The Role of Natural Radiations In Human Leukemogenesis

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Abstract: Some 3 billion years ago, life arose from a warm pool of primordial ooze amid a constant drizzle of radiation. Steadily, man evolved from the lesser forms of life because of or in spite of his natural background-radiation environment. This study is an attempt to determine to what extent these background radiations are responsible for human disease, namely leukemia. Dose rate data were compared with data on all forms of leukemia in the 50 United States for four population subgroups. For the total U.S., no relation between background radiation and leukemia is apparent. A positive correlation appears, however, if various states are deleted from the analysis. It appears that conditions relative to populations and their environment could mask a radiation effect if in fact one is present. (Am. J. Public Health 66:31-37, 1976)

Introduction

Since the beginning of the nuclear age, the general public has harbored an intense fear of radiation. From its inception in 1945 through its first decade, the nuclear age was synonymous with death and destruction. The second and third decades of the nuclear age saw the development of many peaceful uses of nuclear energy including medical diagnostic and therapeutic procedures and the production of electricity by nuclear power.

During these three decades, much knowledge was gained about the biological effects of high doses of radiation given for short periods of time. This knowledge came from careful observations of controlled experiments on animals, accidental exposures involving humans, therapeutic exposures to humans, and survivors of atomic bombs. Much less has been learned about the biological effects of chronic exposures to low doses of radiation. With the proliferation of radiation sources such as nuclear power plants, there is a growing need for quantitative assessment of human health hazards from small amounts of ionizing radiation.

Presently, we must *assume* there is always a health hazard associated with radiation exposure even at the smallest doses. However, there are benefits to be realized from the productive exploitation of this form of energy. Thus, the problem comes down to balancing the *benefits derived* against the *risks involved*. This is a problem for several reasons: benefits may be difficult to describe and to measure; the person who receives the benefits may not be the one who takes the risks; and, the type and degree of risk are difficult to assess.

Of the several types of radiation-induced somatic effect, malignancies are the most important because they are most feared and they appear to be increased by smaller doses of radiation than do the many other somatic effects.[1] Data pertaining to the induction of malignant diseases by ionizing radiation are most complete for leukemia because: (1) the strength of the association between incidence of leukemia and radiation dose is greater than for other malignancies; (2) the forms of leukemia produced by radiation are usually fatal and easily traced; and, (3) the latent period between radiation exposure and medical diagnosis is shorter for leukemia than for other malignant diseases, *i.e.*, less than 5 years.[2]

Today, we are certain that ionizing radiation plays a role in human leukemogenesis but several principal questions remain:

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1. What are the mechanisms by which the energy absorbed from radiation produces overt diseases?
2. What is the importance of related factors such as environment, sex, age, and race?
3. What is the relation between incidence of leukemia and radiation dose, especially at very low doses?

This paper addresses only the latter point.

Background

The General Dose-Response Relation

For high doses and high dose-rate exposures, the relation between radiation and leukemia is clear. The best data are those from the Atom Bomb Casualty Commission in Japan which provide dose-specific analyses of leukemia in bomb survivors. For Hiroshima, the dose-response is reasonably linear: one rem of ionizing radiation is observed to increase the incidence of leukemia approximately two cases per year per million exposees.[3] This linear relation applies to doses around 100 rem and downward to 20–50 rem. Assessment of radiation risk below this range requires the guesswork of extrapolation.

Even this large, thoroughly studied population of irradiated Japanese (116,968 survivors in the two cities, and 46,799 controls) fails to provide an unequivocal description of the dose-response relation for leukemia. While the dose-leukemia relation for Hiroshima appears linear, that for Nagasaki is apparently non-linear and possibly has a threshold.[2] The observed differences of radiation response between these two populations may reflect differences in fissionable bomb material used, errors in dosimetry, or epidemiological differences between the populations of these two cities.

The next best set of data on irradiated humans is that of the ankylosing spondylitics (13,352 patients).[4] These patients and others such as children irradiated for enlarged thymus glands, patients irradiated for hyperthyroidism, and early professional radiologists, to mention a few, fail to shed light on the shape of the dose-response relation, especially at low doses. These irradiated populations are so varied that their radiation exposure is the one common factor by which they are united. They are not much help.

Today, experts do not agree on the shape of the dose-response curve for leukemia, but enlightened theories suggest three, perhaps four possibilities. Figure 1 illustrates our synopsis of the possible forms of the leukemia-dose curve at doses less than 5000 mrem (<5 rem). The curve on the left (Response [R] $\propto D^{0.5}$) represents the form suggested for populations heterogeneous in their radiation sensitivity wherein the most radiosensitive subgroup of that population responds dramatically to very low doses.[5] This form has attracted few proponents. The next form to the right ($R \propto D^{1.0}$) represents the "linear hypothesis" and serves as the basis of the radiation safety guides under the presumption that it will provide estimates of the upper limit of risks associated with los dose irradiation. The third curve to the right ($R \propto D^{2.0}$) is a typical quadratic and is supported by many studies such as those directed toward chromosomal radiation damage.[6] These first three possibilities all imply that there will be some biological response to any radiation dose greater than zero. The fourth possibility, the 'Threshold' response, suggests that a dose exists below which leukemia or other radiation response will not be induced. The concept is an attractive one and is supported by well-confirmed non-linear responses to radiation in the experimental literature.[2] In human radiation carcinogenesis the threshold concept may have value in the design and interpretation of studies, but its application to the establishment of guidelines for radiation safety must be avoided until all uncertainties have been eliminated.

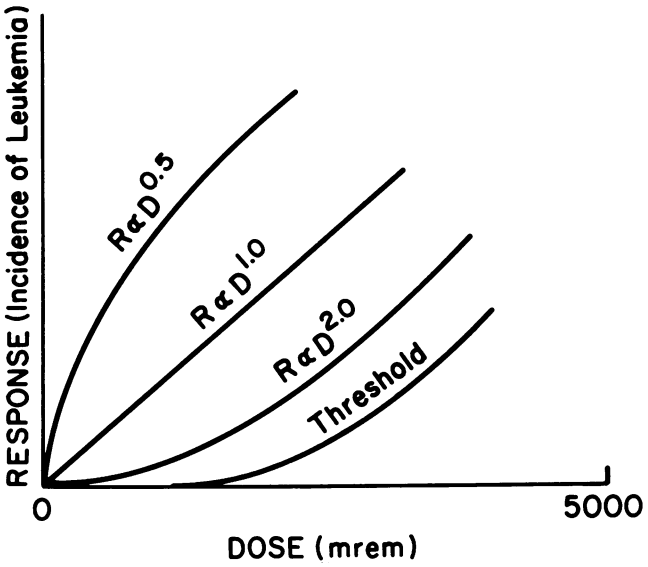

FIGURE 1: Theoretical shapes of the dose-response relation to leukemia below 5000 mrem. Response (R) $\propto D^{0.5}$ = "hyperlinear", $R \propto D^{1.0}$ = linear, $R \propto D^{2.0}$ = quadratic.

Before moving to the relation between leukemia and natural radiations, a brief review of some typical dose-rates will place the discussion in perspective. Table 1 compares typical

TABLE 1—Radiation Dose Rates in Perspective

SOURCES	DOSE RATE (mrem/year)
Natural (US)	
Terrestrial	
Cosmic	60-150
Internal	
Medical Diagnosis	55
Nuclear Power & Explosives (to year 2000)	<5
Color Television	0.5
Radiation Safety Guides	
Occupational	5000
General Public	
Maximum	500
Average	170

dose-rates from some common sources against those of the current radiation safety standards. Note that the dose limit of 500 mrem/year is the *maximum* allowable for any member of the general public; the *average* citizen is allowed no more than 170 mrem/year. Official radiation protection committees and other experts believe that even by the year 2,000 the average citizen will receive less than 5 mrem/year from man-made radiation sources exclusive of medical diagnostic radiation.[2, 7]

Leukemia and Background Radiation

One approach to establishing "safe" radiation standards has been based on the philosophy that exposure to man-made radiation at levels considerably less than the natural radiation dose-rate of about 120 mrem per year will produce additional effects but that these will be *less in quantity* and *no different in kind* from those which man has experienced and has been able to tolerate throughout his evolution.[8] In time we will know accurately the background radiation dose-rates to humans and, likewise, we will know accurately the dose contribution to humans from man-made sources. If we can determine to what extent background radiation contributes to human disease, we will have an effective means of assessing the risks associated with very low doses of ionizing radiation.

A variety of studies have been done to establish these risks. MacMahon and Clark[9] studied the incidence of leukemia attributable to irradiation from natural background sources by using an assumed dose-rate of 100 to 200 mrem/year, the mean age of people in the borough of Brooklyn (33.7 years), and an estimated probability for radiation-induced leukemia of 2×10^{-6} cases per person per year per rem. Using 64.4 cases per million per year as the total spontaneous incidence for leukemia, they conclude that 10 to 20 per cent of the spontaneous incidence for leukemia is attributable to background radiation.

In 1960, Wesley concluded that ". . . at least 96 per cent of all deaths due to congenital malformation are caused by background radiation."[10]

Court-Brown, et al,[11] have studied the possible relationship between background radiation in ten areas of Scotland. Direct measurements of background radiation were compared to leukemia death rates for those areas for the period 1939 to 1956. Residents of Aberdeen received an average bone marrow dose of 101 mrem/year and recorded a leukemia death rate of 46 per million persons per year. Residents of Dundee received a lower dose-rate (86 mrem/year) and recorded fewer leukemia deaths (29 per million per year). Residents of Edinburgh received lower dose-rates but recorded a leukemia death rate higher than residents of Dundee. The authors concluded that while a correlation between background radiation and leukemia seemed likely, they doubted that radiation accounted for much more than 1 per cent of the observed differences in mortality. They also expressed doubt that dose-rates of 100 mrem/year or less are even leukemogenic.

Variations in the neonatal death rates in selected areas of the western United States have been studied with reference to geologic environment and the presence or absence of known uranium and helium reserves. While the neonatal death rate is unquestionably higher in the mountain regions, this does not appear to be attributable to higher levels of terrestrial radiation. A significant positive relationship does exist between death rate and altitude, however. This effect may be related to cosmic ray intensity or hypoxia, both of which vary with altitude.[12]

Very recently, Mason and Miller conclude that ". . . background radiation either does not affect human cancer mortality, or that the increase is too small to be detected among the many other factors influencing occurrence and diagnosis."[13] Similarly, Eckhoff, et al, believe that if background radiation is a contributing factor to leukemia mortality its influence is much smaller than other leukemogenic agents.[14] Frigerio, et al, reaches a similar conclusion.[15]

Method

As a contribution to the issue of whether doses and dose-rates similar to those of our ambient radiation environment increase the risk of leukemia, we have compared recent data for the average dose-rate due to terrestrial, cosmic, and internally deposited sources for each state of the United States[16] against static geographic distribution of all forms of leukemia in four different population subgroups for each state.[17] The comparisons are found on Table 2.

Figure 2 is presented as an example of the method used in our analysis. Static geographic distribution for each state, for all types of leukemia, and for the white male is plotted against each state's total external dose-rate arranged in increasing order. The 8 Rocky Mountain states and Alaska are indicated and will be referred to below. Data are lacking for dose-rates below about 60 mrem/year (Florida is lowest with 63 mrem/year).

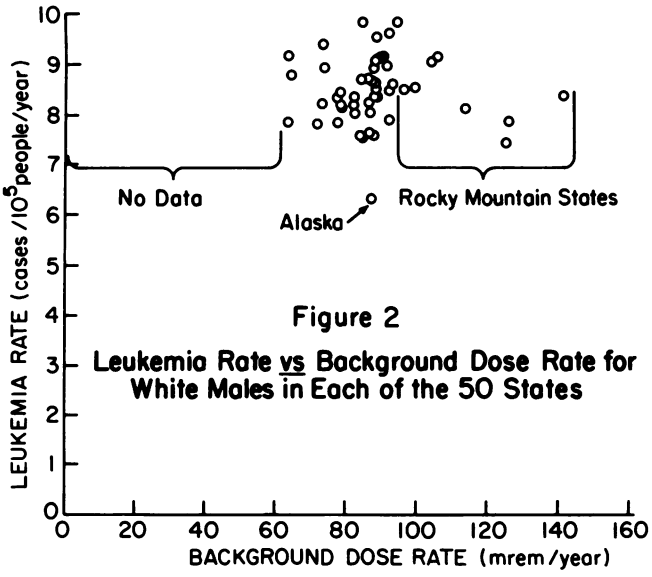

Figure 2
Leukemia Rate vs Background Dose Rate for White Males in Each of the 50 States

FIGURE 2: Leukemia cases vs. background dose rate for each of 50 United States. These data are for white males only.

TABLE 2—Static geographic distribution of all leukemia deaths in four population subgroups for each of 50 states[17] compared to the background radiation dose-rate for each state.[16]

State	Dose Rate (mrem/year)	(Age adjusted death rate per 100,000) Male white	Male nonwhite	Female white	Female nonwhite
FL	63.4	7.87	4.80	4.94	3.34
LA	63.9	9.19	5.81	5.59	4.55
MS	64.5	8.77	5.00	5.88	3.37
DE	72.0	7.82	4.83	5.89	2.92
DE	72.0	7.82	4.83	5.89	2.92
MD	73.3	8.23	5.89	5.56	3.66
AR	73.4	9.39	4.49	5.63	3.25
TX	73.6	8.92	5.52	5.75	4.15
AL	77.4	8.37	4.86	5.50	3.29
VA	77.7	7.83	5.01	5.29	3.85
CA	78.6	8.47	6.39	5.76	4.37
PA	78.8	8.19	6.55	5.63	3.77
SC	78.9	8.15	4.52	5.55	3.33
GA	82.2	8.17	3.97	5.29	3.34
NC	82.4	8.01	5.82	5.62	3.63
TN	82.8	8.36	5.71	5.48	3.76
RI	84.2	7.57	6.47	5.27	1.50
NJ	84.6	7.58	5.08	4.95	3.87
IL	84.7	8.72	5.83	5.73	4.22
MN	84.9	9.83	7.11	6.58	5.19
NY	86.6	8.71	6.04	5.91	4.00
MA	86.7	8.24	6.63	5.53	3.44
HI	86.9	6.66	6.54	4.96	5.01
KY	87.0	8.04	6.38	5.14	3.91
AK	87.2	6.31	3.39	4.97	2.33
OH	87.3	8.68	6.49	5.68	4.46
ME	87.5	7.61	9.22	4.80	1.39
WA	88.0	8.92	5.23	5.80	3.87
MO	88.1	8.36	5.85	5.64	4.39
IN	88.2	8.36	6.49	5.62	3.79
VT	88.4	8.64	17.16	5.66	10.86
NH	88.6	9.08	0.0	5.8	13.46
MI	88.8	8.53	6.35	5.46	3.61
OR	88.9	9.54	4.17	5.69	7.44
WI	89.3	9.06	6.35	6.04	5.20
IA	90.2	9.17	7.23	6.09	4.99
OK	90.8	9.15	6.43	5.92	3.94
KS	91.9	8.95	7.84	5.74	4.16
NE	92.1	9.62	6.04	6.27	7.69
WV	92.4	7.90	5.90	5.39	3.43
CT	92.5	8.51	6.57	5.64	3.69
ND	93.1	8.62	3.15	5.32	3.26
SD	94.6	9.81	3.25	5.96	3.84
AZ	96.7	8.49	6.02	5.26	3.39
NV	99.6	8.55	8.29	5.09	1.91
MT	104.6	9.04	7.87	6.14	1.11
ID	106.0	9.16	6.65	5.77	5.05
UT	114.0	8.11	2.89	5.39	5.17
NM	125.5	7.44	3.81	5.07	1.16
WY	126.1	7.86	3.63	4.72	3.02
CO	142.0	8.37	8.74	5.55	3.31

Plots of leukemia rate versus radiation dose-rate, similar to the example shown in Figure 2, were made for the other three population subgroups studied. Regression analyses for all of the population subgroups of Table 2 provide the data for Table 3.

TABLE 3—Slopes and Correlation Coefficients for Four U.S. Population Groups. Background Dose Rates vs. Static Geographic Distribution of All Forms of Leukemia.

Group	Slope	Correlation Coefficient	t	Per Cent Confidence Level
White male	−0.0026	−0.056	0.389	30
Non-white male	+0.0070	+0.043	0.298	22
White female	−0.0038	−0.147	1.030	68
Non-white female	−0.1529	−0.261	1.873	93

Slope units: Cases all leukemia/10^5/yr / mrem/yr

Discussion

An analysis of the values in Table 3 leads us to conclude that no correlation exists between leukemia and radiation dose-rates between 60 and 142 mrem per year. One method of testing the linearity of data with an associated correlation coefficient is to test the hypothesis that the correlation coefficient equals zero. This is equivalent to testing the hypothesis that the slope of a line drawn through the data points equals zero.[18] A zero slope suggests no dependence of the y values on the x values. This means that if the hypothesis that the correlation coefficient equals zero can be accepted, then there is no linear relationship. By calculating confidence levels and noting if they include zero, the test hypothesis can be accepted or rejected. For a 95 per cent confidence level and 50 data points, it is necessary to have a correlation coefficient with an absolute value grewer than 0.28 to assume there is any linear relationship using this test. This holds true for a 99 per cent confidence level when the absolute value of the correlation coefficient is greater than 0.37. this indicates that even at the lower confidence level of 95 per cent, there is no linear relationship between leukemia and background radiation in the United States using data presented here.

Assuming that the data actually do produce zero slope, we have constructed Figure 3 as a means of placing our data into perspective with other data pertaining to radiogenic leukemia. There is no longer any doubt that ionizing radiations increase the risk of leukemia in exposees.[1-4] The extent of this risk for humans is estimated to be between 1 and 2 extra cases of leukemia per million exposees per rem of exposure per year at risk.[19, 20] The extensive data of the Atomic Bomb Casualty Commission show that in Hiroshima a significant excess of leukemia was observed at and above doses of 20 to 49 rem. In Nagasaki, the excess leukemia was not statistically significant below about 100 rem.[21] Thus, estimates of leukemia risk for adults are scientifically reliable only within the range of observations above 20 rem or so. Any statement about this risk below 20 rem is likely to be seriously in error.

Notwithstanding this caveat, we wish to present another approach to the question of whether the public radiation safety standard of 170 mrem/year is safe or not. In Figure 3, the incidence of leukemia for the U.S. is plotted against the radi-

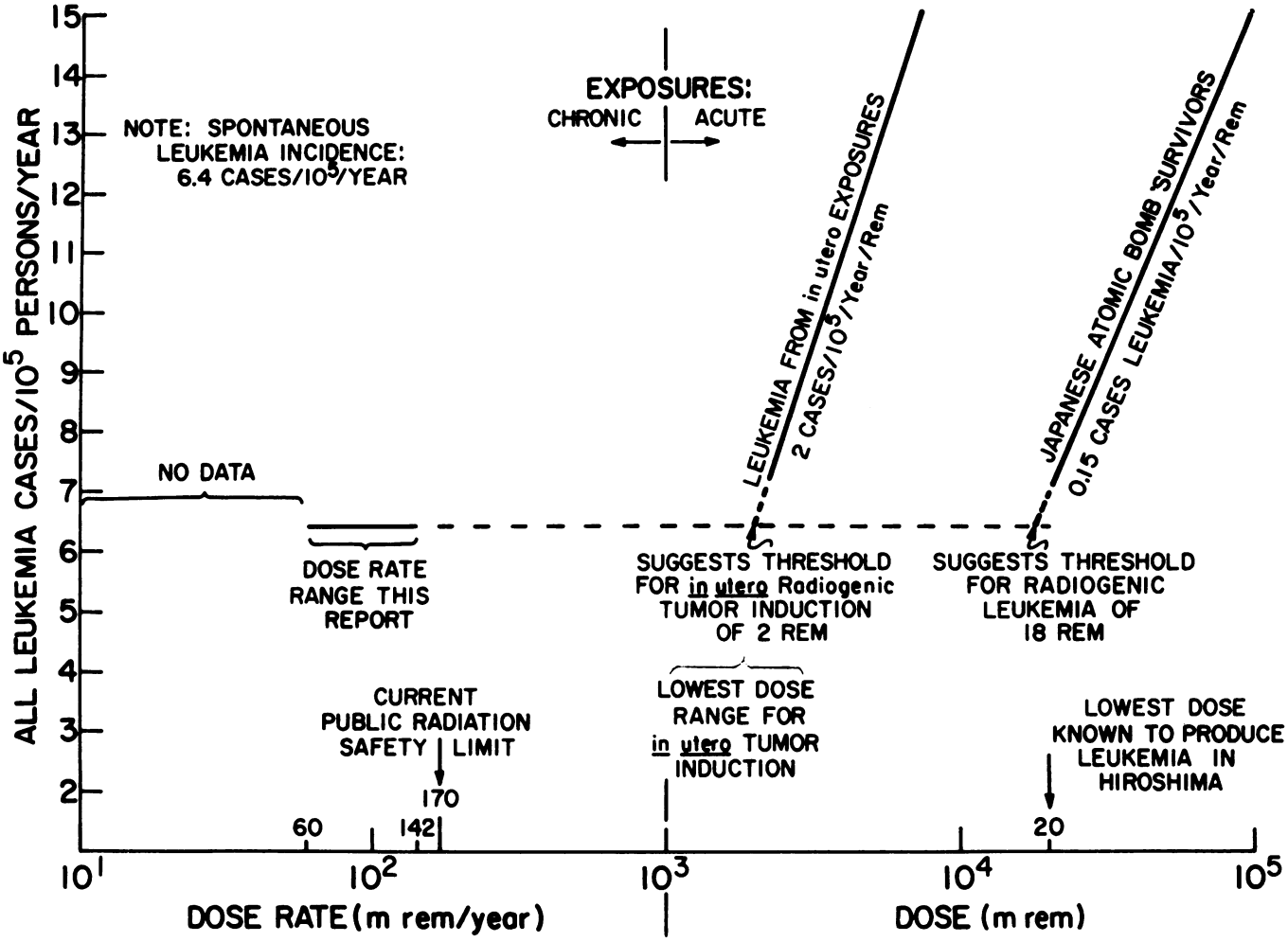

FIGURE 3: Leukemia cases vs. dose-rate (left) and dose (right) for three sets of data: data from this report; antenatal exposures; and Japanese exposures. Dashed lines represent extrapolation beyond reliable data.

ation dose-rate for three sets of data: ours, antenatal or *in utero* exposures, and the Japanese exposures. Several points about Figure 3 are important: (1) Below dose-rates of about 60 mrem/year there are few, if any, reliable data that show any bioeffects whatsoever. No data exist for radiogenic leukemia below this dose-rate. (2) Our data cover the dose-rate range between 60 and 142 mrem/year. The average leukemia incidence over this range and the incidence of spontaneous leukemia are the same ($6.4/10^5$/year). (3) Just to the right of the highest dose-rate we studied lies the public radiation safety limit of 170 mrem/year. The question remains whether this limit is safe or not.

If the zero-slope line of our data is extrapolated to the right in Figure 3, it intersects the Japanese data at about 18 rem. Since no leukemia was produced in Japan below about 20 rem, this intersect suggests a threshold for radiogenic leukemia of about 18 rem for "average" adults. The radiation safety limit appears to be safe by a factor of 100, at least for adults.

However, the overall risk per rem for radiogenic leukemia is greater for antenatal exposure than for children or adults.[22] This risk factor is estimated to be as high as 2 cases/10^5 exposed *in utero*/year/rem.[1] As with the analysis of Japanese data, consideration of an especially radiosensitive population subgroup such as embryos lowers the leukemia "threshold" to about 2 rem. Thus, the safety factor is reduced to 10. This threshold value is strengthened by the fact that the lowest doses known to produce tumors *in utero* lie between 1 and 3 rem.[23] We assume the mechanisms for induction of solid tumors and leukemias are similar. Thus, our analysis tends to support the threshold hypothesis for the shape of the leukemia-dose relationship at very low doses, presented in Figure 1. Because of a lack of confidence in data which support the threshold hypothesis, risk estimates have been and still are being made by *assuming* the dose-response relationship is linear and extrapolates to zero effect at zero dose.[2]

It is believed by many that a threshold shape can arise for at least three reasons: (1) no effect whatsoever occurs at doses below the threshold; (2) even though effects occur, no effect is *measurable* below the threshold for technical reasons related to minimum detectable levels of damage; and (3)

at low doses and dose-rates biological repair processes expunge damage before it reaches detectable levels.

The latter point is most important. A coeval radiobiological axiom states that reduction of the dose-rate by protraction and fractionation of exposures over extended time periods generally permit marked recovery of cells and tissues from radiation-induced damage.[24] In other words, at dose-rates comparable to background radiation exposure, especially for electromagnetic radiations, repair of pre-cancerous damage may be sufficient to alter the slopes of the dose-response relationships by amounts significantly different from those measured at acute doses above about 100 rem or so. Our data correspond to very low dose-rates whereas data for *in utero* and Japanese exposures derive from acute irradiations. Thus, Figure 3 is divided into halves: the left half represents doses in mrem delivered more or less uniformly over a period of a year; the right half represents doses in rems delivered in periods less than a day. The importance of dose-rate in producing biological damage diminishes at low dose rates.[2] To quote from the BEIR report:

> "The dose rate characteristic for background radiation (approximately 0.1 rem/year) is one-hundred-million to one-billion times lower than the dose rate at which effects have been observed in most irradiated study populations. At background radiation levels, ionizing events in individual mammalian cell nuclei occur at a rate of much less than one per day, whereas at the higher dose rates mentioned, ionization events occur in cells at a frequency of the order of 2600 per second. This enormous difference may have important implications with respect to the production of radiation damage within cells and its repair at the molecular level. On the basis of the likelihood of such repair, the risk of cancer induction at low doses and low dose rates might be expected to be appreciably smaller per unit dose than at high doses and dose rates, as has been observed to be the case in certain radiation-induced tumors of experimental animals." (BEIR, p 88)

The radiation safety limits of 170 mrem/year is comparable to background radiation dose-rates and should not produce effects beyond those caused by background levels. Levels substantially above the U.S. background dose-rates such as those in Kerala, India, where the average dose-rate is about 1300 mrem/year have not produced statistically significant effects in the human population.[25] It is important to note that the average exposure to U.S. citizens even by the year 2000 will not approach the safety limit but will very likely amount to less than 5 mrem per year in spite of continued nuclear power facility proliferation.[7]

A variety of factors could mask a leukemogenic radiation effect at background dose-rates if, in fact, one exists. For example, the exposure to individuals in each state is not uniform but varies for several reasons. Altitude, geological structures, and living habits can produce marked changes in average dose-rates.[16] The dose-rate values used in our analysis were based on aerial radiation surveys of selected areas within each state. Surface dose-rates were calculated from measurements taken at various altitudes. Other calculations were made on the basic knowledge of the distribution of the population with elevation. Still other calculations were made using published data of internal radioactivity in persons. The range of dose-rates in the United States is 40 to 300 mrem/year. Most of the population, however, receives less than 170 mrem/year.[16] Thus, values of average dose-rates are the best available but fall short of representing dose-rates to individuals. Studies such as those suggested by Becker are needed.[25]

An inverse relationship between elevation and mortality from leukemias and lymphomas has been reported.[27] These studies did not show an effect of the altitude-dependent cosmic ray intensity on leukemia mortality. However, there does seem to be a positive association between size of metropolitan areas and the reported mortality of leukemia and lymphoma. Our unpublished data show no such association.[28]

Gentry, et al, reported a relation between the incidence of congenital malformations and the presence of radioactive rocks.[29] Grahn and Kratchman feel that the high neonatal death rate in mountain regions is not due to radiation but due to the reduced partial pressure of oxygen at higher altitudes.[12]

Other factors which could mask an effect of radiation on leukemia induction include: different cancer rates among different socioeconomic groups, variations in susceptibility among different ethnic groups, mobility of people, presence of other leukemogenic factors besides radiation, variations in the standards of diagnosis from state to state, consanguinity, differences in the extent of health care and reporting methods, and variations among medical diagnostic radiation exposures which average about 55 mrem/year for U.S. citizens.

Conclusion

Our approach to estimating the leukemogenic risks due to background radiations leads to the same conclusion that other before us have reached; that is, if a risk is present, it is much smaller than that from other leukemogenic agents. Thus, it is difficult for us to believe that the current radiation safety standard is not adequate. We estimate that this standard is safe by between a factor of 10 and 100. Further, if other effects of radiation are considered, we expect their frequency of occurrence per unit exposure and the consequences to human health to be considerably less than that for leukemia.

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SEVENTH FACULTY INSTITUTE ON MEDICAL CARE SCHEDULED

The Seventh Faculty Institute on Medical Care, sponsored by the American Public Health Association, will be held June 14-25, 1976, at the University of Michigan, Ann Arbor.

The Institute, designed to expand knowledge of and promote research on medical care organization, will be conducted by a nationally known faculty. It offers a course in medical care concepts and issues and eight specialized courses: epidemiologic basis of health services, health economics, politics of health care, quality assurance, organization of ambulatory health services, international perspective of health policy issues, health law, and the organization of services for long term illness.

Attendance to the Institute is open to individuals with teaching, research, or administrative responsibilities in medical schools, schools of public health, programs of hospital administration, and other health professional schools, and to other qualified individuals with significant responsibilities in health program administration.

Individuals who have previously attended the course on medical care concepts and issues, or an equivalent course, may register for the specialized courses, and may choose three of the eight offerings.

A tuition fee of $400.00 will be charged. Early registration is advised, since enrollment in the program is limited. Applications may be obtained from: Barbara Black, Department of Medical Care Organization, M3150, School of Public Health, University of Michigan, Ann Arbor, MI 48104.