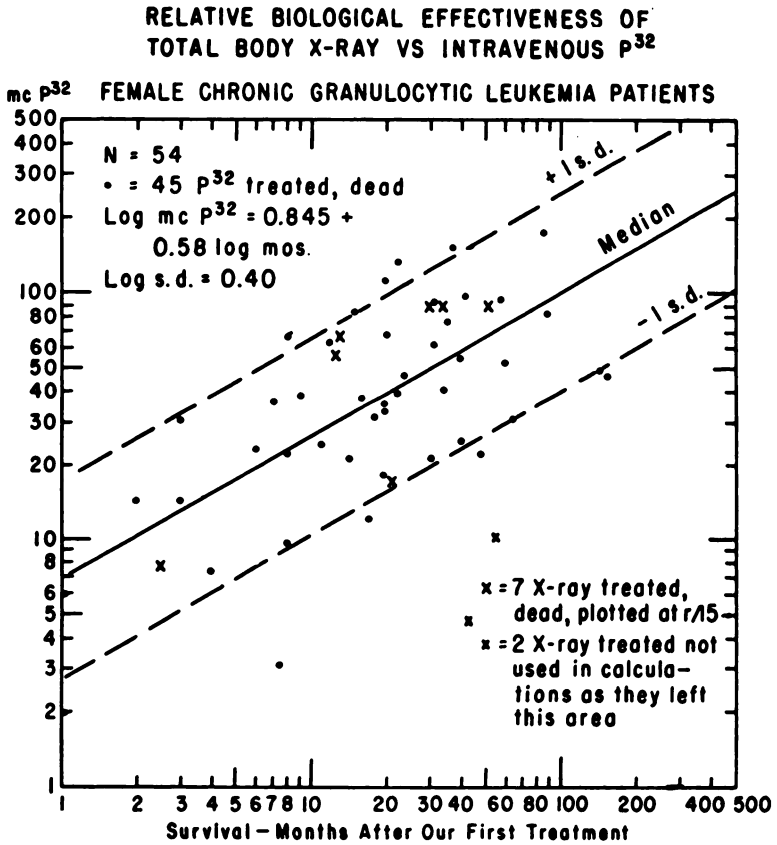

Fig. 4. Log-log plot of female patients with chronic granulocytic leukemia. See Fig. 1 for explanation. The total-body x-ray therapy given to the two women, indicated by the small x's, was received during the first two months for the one at 155 r and within the first three months for the one at 70 r. These patients then moved to distant parts of the country where they were treated by local irradiation to lymph nodes and spleen.

By comparing this figure with Fig. 3, it will be noted that a total of nine of the 16 x-ray treated patients are above the median.

In all the figures, note the extremely wide standard deviation even for patients of the same sex with the same disease and similar survival time.

sion since then. As shown in Fig. 1a of Reference 6, under local radiation treatment for the first 7.8 years, he was able to work only two years. Details of his treatment from February, 1944, to July, 1952, are shown in Fig. 1b of this reference. He had a 300,000 leukocyte count just before we saw him, and although his leukocyte alkaline phosphatase has remained negative, he now requires only 10 r every 20 weeks. He drives a bus for the San Francisco transportation system. During these 235 months he has missed only 6 months of work, and this absence was due to a strike, not to illness. He is still living 27 years after first specific treatment for chronic granulocytic leukemia.

Figure 1b of Reference 6 shows that dose requirement may decrease with time and Figs. 1, 2, and 3 of Reference 2 show that in other cases the dose requirement may suddenly increase. We have found no way to predict when this sudden decrease or increase in requirement may occur, and attribute it to somatic mutation. In many patients the dose and interval has remained unchanged.

Either in the individual or between individuals with the same disease, the size of the individual dose, the interval between doses, and the dose rate per year (2) may vary by a factor of 10. Initially we varied initial doses of ^{32}P with body weight, but since body weight varies by a factor of only about 2, whereas the ^{32}P requirement varies by more than a factor of 10, this seemed an unnecessary refinement.

COMPARATIVE ANALYSIS OF DATA

Rossi (7) has pointed out the extreme difficulty of determining the relative biological effectiveness of different modalities of radiation. We have tried many different methods of making this comparison. While, ideally, dose should be compared in rads, this method of comparison would probably introduce more, rather than less, uncertainty. We have provided data from which the fraction of the administered dose of ^{32}P in each type of blood cell and in other tissues may be calculated (8-11), but the distribution of these cells in the body is so variable and the variation between individuals with the same disease and in the same individual between different time periods is so great, that we have not attempted such calculations.

At first we considered expressing the dose of ^{32}P in microcuries per kilogram of body weight but the individual variations were so great in time in one individual and between individuals that this scarcely reduced the total variability. With time under treatment varying from less than 1 month to more than 20 years, and with sex differences being far greater than could be accounted for by differences in body weight, especially in the granulocytic cases, weighting of the data would be difficult. Even to convert the x-ray doses to rads would be difficult because of differences in body build, bone density, and size of spleen and lymph nodes. Furthermore, the 3-year-old child with chronic granulocytic leukemia required the highest total dose and dose rate while one of the heavier men required one of the lowest doses and dose rates in terms of total dose and dose per year. The one relatively small woman who received x-ray treatment for lymphocytic leukemia took the highest dose rate of any of the x-ray treated lymphocytic leukemia patients, although the ^{32}P

requirement for women was significantly lower than it was for men in the total ^{32}P series.

The total individual doses of ^{32}P and the total individual doses of x-ray, however, each fit a logarithmic probability distribution as did the distribution of survival times (1, 2). The most satisfactory method of comparison, therefore, seemed to be that illustrated in Figs. 1 to 4; namely, plotting on log-log paper total dose received in millicuries of ^{32}P against survival time after our first treatment, and then determining the line of best fit for the median and plus or minus one standard deviation. In making these calculations, those few patients who had moved away or had failed to return for therapy were omitted but they are included on the graphs so there are no omissions from the total population. Similar plots were made separately for the x-ray treated group. The single ratio between the x-ray dose and the ^{32}P dose, which was necessary to maintain and control these patients and which would best fit the median and standard deviations of the larger ^{32}P series, was then determined by trial and error. This ratio was found to be 15 r of x-ray was equivalent to 1 mc of ^{32}P intravenously. In other words, the factor 16 and the factor 14 gave a poorer fit to the ^{32}P required than did the factor 15. This method has the advantage of showing exactly how much radiation each patient received and in what total time; and the exact distribution, in units of millicuries given intravenously, or in total r received in terms of conventional methods of measurement. Anyone who wishes to attempt a more refined analysis may do so.

This method of analysis made it possible to include in the x-ray treated series the 10 patients who lived into the period when ^{32}P was available and who were transferred to ^{32}P therapy when nausea and vomiting developed on the higher doses of x-radiation required. We simply divided the total dose of x-ray received to that date by 15 and added the subsequent millicuries of ^{32}P, which varied from 1.3 to 50.5. The preceding x-ray doses varied from 40 r to 1120 r. Therefore, the total x-ray equivalent for each of the x-ray treated patients may be read from the graphs by multiplying the millicurie scale by 15.

RESULTS

As may be seen from Figs. 1 through 4 by using the factor of 1 mc ^{32}P given intravenously is equivalent to 15 r x-ray, as herein defined, 14 of the 27 x-ray treated patients fell above the median and 13 fell below, with 2 of the 27 above $+1$ standard deviation and 4 below -1 standard deviation. Two patients of this last group were not counted since they had moved to a distant part of the country, early in the course of treatment, where they were treated by local radiation, notwithstanding our recommendation that our program be continued. These two are represented by the small "x's" in Fig. 4. A few of the patients on ^{32}P therapy who did not keep appointments, thus receiving far less ^{32}P than they should, were also omitted in determining the best lines for median and standard deviation. However, they are all included in the figures, since the exact status of every patient started on therapy is known. The regression equations and standard deviations are given in the figures.

It is important to recognize, in analyzing these figures, that they represent survival time after our first treatment. Survival time after first specific treatment and after onset of definite symptoms of the disease are reported elsewhere (1) and should be referred to. It is also important to recognize that these figures represent what we were able to accomplish during this study, some of it covering the period before steroids were available for treatment of hemolytic anemia (12) and much of it before we had determined the most satisfactory initial dose (2). Nearly all the granulocytic leukemias, therefore, were undertreated in the first 12 weeks and some of the lymphocytic leukemias terminally, death occurring before ^{32}P was available. This study shows what can be accomplished in real life and not what might be accomplished if patients were perfect in following directions or if patients were referred for treatment as soon as the diagnosis is established.

It should not be concluded, because of the relatively long survivals of a few patients who received low dosages, that the lower the dose the better the result. Other patients who received low dosage through failure to follow directions had to return for therapy when symptoms recurred. Obviously, the patient who has no symptoms is more likely to refrain from following directions than the patient who develops symptoms. Also, some patients who received the smaller dosage were treated elsewhereby another modality. A very few of our patients were given other agents in the terminal phase (see Fig. 3 in Reference 2), but the total time under such other treatment was for so few months, involved so few patients, and was so unsatisfactory in prolonging life that it did not seem worth while to make this correction.

Other methods of analysis employed (including pairs matched for age, sex, and total duration; mean total dose per individual under x-ray therapy versus mean total dose of ^{32}P per individual under ^{32}P therapy; median dose rate per year to maintain, and median dose rate to control in the first 12 weeks) all gave values between 11 and 18 r equals 1 mc ^{32}P intravenously. As a rule, the lower value was for the lymphocytic cases and the higher value for the granulocytic cases.

A number of interesting points are evident from examination of the figures. As Crosby (13) has pointed out, male granulocytic leukemias require larger doses of radiation than female patients with this disease. Patients with granulocytic leukemia require approximately twice as much radiation as patients with lymphocytic leukemia. Total doses required may reach levels far higher than many had thought could be tolerated; therefore, cumulative fractionated dose should not be equated with a single dose.

Our studies have shown (3) that the leukemic cell is far more sensitive than the normal cell in the same patient, since, in lymphocytic leukemia, cells of the granulocytic series increase in number as cells of the lymphocytic series decrease; and in granulocytic leukemia, cells of the lymphocytic series increase in number as cells of the granulocytic series decrease, even though patients with granulocytic leukemia require far larger doses in the majority of instances than are required to control and maintain patients with lymphocytic leukemia.

Dose and interval were found not to be interchangeable. Repeating an inadequate dose did not lower leukocyte counts in either the lymphocytic or granulocytic leukemic cases and might have led to a greater total cumulative dose than would adequate doses at proper intervals (2, 3, 4). Conclusive evidence was obtained that a true radiation resistance of the leukemic cell, as well as of the normal hemic cell, develops in some patients while increased radiation sensitivity develops in others. These changes occur so suddenly that it seems probable they are due to a somatic genetic alteration leading to replacement of one cell population with another.

None of the patients developed skin changes that might be attributed to radiation, not even the patient who had had a total of 8,900 r to spleen and long bones during the 7.8 years prior to his referral to our care, and total body x-ray therapy totaling 1,770 r in the 235 months since our therapy was started.

Most of the patients with either chronic granulocytic or chronic lymphocytic leukemia have received more total radiation than is necessary to control and maintain patients with polycythemia vera (15), but this is due to the far less frequent dosage required in the latter. The initial dose in polycythemia vera required to reduce erythrocyte count was usually higher than for either type of chronic leukemia. Thus, leukemic leukocytes are more sensitive to radiation than the polycythemic erythrocytic series, in terms of a single dose, but less sensitive in terms of maintenance requirement since hemoglobin and erythrocyte count increased in the leukemic patients under a maintenance treatment that averaged more in mc per year than was required to maintain polycythemia patients in ideal status.

The only clear-cut complication of radiation therapy was the development of acute leukemia of a different type than the initial chronic leukemia. Five acute monocytic leukemias were observed among the 201 lymphocytic leukemias treated with ^{32}P. One of these occurred within the first month of treatment, so it was probably present before he received any ^{32}P therapy. These cases are indicated by the triangles in Figs. 1 and 2. Three acute monocytic and 1 acute lymphocytic leukemia developed in patients with chronic granulocytic leukemia, but these have not been indicated in the graphs since the differentiation between acute monocytic leukemia and the acute terminal phase of chronic granulocytic leukemia is difficult (14) and we may have missed some of these.

As we have reported elsewhere (15), a far larger proportion of patients treated with ^{32}P for polycythemia vera develop acute leukemia. These are also randomly distributed in terms of total dose, dose rate, time of onset after first dose, and in none of these has there been an apparent shortening of life span relative to the corresponding series in which an acute leukemia did not develop. In each disease, the patient who developed acute leukemia of a different type did not differ significantly in survival time from the patient who did not develop this complication.

Obviously, what we have actually determined is that dose of x-ray measured by conventional methods which, given within the same time period, has identical effects on the cells of the lymphocytic series as does the intravenously adminis-

tered ^{32}P, given within those same time limits; and exactly the same thing for cells of the granulocytic series.

SUMMARY

Data is presented which indicates that when comparisons are made at equal time intervals after the first dose, 1 mc of ^{32}P given intravenously is equivalent in effect to 15 r of total-body x-ray irradiation, as herein defined, in its effect on the leukemic cells of the lymphocytic or the granulocytic series in chronic leukemia. With this ratio, clinical therapeutic effects were equal, as well as effects on the total cell population of the involved cell series. For the effects measured there is a definite threshold below which, in each patient, leukocyte counts and spleen and lymph node size are not reduced.

True radiation sensitivity of cell populations may differ greatly in different individuals and may change suddenly, either up or down, in the same individual at different times.

ACKNOWLEDGEMENTS

I wish to express my appreciation to all members of the staff of the Division of Experimental Medicine who have participated in this study since 1941 and also to all the radiotherapists who collaborated in this study.

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^{90}Strontium Content in Human Bone, 1962-1963 G. W. Gaffney, R. M. Hallisey, M. S. Miller and A. S. Goldin, *(Radiological Health Data 5:620-628,* December 1964).

Since late 1961, the Public Health Service's Division of Radiological Health, jointly with pathologist and medical examiners throughout the United States, has conducted a program for analysis of ^{90}strontium in human bone specimens collected at autopsies. The report analyzes results obtained in the program through June 1964, and gives detailed results for determinations completed in the interval from November 1963 through June 1964. The data analyzed are for ^{90}strontium content in bones, mostly vertebrae, for 322 individuals who died in 1962 and 1963 at ages less than 25 years. The frequency distribution for strontium units (pc ^{90}Sr/g Ca) in bone is log-normal. Justification is given for reporting mean values, as well as standard errors in these, in addition to median values. For age groups 0-4, 5-9, 10-14, 15-19 and 20-24 years, the mean strontium units found in 1963 deaths were 4.7, 4.2, 3.1, 2.9, and 2.4, respectively. The strontium units for corresponding age groups for 1962 deaths were 3.2, 2.8, 2.3, 2.2, and 1.9, respectively. In the age group 1-4 years the mean strontium units were higher than in ages 0-12 months (5.0 versus 2.2 for 1963 deaths; 3.5 versus 2.5 for 1962 deaths). The higher values observed in the 1-4 year age group, compared with those found in deaths occurring at 0-12 months of age, is believed to be influenced predominantly by the discrimination between strontium and calcium by the mother in absorption, excretion and transplacental passage, although diets frequently lower in strontium units in the first few months after birth may also play a role. Federal Radiation Council guidance is used to provide some perspective on radiological hazard of ^{90}strontium burden, even though this guidance does not indicate when protective action should be taken against fallout from nuclear weapons tests.

From the bone data there is some suggestion that the skeletal concentration of ^{90}strontium considered to correspond to the upper limit of Federal Radiation Range 1 for "population average" was reached in 1963 in the 1-4 year group. The upper limit of the skeletal concentration related to FRC Range 1 for individuals was approached in one 1963 case; the value was 13 strontium units.

G.W.G.