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Leukemia and Ionizing Radiation

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Quantitative estimates of the genetic effects of ionizing radiation on human beings have been carried out by a number of investigators (*1–3*). Estimates of this kind involve extrapolating from induced mutation rates in such organisms as *Drosophila* and mice. Quantitative estimates of the somatic, or "direct," effects of radiation must also be attempted if the biological hazards of ionizing radiation are to be fully assessed. In the case of direct effects, it is particularly difficult to extrapolate from results with lower organisms, and it becomes important to have data on man himself.

It is the purpose of this article to examine the evidence for the induction of leukemia in man by ionizing radiation. Although ionizing radiation has been implicated in the production of other human malignancies, such as bone tumors (*4*) and thyroid carcinoma (*5, 6*), only the data on induction of leukemia seem sufficiently extensive to warrant a study at this time of the quantitative relationship between incidence of the disease and dose of radiation. Evidence bearing on this relationship is drawn from studies of leukemia among four groups of individuals: (i) survivors of atomic bomb radiation in Japan; (ii) patients irradiated for ankylosing spondylitis; (iii) children irradiated as infants for thymic enlargement; and (iv) radiologists. An estimate of the probability of developing leukemia per unit dose of radiation (*7*) per time unit is derived for each of these groups. This probability of radiation-induced leukemia is discussed and its application to a specific example of a possible radiation hazard—namely, radiostrontium—is outlined. Certain properties of the disease, relevant to the radiation studies, are presented first.

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Description of the Disease

Leukemia is a malignant disease in which the leucocytes undergo a more or less unrestricted proliferation. The "acute" form of leukemia differs from the "chronic" form, not only in being usually of shorter duration, but also in being a more severe disease with a higher percentage of immature white blood cells in the circulating blood. Another classification of the leukemias is based on the type of white blood cell predominating in the marrow or in the circulating blood. The two most common of these types are known as "granulocytic" (or myelogenous) and "lymphocytic" (or lymphatic). The presumption is that the granulocytic type arises in the red bone marrow. The lymphocytic type is thought to arise in the lymphatic elements of the blood-forming system (thymus, spleen, and other lymph glands), although the marrow is not excluded as a source for this type.

Spontaneous Incidence of Leukemia

In 1947 Sacks and Seeman (*8*) reported that the recorded death rate from leukemia had increased steadily from 1900 to 1944 and at an accelerated rate after 1930. The death rate has continued to increase (*9*). By 1954 the crude mortality rate for leukemia among the U.S. white population had reached 68 per million individuals per year (*10*) compared with 42 per million in 1940 (*11*). The male and female crude death rates in that population were 79 and 58 per million per year, respectively, in 1954 (*10*). The observed increase in death rate from this disease may be partly due to improvements in diagnosis. Other factors may also be responsible, such as the increased exposure of the population to ionizing radiations employed in medicine and dentistry, as was recently discussed by Dameshek and Gunz (*12*).

MacMahon and Clark (*13*) have recently studied the spontaneous incidence of the common forms of leukemia. They have attempted to determine the total number of valid cases diagnosed among residents of the borough of Brooklyn from 1943 to 1952, inclusive. In this study the over-all ratio of acute to chronic forms among the white population was nearly 1/1 (726/732), but there were marked differences in the incidence of these two forms with respect to age at time of diagnosis, as is shown in Table 1 (*14*). The ratio of granulocytic to lymphocytic types in the Brooklyn study was 1.6/1 (512/318).

Leukemia in Hiroshima and Nagasaki

Studies of the incidence of leukemia among survivors of the atomic bomb bursts over Hiroshima and Nagasaki have established that ionizing radiations induce leukemia in man (*15–17*). Table 2 summarizes the incidence of leukemia in terms of four concentric zones about the hypocenter (the point on the ground under the aerial burst). This table includes only those cases of leukemia which were (i) diagnosed during the period January 1948 to September 1955, inclusive; (ii) resident in the city at the time of diagnosis (Hiroshima) or at the time of death (Nagasaki); and (iii) considered by several criteria to be valid cases of the disease (*18*). For each zone, the estimate of the number of exposed survivors resident in Hiroshima as of October 1950 (*17*) has been combined with the corresponding number for Nagasaki (*15*) to obtain a combined population estimate for both cities.

Lange *et al.* (*16*) have studied the pattern of types of leukemia in the exposed and unexposed populations of Hiroshima and Nagasaki. They conclude that radiation induces the same pathological types that are found spontane-

Table 1. The spontaneous incidence of leukemia for the white population of Brooklyn, N.Y., 1943–52, according to chronicity. Data of MacMahon and Clark (*13*).

Age	Percentage in age interval	Incidence per million per year*		
		Acute	Chronic	Total
0– 9	15.3	48	1	49
10–19	13.5	24	2	26
20–29	16.5	12	6	18
30–39	16.5	20	14	34
40–49	14.8	22	28	50
50–59	11.8	44	64	108
60–69	7.6	58	133	191
70+	3.9	59	182	241

* The incidence of "subacute" and unknown types of leukemia have been allocated to the observed incidences for the acute and chronic forms in the proportions in which the latter were diagnosed at each age interval (*14*).

ously and, as far as can be judged by the limited data, induces them in roughly the same relative proportions that occur spontaneously. This is especially evident in the case of chronic lymphocytic leukemia, which is rare in both the exposed and unexposed Japanese populations, whereas it is the most common form of leukemia after age 50 in the United States (*13*). Lange *et al.* found no marked influence of sex or age on the incidence of leukemia among the exposed populations. However, they point out that, for a number of reasons, the data are not very satisfactory for assessing the incidence in individuals under 5 years of age (*19*).

The published accounts of leukemia in Hiroshima and Nagasaki have not contained estimates of the doses received by the bomb survivors. Recently, however, distance-dose curves for these cities have been published (*20*). These curves give, for each city, the relationship between the slant distance from the burst and the "air" (unshielded) dose of gamma rays and of neutrons. From this information, curves have been constructed (Fig. 1) showing the relation between distance from the hypocenter and the combined "air" dose from gamma rays and neutrons (Fig. 1) in rem (*7*). In computing the latter dose, it has been assumed that the relative biological effectiveness (RBE) of neutrons for inducing human leukemia is 1.7. This value is chosen since Dunning has recently stated that "for generalized whole-body effectiveness it is thought that 1.7 is a reasonable representative value for neutrons from a nuclear detonation" (*21*). This is believed to be a conservative estimate for the RBE, since Upton *et al.* (*22*) found that the RBE for induction of leukemia in mice by fast neutrons is somewhat lower than this.

In the absence of precise knowledge of the distribution of survivors within the different zones about the hypocenter, it is conservative to take the mean "air" dose for a zone as the average "air" dose received by survivors in that zone. The zone from 0 to 999 meters, which is designated here as zone A, is a special case, however, since there was heavy mortality near its center. The mean dose for this zone has been computed for the portion of this zone extending from 850 to 999 meters. The majority of leukemia cases in zone A occurred in this latter region (*15*); moreover, two (among five) cases at a distance closer than 850 meters had the type of shielding specified, and in each case it was listed as heavy (*18*). Since the doses for the two cities are slightly different at a given distance from the hypocenter, the average value of these two doses is used without correcting for differences in population size. In this way, a dose of about 1300 rem is arrived at for zone A. For zones B (1000 to 1499 meters) and C (1500 to 1999 meters), the mean doses are approximately 500 rem and 50 rem, respectively. At 2000 meters the dose has fallen to 14 rem and by 2500 meters to less than 5 rem. Since the majority of the population in zone D (from 2000 meters on) was beyond 2500 meters, the average dose is under 5 rem and is thus so low that zone D can be treated as if it were a "control" zone.

The relation of dose, estimated as described in the preceding paragraph, to the incidence of leukemia per year, based on the combined Hiroshima and Nagasaki data, is shown in Table 3. The incidence per year in the "control" zone, D, is subtracted from the incidence in each of the other zones to obtain the "incidence of induced leukemia per year" in these zones. The values of the incidence of induced leukemia are likely to be minimum ones, since, as Lange *et al.* have noted, "some cases of leukemia have undoubtedly been missed and other cases have been omitted because of lack of adequate material to confirm the diagnosis" (*16*). The incidences of induced leukemia in zones A, B, and C have been divided by the respective mean "air" doses in rem, derived in the preceding paragraph, to give estimates for the probability of induced leukemia for these zones. The values for this probability are seen to range from 0.7×10^{-6} to 0.9×10^{-6} per individual per rem per year. These

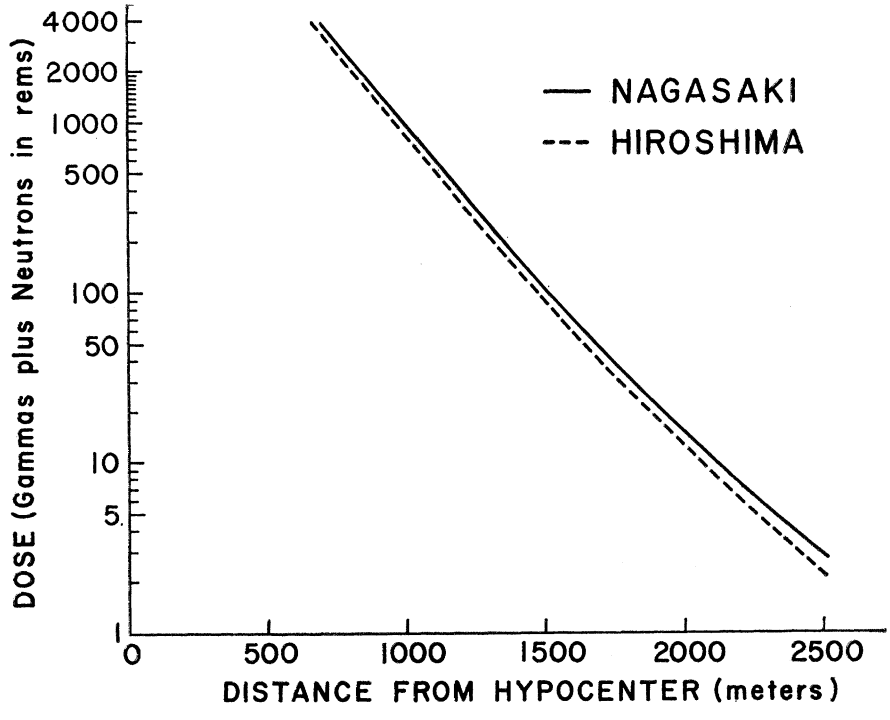

Fig. 1. Distance-dose curves for atomic bomb blasts at Nagasaki and Hiroshima.

are minimum estimates of the probability of induced leukemia, since the survivors were shielded in varying degrees from the "air" doses, calculated in the preceding paragraph. The shielding of survivors has two major components: (i) the body's own shielding of its blood-forming tissues by the surrounding bone and soft tissues; and (ii) external shielding by buildings or other shelters. A shielding factor of 2 is believed to be a conservative one for correcting for both of these components—the true factor might be at least 4 (*23*). The "best" estimate for the probability of induced leukemia from these data is, therefore, taken as approximately twice the aforementioned minimum estimates of 2×10^{-6} per individual per rem per year (of the 7.75-year period). A rough range for this probability is 0.7×10^{-6} to 4×10^{-6}.

Leukemia and Ankylosing Spondylitis

Court Brown and Doll (*24*) and others (*25, 26*) have investigated the incidence of leukemia among patients treated with x-rays for ankylosing spondylitis—a hereditary disease of the spine. Among 11,287 male patients irradiated during the period from 1935 to 1954, inclusive, 37 cases of leukemia were discovered. The average period of follow-up of these patients was "just under five years" (*24*). The distribution of cases by amount of treatment, measured as maximum dose in roentgens (7) to the spinal marrow, is shown in Table 4. A highly significant increase in the incidence of leukemia is apparent among those receiving the heavier treatments.

Court Brown and Doll have estimated the expected incidence of leukemia in a comparable group of unirradiated normal males as 50 cases per million individuals per year. Subtraction of this expected incidence from the observed incidence of leukemia per year in the irradiated patients gives an estimate of the incidence of radiation-induced leukemia per year. This calculation has been carried out for each of the groupings of leukemia cases according to amount of treatment. For each such grouping between 500 and 2750 roentgens, an average maximum dose to the spinal marrow is taken as the mid-point of the dose range (for example, for leukemia cases developing after treatments ranging from 500 to 999 roentgens, 750 roentgens is taken as the average dose). By dividing the calculated incidence of radiation-induced leukemia for each of the four groupings of this kind (column 5, Table 4) by the respective average maximum dose (column 2, Table 4), a set of four minimum estimates of the probability of leukemia per individual per roentgen (to the spinal marrow) per year is obtained.

Table 2. Incidence of leukemia among the combined exposed populations of Hiroshima and Nagasaki by distance from the hypocenter (January 1948–September 1955).

Zone	Distance from hypocenter (m)	Estimated population of exposed survivors (Oct. 1950)	Number of confirmed cases of leukemia	Percentage of leukemia
A	0– 999	1,870	18	0.96
B	1000–1499	13,730	41	0.30
C	1500–1999	23,060	10	0.043
D	2000 and over	156,400	26	0.017

These latter estimates are seen to range from 0.3×10^{-6} to 0.6×10^{-6} per individual per roentgen per year (column 6 of Table 4). It seems likely that the absorbed dose to the entire red-marrow system would be lower than the stated doses to the spinal marrow by a factor of at least 2 or 3. Therefore, it is estimated that the probability of leukemia ranges from about 0.6×10^{-6} to 2×10^{-6} per individual per rad (to the red-marrow system) per year.

Leukemia and Thymic Enlargement

Simpson *et al.* (*6*) have traced a series of 1400 individuals who had been irradiated as infants for an enlarged thymus condition. The average period of follow-up appears to have been about 15 years. As a "control" 1795 unirradiated siblings were also traced. In the irradiated group there were seven confirmed cases of leukemia (and one unconfirmed case), while there was none in the control group. The calculated number of cases of leukemia that would have been expected in a sample of comparable size and age from the general population was 0.6. The difference between this expectation and the observed number of cases (seven) is statistically significant (P less than 0.01).

In the majority of the 1400 infants, the radiation (x-rays) had been more or less restricted to the chest region. It was estimated that the "air" dose to the thymus region was more than 200 roentgens ("the great majority being less than 600 r") in 57 percent of the treated individuals and under 200 roentgens in the remainder. The average absorbed dose to the entire lymphatic system is roughly estimated as 100 to 300 rad. On the basis of these dose estimates, the probability of leukemia ranges from 1×10^{-6} ($6.4/15 \times 1400 \times 300$) to 3×10^{-6} per rad (to the lymphatic system) per individual per year. The number of cases (seven) on which this estimate is based is, of course, small. The 95-percent confidence interval for an observation of seven when the frequency is as low as in the present case lies between 3.3 and 13.2 (*27*). Therefore, the probability of leukemia in the thymic enlargement group may well range from 0.4×10^{-6} to 6×10^{-6} per rad (to the lymphatic system) per individual per year.

Leukemia among Radiologists

March (*28, 29*) and others (*30, 31*) have called attention to the fact that among physicians the percentage of deaths from leukemia is much higher for radiologists than for physicians who are not radiologists. The percentage of deaths that are due to leukemia can be a misleading statistic, however, since it is sensitive to differences in age distribution between the groups of individuals being compared. Such differences are marked in the case of radiologists, on the one hand, and all physicians, on the other, as is discussed later. To assess the

Table 3. Incidence of leukemia per year among the combined exposed populations of Hiroshima and Nagasaki (January 1948 to September 1955) in relation to dose of radiation (gammas plus neutrons).

Zone	Average maximum dose (rem)	Incidence of leukemia per million per year	Incidence of radiation-induced leukemia per million per year	Probability of leukemia per individual per rem per year
A	1300	1200	1179	0.9×10^{-6}
B	500	390	369	0.7×10^{-6}
C	50	56	35	0.7×10^{-6}
D	5	21		

Table 4. Incidence of leukemia among ankylosing spondylitis patients receiving different doses of radiation (x-rays). Data from Court Brown and Doll (*24*).

Maximum dose to spinal marrow (r)	Estimated average maximum dose (r)	Number of males developing leukemia	Crude incidence per million males per year	Incidence of radiation-induced leukemia per million males per year	Probability of leukemia per individual per r (to spinal marrow) per year
0			50		
Under 500		2	220	170	
500– 999	750	8	410	360	0.5×10^{-6}
1000–1499	1250	8	420	370	0.3×10^{-6}
1500–1999	1750	8	1130	1080	0.6×10^{-6}
2000–2749	2375	6	1300	1250	0.5×10^{-6}
2750 or more		5	1760		

radiation factor in the leukemia among radiologists, it first becomes necessary to estimate (i) the death rate from leukemia among radiologists (the number of deaths per total number of living radiologists), and (ii) the expected death rate from leukemia among radiologists if they had received no occupational exposure to radiation.

The study of mortality among medical specialists by Dublin and Spiegelman (*32*) has been used here as a guide in computing the afore-mentioned rates and as source of data for the years 1938 to 1942, inclusive. The latter data and additional data for the years 1943 to 1952, inclusive, are summarized in Table 5. The term *radiologist* is restricted here, following Dublin and Spiegelman, to those physicians who were listed in editions of the *American Medical Directory* (*33*) as limiting their practice to radiology (and roentgenology). Since only deaths occurring at ages 35 to 74 years, inclusive, were included in the mortality study for 1938–42, the same practice is adopted here for the supplementary 10-year period.

In order to estimate the mean annual population of radiologists at ages 35 to 74 years, during the entire 15-year period from 1938 to 1952, the age distribution of radiologists is required. This age distribution for the year 1940 was computed by Dublin and Spiegelman from the 1940 edition of the *American Medical Directory* and is shown in Table 6. The age distribution for a similar group of radiologists in 1950, also shown in Table 6, has been computed (*34*) by reference to the 1950 edition of this directory. The 1940 age distribution was based on a total of 1595 radiologists of whom 1451.5 (91.0 percent) can be inferred to have been at ages 35 to 74 years, inclusive (*32*). The 1950 age distribution was based on a total of 2443 radiologists of whom 2250 (92.1 percent) are calculated to have been at ages 35 to 74 years, inclusive, as of 1 July 1950. The mean number of radiologists (at ages 35 to 74) per year from 1938 to 1952, inclusive, is roughly approximated as 1850.7, which is the average of the number of such radiologists in 1940 and the corresponding number in 1950.

Deaths from leukemia occurring at ages 35 to 74 years, inclusive, among radiologists have been located in several ways with the results shown in Table 5. For the period from 1938 to 1942, inclusive, five such deaths are recorded by Dublin and Spiegelman. For the period from 1943 to 1948, inclusive, the carefully documented studies of March (*28*, *29*) record eight such deaths. For the remaining 4-year period from 1949 to 1952, inclusive, four additional deaths from leukemia have been located by reference to death notices in a medical journal (*35*). Thus, a minimum of 17 deaths from leukemia has been located among radiologists who died between the ages of 35 and 74 years during the 15-year period from 1938 to 1952. The upper and lower 95-percent confidence limits for this observation of 17 deaths are 25.5 and 10.8 deaths, respectively (*27*). Thus, a likely range of values for the average death rate from leukemia among radiologists at ages 35 to 74 years is 390 ($10.8/15 \times 1850.7$) to 920 ($25.5/15 \times 1850.7$) deaths per million per year, and the "best" estimate is 610 ($17/15 \times 1850.7$) deaths per million per year (of the 1938–52 period).

The expected death rate from leukemia among radiologists, if they had received no occupational exposure to radiation, is estimated by first calculating the death rate they would have experienced if subject to U.S. white male death rates from leukemia. This calculation has been made for a 3-year period from 1939 to 1941 by first computing (*36*) the mean annual age-specific U.S. white male death rates from leukemia (Table 7) and then applying them to the 1940 age distribution of radiologists (Table 6), restricting the computation to the 35–74-year age interval. The resultant expected death rate for the latter age interval is 63 deaths per million per year.

The same type of calculation has been carried out for a 3-year period from 1949 to 1951 by computing (*36*) the appropriate age-specific death rates for that period (Table 7) and applying them to the 1950 age distribution of radiologists. The resultant expected death rate is 88 deaths per million per year.

The average of the rates for the 1939–41 and 1949–51 periods is 76 deaths per million per year. The latter rate should roughly approximate the mean annual death rate from leukemia which radiologists would have experienced during the 1938–52 period if they had been subject to U.S. white male death rates for this disease. The observed death rate for this period was 610 deaths per million per year (Table 5), which is 8 times the expected rate, just calculated.

It is possible, however, that reasons other than radiation exposure may account for the high death rate from leukemia among radiologists. For example, leukemia might be more likely to be diagnosed among radiologists than among the group of all U.S. white males. To correct for such possibilities as this, the expected death rate of 76 deaths from leukemia per million per year, calculated in the preceding paragraph, is multiplied by a correction factor of 1.6.

Table 5. Deaths and death rates from leukemia among radiologists, at ages 35 to 74 years, by 5-year periods from 1938 to 1952, inclusive.

Period	Estimated number of radiologists at mid-point of period	Number of deaths from leukemia	Observed death rates per million per year	Expected death rates per million per year	Incidence of radiation-induced deaths per million per year
1938–42	1451.5	5	690	101	589
1943–47	(1850.7)*	6	650	(121)*	429
1948–52	2250.0	6	530	141	389
(1938–52)	(1850.7)*	17	610	(121)*	489

* The arithmetic average of the values for the 1938–42 and 1948–52 periods.

This factor is the ratio of the observed number of deaths from leukemia among physicians who were nonradiologists to the expected number of deaths calculated on the assumption that such physicians were subject to U.S. white male age-specific death rates for leukemia.

This factor of 1.6 has been inferred from data for the 1938–42 period given by Dublin and Spiegelman (*32*) and is applied throughout the entire 15-year period from 1938 to 1952 to give the expected death rates shown in Table 5. It is a conservative factor in the sense that it is possible that the increased death rate from leukemia among physicians who are nonradiologists is partly due to exposure of some of them to ionizing radiation (*31*). Thus, 121 (1.6×75.5) deaths per million per year is probably a conservative estimate of the expected death rate from leukemia among radiologists in the 1938–52 period, if they had received no exposure to radiation.

The expected death rate from leukemia, just calculated, would be expected to yield 3.4 ($15 \times 1850.7 \times 121 \times 10^{-6}$) deaths among radiologists during the 1938–52 period. It is appropriate at this point to compare this with the observed number—namely, 17 deaths (Table 5). The probability of observing 17 or more when the expected number is 3.4 is readily obtained from the Poisson distribution and is found to be less than 1×10^{-6}. Hence, the observed value exceeds the expected value at a statistically highly significant level.

The difference between the expected death rate from leukemia calculated on the assumption of no occupational exposure to radiation and the observed death rate is designated the "incidence of radiation-induced leukemia," L. For a stationary population chronically irradiated at a constant dose rate, D, the incidence, L, can be approximated if it is assumed that the probability of leukemia per rad of accumulated dose per year, P_L, is a constant for all age groups in the population and for all values of the accumulated dose. On these assumptions, a stationary population exposed for a mean number of years, E, to the dose rate, D, will have an incidence of radiation-induced leukemia that can be expressed as follows:

$$L\ (=)\ (D) \cdot (E) \cdot (P_L)$$

To estimate the value of E, it is assumed that occupational exposure of radiologists starts at age 25 and ends at age 65. The value of E for individuals who were at ages 35 to 74 in 1940 can then be approximated from the age distribution of radiologists for that year (Table 6) and is found to be 24.7 years. The corresponding value of E approximated from the 1950 distribution (Table 6) is 24.1 years. The average of these two values, 24.4 years, is used as the value of E for the population of radiologists who were at ages 35 to 74 years in the 1938–52 period. The "best" estimate of L is 489 deaths per million per year, (Table 5), and a likely range of values for L is 270 to 800 deaths per million per year, based on the 95-percent confidence limits for the observed death rate of 610 deaths per million per year. For reasons discussed later, the value of D is estimated to lie between 3 and 30 rad per year.

Table 6. Age distribution of radiologists. in 1940 (*32*) and 1950.

Age	Percentage distribution as of	
	1940	1950 (1 July)
Under 35	8.3	6.1
35–44	31.3	38.9
45–54	33.8	26.6
55–64	19.8	18.7
65–74	6.1	7.9
75 and over	0.7	1.8
Total	100.0	100.0

The "best" estimate for the range of values of P_L is then given by the expression

$$P_L\ (\text{likely range}) = \frac{489}{24.4 \times (3 \text{ to } 30)} = (0.7 \text{ to } 7) \times 10^{-6}$$
per individual per rad per year

A broader range, based on the confidence limits for L, is $(0.4 \text{ to } 11) \times 10^{-6}$ per individual per rad per year.

Since the dose rate, D, in the foregoing discussion, represents the average absorbed dose rate to the leucocyte-producing system, it is likely to be lower by at least a factor of 2 than the "air" dose rate to which radiologists were exposed. The recommended maximum dose rate (in air) for such workers was set at 0.2 roentgen per day in 1931 by the U.S. National Committee on Radiological Protection; this rate was reduced to 0.1 roentgen per day in 1936 and to 0.05 roentgen per day in 1949. Although some radiologists may well have exceeded the recommended dose rates, it seems unlikely that the average dose rate for all radiologists in the group under consideration would have exceeded the permissible limits set in 1931. Thus 30 rad per year has been taken as an upper limit for the absorbed dose to the leucotyte-producing system. The lower limit for D has arbitrarily been taken as one-tenth of this or 3 rad per year.

This estimate that D might be much less than 30 rad per year is somewhat at variance with the following conclusions from a recent study of longevity among radiologists (*37*). "In comparison with non-exposed physicians the shortening of life of radiologists is 5.2 years or 11% of the adult life span (after 20 years). If extrapolation from the animal data . . . is permissible, this would be expected to result from chronic whole body exposure to about 1.5 LD_{50} dose or possibly 1000 roentgens. Although this exposure was partial body and possibly less effective, it seems unlikely that the equivalent whole body exposures differed from the above value by a factor greater than 2 or 3. Consequently it appears that, within these limits at least, extrapolation from short-lived animals to man may be made with some confidence on the basis of per cent life-shortening per unit dose."

The shortening of life by 5.2 years just cited is based on the observation that during the period 1930–54 the difference between the mean age at death of physicians estimated to have had "no known contact with radiation" and the mean age at death of radiologists was 5.2 years (*37*). It can be calculated (*38*), however, that a difference of at least 6 years would be expected in this case solely as the result of differences in age distribution (as of 1940 or 1950) between radiologists, on the one hand, and all physicians, on the other. That is, radiologists may have a slightly longer life-span than physicians as a whole. Moreover, for the 1938–42 period, Dublin and Spiegelman showed that, after appropriate adjustment for differences in age distribution, the total death rate from all causes was lower for radiologists than it was for all physicians combined; however, this rate was slightly higher for radiologists than it was for all specialists combined. Thus, either a chronic whole-body exposure of 1000 roentgens does not have a marked effect on longevity or, more probably, radiologists have *averaged* much less than this as a life-time absorbed dose.

Discussion

Table 8 summarizes the various estimates of the probability of leukemia derived from the four sets of data reviewed here. For acute whole-body irradiation, the "best" estimate of this probability will be taken as 2×10^{-6} per individual per rad per year. This value is based on the studies of leukemia among

Table 7. United States white male death rates from leukemia per million per year.

Age	Period	
	1939–41	1949–51
25–34	18	26
35–44	29	34
45–54	55	68
55–64	104	149
65–74	154	276
75 +	181	385

survivors of atomic bomb radiation. For acute partial-body irradiation, the available data are conveniently discussed in terms of a probability of leukemia "of bone-marrow origin" (ankylosing spondylitis patients) or a probability of leukemia "of lymphatic origin" (thymic enlargement patients).

As has already been noted, granulocytic and lymphocytic leukemias may have bone-marrow and lymphatic origins, respectively. Since these two types of leukemia constitute the majority of all leukemias and occur in proportions which are, for present purposes, roughly equal, it is assumed that the "best" estimate of the probability of leukemia of bone-marrow origin is one-half of that for all leukemia, or 1×10^{-6} per individual per rad to the red marrow per year. Similarly, the "best" estimate of the probability of leukemia of lymphatic origin is taken as 1×10^{-6} per individual per rad to the lymphatic system per year.

These estimates fall within the range of values calculated for either the ankylosing spondylitis patients or the thymic enlargement patients. Moreover, there is some evidence that leukemia following irradiation of the spinal marrow is primarily granulocytic (*26*). Whether lymphocytic leukemia predominates in the thymic enlargement series (*6*) is uncertain on two grounds: (i) it is difficult to differentiate granulocytic and lymphocytic types in infants and children; and (ii) some irradiation of bone marrow would, in any case, be expected in this series of patients (*39*). Finally, the "best" estimate of the probability of leukemia following chronic whole-body irradiation is taken as identical with that for acute whole-body irradiation—namely, 2×10^{-6} per individual per rad (of accumulated dose) per year. This value is seen to be close to the lower limit of the range of values deduced for radiologists.

Simpson *et al.* (*6*) and Court Brown and Doll (*24*) point out that their studies lack a control in the form of an unirradiated series of patients. Thus, the possibility is not excluded that thymic enlargement and ankylosing spondylitis predispose toward leukemia. However, a comparison of the various estimated ranges for the probability of leukemia (Table 8) suggests that patients with the afore-mentioned conditions are no more prone to develop leukemia than are radiologists or the Japanese survivors.

Presently available determinations of the incidence of induced leukemia per year are based on average follow-up periods that are comparatively short in terms of the normal human life-span. Thus, the probability of leukemia per individual per rad per year may not be constant for an indefinite period beyond the initial time of irradiation. By choosing the lower limit for the probability of leukemia at about 0.7×10^{-6} per individual per rad per year, it is felt that adequate account is taken of the possibility that the incidence of leukemia per year following an acute dose of radiation may, as some have suggested on the basis of the data from Hiroshima (*37*), reach a peak followed by a steady decline. It is noteworthy, however, that Court Brown and Doll have concluded, from an analysis of 108 cases of leukemia among the exposed populations of Hiroshima and Nagasaki, that "the data provide no evidence of a sharp peak in incidence at any particular period after the explosion nor any clear indication that the incidence had yet begun to diminish by the end of the ninth year" (*40*).

The probability of leukemia per individual per rad per year is nearly constant over a rather wide range of doses in the case of the Japanese survivors (Table 3) and in the case of ankylosing spondylitis patients (Table 4). This is presumptive evidence that the relationship between incidence of induced leukemia and dose of radiation is either linear or approximately linear. A striking feature of the Japanese data shown in Table 2 is that the incidence of leukemia in zone C—the zone with a calculated average "air" dose of 50 rem—is significantly higher than in zone D, the "control" zone ($P = 0.02$, by the Chi-square test). Thus, these data provide no evidence for a threshold dose for the induction of leukemia. Moreover, chronic irradiation at a relatively low dose rate (perhaps 0.1 rad per day or less) appears to induce leukemia in radiologists at a rate per rad which is comparable to that observed for the Japanese survivors. This finding also fails to support the concept of a threshold dose below which leukemia will not develop.

A linear relationship between the incidence of leukemia and dose of radiation, which is suggested by the available data for man, may have its explanation in a somatic mutation hypothesis (*41*). Thus, radiation-induced leukemia may result from a somatic gene mutation, presumably occurring in one of the precursor cells destined to give rise to mature leucocytes. Such a mutation might cause the cell, or its descendants, to acquire an unregulated growth habit, or to release, or to respond to, viruslike or hormonal agents—to mention only a few of many possibilities. Thus, the somatic mutation hypothesis and other hypotheses for the origin of radiation-induced malignancies (*42*) are by no means mutually exclusive. Gene mutation has long been known to show a linear relationship with respect to dose of ionizing radiation from studies with *Drosophila*. This linearity has been extended by Spencer and Stern (*43*) to doses of 50 and 25 roentgens. Gene mutation is also known to be directly proportional to the accumulated dose of radiation, even when the radiation is chronically administered at a relatively low dose rate, as in the studies of Uphoff and Stern (*44*).

The concept of somatic mutation is also helpful in attempting to explain the long period of time which sometimes intervenes between irradiation and onset of leukemia. Thus, it may be that some of the precursor cells of leucocytes lie quiescent for years before they are brought into leucocyte production. A somatic mutation in such a cell might, therefore, be long delayed in producing its effect.

In leukemia of "spontaneous" origin, there is also likely to be a somatic mutation component which would be attributable to "spontaneous" mutation in the somatic cells. In addition, there is likely to be a "hereditary" component in spontaneous leukemia—that is, the presence of defective genes (dominant or recessive) which are transmitted through the germ line and which result in, or predispose toward the development of, leukemia. It is well known from the work of MacDowell and associates (*45*) that the pronounced differences among certain strains of mice in susceptibility to leukemia have a genetic basis. In man, there is evidence for familial factors in leukemia from the work of Videbaek (*46*) and others, but the type of inheritance involved is not clear (*47*). It should be noted that cases of leukemia which arise somatically—for example, those which are radiation-induced—will tend to obscure the analysis of the hereditary component in leukemia (*48*).

It is likely that there will be individual differences in susceptibility to radiation-induced leukemia as well as to "spontaneous" leukemia. The indication of a linear relationship between dose of radiation and incidence of leukemia implies that there are some individuals in whom a single radiation-induced event (perhaps a gene mutation) suffices to produce leukemia. There may, however, be other individuals in whom two or more such events would be required before leukemia would be manifested. Thus, the values of the probability of leukemia per individual per rad per year that have been derived here apply to the "average" individual in a given population, but do not necessarily apply equally to each and every individual in that population.

Spontaneous Leukemia and Natural Background Radiation

The possibility that a portion of the "spontaneous" incidence of leukemia may be due to radiation from natural background sources is briefly considered. For this purpose, the same type of approximation procedures employed for assessing radiation-induced leukemia

among radiologists is applied to the data of MacMahon and Clark on the spontaneous incidence of leukemia in the white population in the borough of Brooklyn (Table 1). Thus, the incidence of leukemia, L_B, that would be attributable to irradiation of that population from natural background sources can be approximated by assuming that it is a product of the following three quantities: (i) a constant dose rate, D_n, from all natural background sources; (ii) the mean age, E_B, of the Brooklyn population, which is equivalent to the mean number of years exposed to D_n; and (iii) the probability of leukemia, P_L, per individual per rad per year. The value of D_n is not known but probably is in the range of 0.1 to 0.2 rad per year (*49*). The value of E_B can be readily approximated from the age distribution (Table 1) of the Brooklyn population and is about 33.7 years. The value of P_L is chosen as the "best" estimate from the afore-described radiation studies, namely 2×10^{-6} per individual per rad per year. Thus, L_B can be estimated as 7 to 13 cases per million per year. The observed total spontaneous incidence in this study was 64.4 cases per million per year (*13*). Thus, possibly 10 to 20 percent of the "spontaneous" incidence of leukemia in this Brooklyn population is attributable to ionizing radiation from natural background sources.

A maximum value for the probability of radiation-induced leukemia may also be inferred from the Brooklyn data. The calculation of such a value is based on the incidence of acute leukemia, since in this form of the disease the time of onset and time of diagnosis probably nearly coincide, while in chronic leukemia some years may elapse between these two times. The observed incidence of acute leukemia has a minimum value of 12 per million per year which occurs in the 20–29 age group (Table 1). By assuming that individuals in that age group had an average accumulated dose of not less than 2.5 rad (0.1 rad per year for 25 years) and by further assuming, as an artifice, that all of the acute leukemia in that age group was due to radiation, the probability of acute leukemia may be estimated to have an upper limit of 5×10^{-6} ($12 \times 10^{-6}/2.5$) per individual per rad per year. Since the over-all ratio of acute to chronic forms was about 1/1 in the Brooklyn data, it may be inferred that the maximum value, or upper limit (Table 8), of the probability of leukemia (acute and chronic) is about 10×10^{-6} per individual per rad per year.

Application to Radiostrontium Exposure

The foregoing estimates of the probability of radiation-induced leukemia have been attempted in order to have some basis for assessing direct effects of ionizing radiations on human populations. An example of the application of these estimates to a man-made radiation exposure—namely, that from radiostrontium (Sr^{89} and Sr^{90})—is briefly discussed (*50*).

The maximum permissible concentration (MPC) of Sr^{90} has been set at 1 microcurie for the total body *for workers with radioisotopes* (*51*). A level of 1 microcurie of Sr^{90} per 1000 grams of calcium (the mass of calcium in the average adult individual) has been designated as 1 "MPC" unit of Sr^{90} (*52*). Various estimates are at hand for the level of radiostrontium that is being accumulated in the human body as the result of past testing of atomic weapons (*53*). The present discussion is restricted to examination of the following recent suggestion for a permissible level (presumably of Sr^{90}) *for the population at large* (*54*). "There seems no reason to hesitate to allow a universal human strontium (very similar chemically to calcium) burden of 1/10 of the permissible, yielding 20 rep in a lifetime, since this dose falls close to the range of values for natural radiation background. Visible changes in the skeleton have been reported only after hundreds of reps were accumulated and tumors only after 1500 or more."

A body level of 0.1 MPC is expected to irradiate skeletal tissue at a dose rate of about 0.25 rad per year, on the assumption of uniform distribution of Sr^{90} throughout that tissue. Because of the limited range in tissue of the beta particles emitted in the decay of Sr^{90} and of its daughter element, Y^{90}, the leucocyte-producing cells may receive somewhat less than this dose rate, depending on the exact location of such cells with respect to the surrounding calcium of the bone. This reduction factor, of perhaps 2, tends to be offset by the fact that ingested Sr^{90} is not uniformly distributed throughout the skeletal tissue but appears instead to be concentrated in regions more actively concerned with red-marrow formation (*55*). The dose rate to the leucocyte-producing cells is estimated as 0.1 to 0.2 rad per year for a body level of 0.1 MPC of Sr^{90}. This irradiation will be largely restricted to the skeletal tissue, since (i) the radiation from the decay of Sr^{90} is exclusively of the beta type and (ii) 70 percent of the Sr in the body is estimated to lie in the skeletal tissue (*51*). Hence, leukemia induced by Sr^{90} would be expected to be largely of bone-marrow origin (*56*).

The problem of assessing the incidence of Sr^{90}-induced leukemia from a constantly maintained level of Sr^{90} is essentially identical with that dealt with here for determining the component of the spontaneous incidence of leukemia owing to natural background radiation. Thus, the incidence of Sr^{90}-induced leukemia in a stationary population maintaining a constant level of 0.1 MPC of Sr^{90} is con-

Table 8. Summary of the estimates of the probability of radiation-induced leukemia per individual per rad per year.

Source of estimate	Type of radiation	Region irradiated	Types of leukemia produced	Probability of leukemia of specified type per individual per rad (or rem) to region irradiated per year		
				Estimated range		"Best" estimate
				Lower limit	Upper limit	
Atom-bomb survivors	Gamma rays plus neutrons	Whole body	All	0.7×10^{-6}	3×10^{-6}	2×10^{-6}
Ankylosing spondylitis patients	X-rays	Spine	Granulocytic (only?)	0.6×10^{-6}	2×10^{-6}	1×10^{-6}
Thymic enlargement patients	X-rays	Chest	Lymphocytic (only?)	0.4×10^{-6}	6×10^{-6}	1×10^{-6}
Radiologists	X-rays, radium, etc.	Partial to whole body	All (?)	0.4×10^{-6}	11×10^{-6}	2×10^{-6}
Spontaneous incidence of leukemia (Brooklyn, N.Y.)	All natural background sources	Whole body	All (?)		10×10^{-6}	2×10^{-6}

sidered to be the product of (i) a dose rate of 0.1 to 0.2 rad per year to red bone marrow; (ii) a mean age for the stationary population of 31.7 years, which is that expected from the age distribution of the total U.S. white population as of 1 July 1955 (*57*); and (iii) a probability of leukemia of bone marrow origin of 1×10^{-6} per individual per rad to bone marrow per year. This computation gives an incidence of three to six cases of Sr^{90}-induced leukemia per million per year. For a population of 1.6×10^{8} individuals, the current population of the U.S., the expected number of cases of leukemia induced by a constantly maintained level of 0.1 MPC of Sr^{90} would thus be about 500 to 1000 per year. The range for this estimate is a factor of about 3, giving 150 to 3000 cases per year. Currently (1954), there are about 10,500 deaths from leukemia per year in the U.S. population (*10*). Thus, if Sr^{90} induces leukemia of bone-marrow origin at the same rate (per rad) as x-rays and radiations from atomic bombs, then a constantly maintained level of 0.1 MPC of Sr^{90} would be expected to increase the present incidence of leukemia (in the United States) by about 5 to 10 percent.

Summary

Leukemia in man can be induced by ionizing radiations and also occurs spontaneously. For the "average" individual in a population, the probability of developing radiation-induced leukemia is estimated to be 2×10^{-6} per rad (unit of absorbed dose of radiation) per year. The available data from four independent sources make it likely that this estimate is valid within a factor of about 3, giving a range from 0.7×10^{-6} to 6×10^{-6} per rad per year. It is pointed out that 10 to 20 percent of the spontaneous incidence of leukemia (Brooklyn, 1943–52) may result from radiation from natural background sources. It is estimated that a 5- to 10-percent increase in the current spontaneous incidence of leukemia would occur if the population were to reach and maintain a body level of Sr^{90} amounting to one-tenth of the "maximum permissible concentration."

References and Notes

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34. The 1950 distribution is based only on radiologists listed in the section of the 1950 *American Medical Directory* devoted to membership in radiological societies. Each name in that list was looked up in the main body of the directory to determine year of birth and type of specialization. Only those listed as "R*" (an asterisk signifies that practice is limited to radiology) and resident in the continental U.S. were used in compiling the final age distribution. This procedure therefore fails to include radiologists who were nonmembers of radiological societies; however, this deficiency has been taken into account by establishing that the 12 deaths from leukemia from 1943–52, inclusive, were in fact radiologists whose names were listed in the section of the 1940 or 1950 directory devoted to membership in radiological societies. (I am indebted to Alethea Miller, Janet Chaitkin, and Ioan Lewis for assistance in compiling the 1950 age distribution.)
35. The procedure was to obtain a list of deaths of members of one of the leading radiological societies and to search for the cause of death in the death notices of the *Journal of the American Medical Association.* In the period 1949–52, inclusive, only some 70 percent of all such deaths were found to have a cause of death listed. In order to have a conservative estimate of the incidence of leukemia, no correction for this defect is attempted. The four deaths from leukemia in the 1949–52 period have the following volume and page locations in the afore-mentioned journal: 144, 407; 147, 1065; 148, 218; 151, 488.
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