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INCIDENCE OF LEUKEMIA IN PHYSICIANS

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INTRODUCTION

Early in the history of roentgen and gamma rays, it was noted that excessive exposure of the hands or other parts to high-energy radiation resulted in a dermatitis, which in some cases developed into carcinoma. In 1902 Frieben (1) reported the first case of radiation carcinoma, and in 1911 Hesse (2) was able to bring together reports on 94 such cases. Radiation injury to the blood and hemopoietic tissues was likewise noted at an early date. In 1904-5 Heineke (3), working with animals, observed degenerative changes in bone marrow both of the lymphoid and myeloid series. In a number of instances since that time, leukemia has been reported in human beings who have worked with high-energy radiation. Because of the similarity in character of the damage caused in hemopoietic tissues to that caused in epithelium and because epithelial damage in some cases resulted in malignancy, authors were quick to recognize the possible etiologic significance of radiation in leukemia.

In 1942 Dunlap (4) reported that 24 cases of leukemia in radiation workers were found in the literature:

The 24 victims ranged in age from 29 to 53 years; 20 were men and 4 were women. All had had years of occupational exposure to radiation and several showed radium or roentgen burns of the hands. In 4 of the cases, leukemia followed exposure to radioactive substances and in the remaining 20 it was described as occurring in roentgenologists, radiologists and their assistants, who presumably had been working with X-rays. In 7 of the cases the condition was diagnosed as lymphatic and in 13 as myelogenous leukemia; in 4 the

type was not specified. The disease in these patients did not differ in character and course from spontaneous leukemia. ***Only 3 autopsies are described, and many of the reports give such scanty details that the authenticity of the cases is open to question (4, p. 577).

Somewhat stronger evidence that radiation may bear a causal relationship to leukemia comes from experimental work with animals. Krebs, Rask-Nielsen, and Wagner (5) were the first to study this problem. They treated mice with X-rays and found the incidence of lymphomatosis among 5,500 irradiated animals to be 3.5 per thousand and that among nonirradiated controls to be 0.6 per thousand. Furth (6) gave whole-body treatments of 400 r single exposures at intervals of approximately 1 month and found an increase in leukemia (myeloid and lymphoid) of more than threefold. Hueper (7), using hard X-rays, gave general-body treatment to mice, doses up to 480 r being given in a 6-week interval, and observed an incidence of leukemia as high as 74 percent (in animals which he states had a high but unknown normal incidence of leukemia). Furth and Furth (8) gave single or repeated doses of 200 to 400 r of X-rays to the whole bodies of mice and observed an increase in myelosis of eightfold and in mediastinal lymphomatosis of sevenfold. The actual incidence of lymphomatosis and myelosis, however, did not exceed 13.7 and 7.6 percent, respectively. In work dealing with dosage in the induction of leukoses, Henshaw¹ found increases which in some cases exceed any thus far reported.

¹ Unpublished data.

There are, then, two types of evidence suggesting that high-energy radiation may increase the incidence of leukemia: (1) The fact that this disease has occurred in radiation workers under conditions resembling those in which radiation carcinoma has developed; and (2) the fact that the incidence of leukemia in animals has been increased experimentally by exposure to X-rays.

None of this evidence, however, furnishes any direct proof that radiation actually acts as a carcinogenic agent in the induction of leukemia in human beings. Although leukemia has been seen in persons having radiation employment, this fact alone cannot be taken as *prima facie* evidence that radiation incited the disease. It can be said only that it may have acted as the inciting agent. Since the leukemia found in irradiation workers appears to differ in no significant respect from that found in other persons and since the experimental investigation of this question is not possible in human beings, the problem is not open to direct study and necessitates the use of less direct methods.

As one approach, it would be desirable to compare statistically the incidence of leukemia in two groups of individuals, one occupationally exposed to significant amounts of radiation and the other not so exposed. The most suitable exposed group for such a study would be radiation engineers, miners of radium ore, radiation physicists and technicians, radiologists, etc. So far as we know, however, satisfactory health and death records are not available for significantly large groups of such persons.

Since true leukemia is eventually fatal, a study of deaths from leukemia gives a direct measure of incidence of the disease. Hence it would appear that further information might be obtained by utilizing the death notices of physicians, published each week in the Journal of the American Medical Association, and comparing the results obtained with similar material for the general population, taken from the vital statistics of the United States Bureau of the Census. Although many physicians never work with X-rays or radium and although the

population as a whole includes all persons exposed to high-energy radiation as well as those who are not, it may be presumed that physicians as a group are more exposed to radiation than is the average for the total population. With these points in mind, we undertook to determine the incidence of leukemia in the two groups under conditions as nearly comparable as possible with the available sources of data.

EXPERIMENTAL PROCEDURE

A survey was made of the death lists given in the Journal of the American Medical Association for the 10-year period 1933-42, inclusive, and a record made of various items, as shown in table 1. The various types of leukemia as given in the journal are listed and taken together constitute the main object of interest in this study. The other diseases listed are of related interest, but since appropriate control data are not available, deaths attributed to them are being placed on record for possible future use only. The table also gives the number of deaths that were published; the number of deaths for which causes were given; and the number of deaths from cancer (all types) and also the percentage of deaths.

Because death rates vary with age and because age distributions of the test and control groups may differ in certain respects, it was necessary to obtain age distributions in order that comparisons could be made on an age basis. In table 2, the usable data of table 1 have been arranged according to 5-year age groups. Table 2 gives the number of deaths from all causes, the deaths from cancer, the deaths from leukemia, the ratio (in percentage) of deaths from leukemia and deaths from cancer (all types), and the ratio (in percentage) of deaths from leukemia to total deaths.

It was necessary to select from the material for the general population the kind of data most suitable for comparison, as the Bureau of the Census gives separate listings by sex and color as well as by age. Although the incidence of leukemia is higher in female and in colored groups, and although the physicians'

TABLE 1.—Deaths of physicians¹

Cause of death	Number of deaths during the years—										Total
	1933	1934	1935	1936	1937	1938	1939	1940	1941	1942	
Leukemia.....	4	5	10	4	5	10	7	8	3	1	57
Lymphatic leukemia.....	1	1	6	3	6	4	7	3	3	3	37
Myelogenous leukemia.....	5	3	2	2	2	5	4	9	3	3	41
Monocytic leukemia.....	0	0	0	2	0	2	1	1	2	0	8
Total.....	10	9	18	12	13	21	19	21	13	7	143
Lymphosarcoma.....	1	3	4	2	2	1	7	3	5	4	32
Lymphoblastoma.....	1	0	0	0	0	0	0	0	4	2	4
Myeloma.....	2	2	0	0	0	0	3	0	4	2	13
Hodgkin's disease.....	5	7	4	4	4	5	8	1	2	4	44
Aplastic anemia.....	0	2	1	1	1	7	5	1	4	1	23
Pernicious anemia.....	11	11	5	6	5	12	10	9	9	3	81
X-ray burn.....	2	1	3	3	1	0	1	0	1	1	13
Total deaths..... number.....	3,355	3,392	3,492	3,583	3,393	3,748	3,882	3,640	3,482	3,331	35,298
Deaths (causes given) number.....	2,740	2,688	2,722	2,822	2,571	2,967	2,917	2,637	2,488	2,241	26,788
Deaths from cancer (percent) ²	8.3	8.2	8.4	7.9	8.6	9.5	9.7	10.0	11.0	9.9	9.1

¹ Compiled from death notices in the *Journal of the American Medical Association*, 1933-42, inclusive.

² All types, including the leukemias, lymphosarcoma, lymphoblastoma, and myeloma, but excluding Hodgkin's disease.

³ Based on deaths for which cause was given.

group includes females and colored persons, material for white males was selected as most suitable, and no corrections were made for the female and colored components.

The Bureau has from time to time changed its methods of classifying and reporting data. Because of such changes in 1939, the data for 1939 and 1940 were selected as most satisfactory for our purposes, inasmuch as this 2-year period was near the middle of the interval in which we were interested and the number of deaths was large. The figures are shown in table 3, the same plan of presentation being used as in table 2. The values for deaths from cancer (all types) pertain to the total of the two groups listed in the mortality reports under the headings Cancer and Other Malignant Tumors (rubrics 45-55) and Leukemia (rubric 74).

RESULTS

The totals in table 2 show that 26,788 physicians, for whom the cause of death was given, died during the period studied; 2,443 of these deaths were due to cancer, and of these 143 were due to leukemia. Thus, 0.53 percent of the total deaths and 5.9 percent of the deaths from cancer were ascribable to leukemia. Table 3 shows that 1,361,786 white males of the general population, for whom the

cause of death was given, died during 1939-40; 144,840 of the deaths were due to cancer, and 5,286 to leukemia. In this case, 0.39 percent of the total deaths and 3.6 percent of the deaths from cancer were attributed to leukemia.

TABLE 2.—Deaths of physicians¹

Age range (in years)	Deaths with cause given	Deaths from cancer (all types) ²	Deaths from leukemia ³	Ratio of deaths from leukemia to deaths from cancer	Ratio of deaths from leukemia to deaths with cause given
	Number	Number	Number	Percent	Percent
20-24	19	1	0	0	0
25-29	257	11	4	36.4	1.56
30-34	449	30	12	40.0	2.67
35-39	551	32	8	25.0	1.45
40-44	866	48	8	16.7	.92
45-49	1,243	93	9	9.7	.72
50-54	1,948	135	13	9.6	.67
55-59	3,049	279	15	5.4	.49
60-64	3,963	395	25	6.3	.63
65-69	4,207	433	22	5.1	.52
70-74	3,720	400	12	3.0	.32
75-79	3,061	321	9	2.8	.29
80-84	2,102	191	4	2.1	.19
85-89	974	60	1	1.7	.10
90-94	323	14	1	7.1	.31
95-99	44	0	0	0	0
100-	12	0	0	0	0
Total or percent	26,788	2,443	143	5.9	.53

¹ Compiled from the deaths listed in the *Journal of the American Medical Association* for the period 1933-42, inclusive.

² Including the leukemias, lymphosarcoma, lymphoblastoma, and myeloma, but excluding Hodgkin's disease.

³ Leukemia and lymphatic, myelogenous, and monocytic leukemia.

⁴ Based on totals.

TABLE 3.—Deaths in the general population¹

Age range (in years)	Deaths with cancer given	Deaths from cancer (all types) ²	Deaths from leukemia ³	Ratio of deaths from leukemia to deaths from cancer	Ratio of deaths from leukemia to deaths with cause given
	Number	Number	Number	Percent	Percent
0-4	123,892	975	491	50.4	0.396
5-9	11,488	607	273	45.0	2.38
10-14	11,752	514	202	39.3	1.72
15-19	19,059	789	228	28.9	1.197
20-24	23,559	899	160	17.8	.679
25-29	24,835	1,084	165	15.2	.664
30-34	28,494	1,541	179	11.6	.628
35-39	35,611	2,396	225	9.4	.631
40-44	48,946	4,445	274	6.2	.560
45-49	70,330	7,748	370	4.8	.526
50-54	94,657	12,252	443	3.6	.468
55-59	114,450	16,201	453	2.8	.396
60-64	133,224	20,023	558	2.8	.419
65-69	152,526	22,466	472	2.1	.310
70-74	155,631	21,632	371	1.7	.238
75-79	140,306	17,230	267	1.5	.191
80-84	103,997	9,657	127	1.3	.122
85-89	50,391	3,513	21	.6	.042
90-94	15,331	739	7	.9	.045
95-99	2,896	129	0	0	0
100	411	0	0	0	0
Total or percent	1,361,786	144,840	5,286	3.6	.39

¹ Compiled from U. S. Bureau of the Census reports for 1939-40.
² Including the leukemias, lymphosarcoma, lymphoblastoma, myeloma, but excluding Hodgkin's disease.
³ Leukemia and lymphatic, myelogenous, and monocytic leukemia.
⁴ Based on totals.

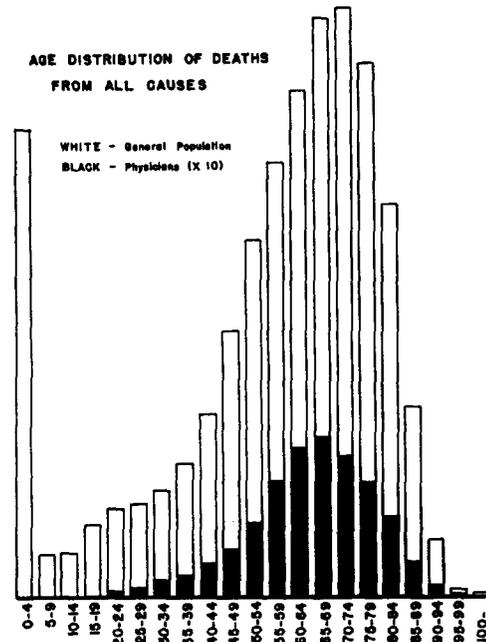


FIGURE 1.

AGE DISTRIBUTION OF DEATHS FROM LEUKEMIA

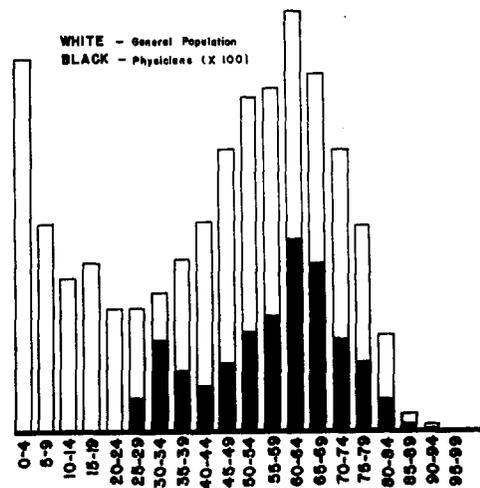


FIGURE 2.

While these findings provide one type of comparison, it was apparent that more reliable comparisons could be made by analyzing the data on an age basis. Figure 1 shows the age distribution of deaths from all causes, the data being taken from tables 2 and 3. The values for physicians have been increased by a factor of 10 for the graph in order that the distribution can be seen more plainly.

The picture for the general population is the familiar one, the number of deaths being high in infancy, relatively low during childhood, but increasing again with age to a peak at 65 to 75 years of age. As would be expected, there were no deaths among physicians before the age of 20. Beyond this age, the distribution of deaths was generally similar to that for the general population except that the greater number of deaths occurred at a slightly earlier age, 60 to 70 rather than 65 to 75.

Figure 2 shows the age distribution of deaths from leukemia. In this case the values for physicians were increased by a factor of 100 to facilitate visual comparison. This graph shows that the number of deaths from leukemia (for the general population) was high in early childhood, that it dropped to a low at the ages of 20 to 30, and that it rose again,

reaching a peak at 60 to 65. Above the age of 40, the material for physicians showed essentially the same pattern.

In the last two columns of tables 2 and 3, the ratios of deaths from leukemia to deaths from cancer, and of deaths from leukemia to deaths from all causes are given for the different age groups. The values obtained for ages up to and including 84 were plotted in figures 3 and 4,

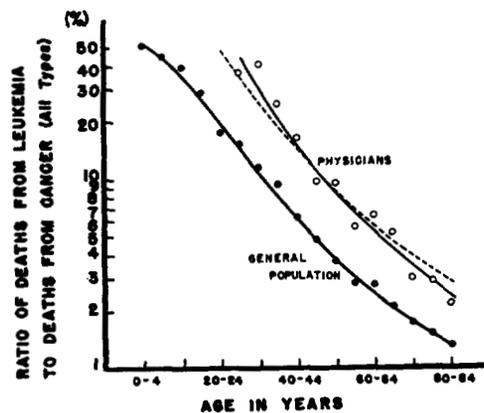


FIGURE 3.

respectively. Beyond the age of 84 the data were too unstable to be of interest.

In figure 3 the curves for the general population show that approximately 50 percent of all cancer deaths in persons under 5 years of age were due to leukemia and that as age increases, the ratio of leukemia to total deaths decreases. The curve for physicians follows the same general course but lies distinctly above that for the general population, indicating a higher incidence of leukemia. The solid line shows the best smooth curve that could be drawn among the points by inspection, and the dotted line is drawn with a constant relationship to the curve for the general population. The fact that the points in the two cases follow so nearly a parallel course when plotted on a semilogarithmic scale shows that the factor of difference for the two groups was nearly constant for all ages.

The extent of difference may be obtained by ascertaining the ratio at some representative age. By taking this at 60,

where the curves are most stable, the incidence of leukemia in physicians was found to be 2.2 times greater than in white males of the general population.

In figure 4, deaths from leukemia are compared with total deaths. In the general population, the ratio of deaths from leukemia to deaths from all causes is relatively low during infancy, high during childhood, and drops off rapidly during adolescence. The lowness of the point for 0-4 years might appear at first to be at variance with the results in figure 3. However, it should be understood that its location is determined largely by high infant mortality from causes other than cancer. Beyond the age of 25, the ratio of deaths from leukemia to deaths from all causes decreases with age. Again, all the points for physicians fall distinctly above the curve for the general population. Although the first three points for the physicians' data appear to be proportionately higher than the other points, it must be remembered that the data for the youngest as well as the

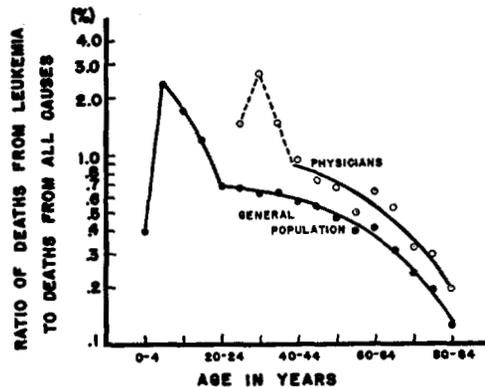


FIGURE 4.

oldest age groups are less stable than those for the intermediate. For the age period 40 to 84 years the physicians' curve was drawn with a constant relationship to the curve for the general population. Since this curve fits the points as well as any that could be drawn, the relative incidence of leukemia in the two groups can be determined by taking the ratio at any point along the

curves. It was found in this case to be 1.5 times higher in physicians.

Thus, from two types of comparison, the incidence of leukemia in physicians was found to be higher than in the general population (2.2 and 1.5 times higher, respectively, by the first and second methods). Since, however, the differences observed were entirely relative, it was impossible to say whether they were due actually to more leukemia or to less deaths from other causes in physicians. From tables 2 and 3 (age groups 40 to 84, inclusive) it may be determined that only 9.5 percent of the physicians died of cancer while 13.0 percent of the general population died of this malady, indicating that the difference in part at least was due to less cancer in physicians.

In order to test the data still further, a third method of analysis was used. In this case, the death ratios were calculated. Figures for the total population were obtained from the Census Reports for the year 1940, and figures for leukemia (table 3) were adjusted to give the average number in 1 year. The death ratios from leukemia in the total population were then calculated for the 5-year age groups from 25 to 74 years, all above 74 years being grouped. The values were plotted in figure 5 as solid circles. Similar figures for the number of physicians living during the year 1940 were obtained from unpublished compilations of the Division of Public Health Methods, United States Public Health Service, and related to the figures for leukemia in physicians (table 2), the latter being divided by 10 to give the average yearly incidence. Death rates based on these values are plotted as open circles in figure 5.

Again the points for physicians fall above those for the general population. The best smooth curve was drawn by inspection through the points for the latter. From further inspection, it became apparent that the best curve through the points for the data for physicians would run nearly parallel to that for the general population and also that the ratio of difference in incidence would be very nearly 1.5, the same as that obtained by comparison on the basis of deaths from all

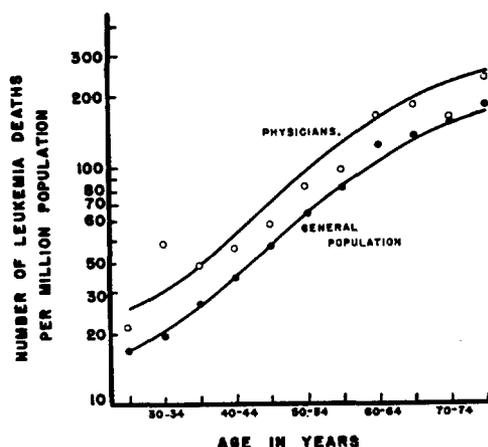


FIGURE 5.

causes. The upper curve, therefore, was drawn to show a constant difference of 1.5. When the curve is dropped so that an equal number of points in this middle section appears on either side, the ratio becomes 1.3; but this value needs further correction.

Table 1 shows that while 35,298 physicians died during the period 1933-42, the cause of death was reported for only 26,788, or 76 percent. Thus, since the control data obtained from the Public Health Service pertained to all physicians living in the period considered, it was clear that all the points for the data for physicians (fig. 5) should be raised by a ratio of 76:100. When such adjustments were made, the value 1.3 was changed to 1.71. This figure may be taken as the best estimate made on the basis of death rates; and since it is intermediate to those obtained previously, it probably represents the most satisfactory figure indicating the relative incidence of leukemia in physicians that can be obtained at this time.

DISCUSSION

It is recognized at the outset that the methods of obtaining and reporting data used by the American Medical Association and the United States Bureau of the Census are not identical. Since physicians' deaths are reported mainly as news items, the deaths are sometimes announced before a statement as to the cause of death is at hand. As already

indicated, the cause of death was given in only 26,788 of the 35,298 cases reported, a difference of 8,510. If we assume that leukemia might be more promptly reported than other causes (causes which might reflect on the integrity of the individual) and if we go so far as to assume that none of the 8,510 doctors had leukemia, on the basis of the age distributions at our disposal, the differences observed would be reduced appreciably although in no case would they disappear completely.

This matter was taken up with the American Medical Association, and we were told (1) that the association exercises no selection whatsoever in reporting causes of death, and (2) that the records concerning causes eventually become very nearly complete. In order to answer the question whether selection of some kind was inadvertently exercised by friends or relatives reporting the deaths, the association very kindly went through its more complete files for the year 1942 and obtained figures for leukemia. The total figure was 18 (leukemia, 4; myelogenous leukemia, 6; lymphatic leukemia, 8; monocytic leukemia, 0), whereas our total was 7 (table 1). It should not be presumed that so great a difference would be maintained for the other years if complete data were available, as table 1 shows that our value of 7 is unusually low for 1942. It seems unlikely, therefore, that any selection was used either inadvertently or otherwise, and that the differences observed would not be significantly reduced if complete information on physicians were available.

Very few published data are available pertaining to the incidence of leukemia among physicians. One report (Decennial Supplement, Part IIa, Occupational Mortality, Report of the Registrar General of England and Wales, 1931) shows that five deaths from leukemia occurred among English and Welsh physicians, ages 20-65, where three would have been expected on the basis of ages of all males in those years. Of related interest was the fact that males in the professional classes as a whole had an incidence of leukemia 53

percent above the average, whereas the unskilled workers had an incidence 15 percent below the average. In a comment on these observed differences it is stated:

Differing precision of diagnoses of these diseases in the different social strata might account for some part of these variations, but it seems unlikely that it could account for the great contrasts which are observed.

Whether or not differences in these incidence rates of leukemia are in any way attributable to radiation is unknown, but the results of this English study make it desirable that data pertaining to physicians be controlled by data on professional groups not potentially exposed to radiation. This could not be done with the material at our disposal.

If we accept the available evidence that leukemia is higher among physicians than among the general population, it does not follow necessarily that radiation acted as the inciting agent. Eventually it may be found that some factor quite apart from radiation is responsible for the apparent higher incidence. It has been suggested that if radiation were responsible for the greater proportion of leukemia in physicians, the continued exposure during their lifetimes should produce a continually increasing difference with age, making the curves (figs. 3, 4, and 5) divergent. But until more is known about the mechanism of radiation-induced neoplasia (the significance of dosage, rate of administration, methods of exposure, biologic factors, etc.), it will be impossible to discuss this feature with profit.

Perhaps the most significant aspect of this study is the fact that the findings are in accord with experiments with animals. Animals receiving single or repeated doses of a few hundred r showed a higher incidence of leukemia. Judging from the series of recent reports dealing with the problem of stray radiation around X-ray and radium units (9-13), we find that doses in the same range are frequently received by operators in a period of days, months, or years. The full meaning of the data presented can

become apparent only after further developments.

SUMMARY

A comparison was made of the incidence of leukemia in physicians and in the general population.

Data were obtained from the death lists of the Journal of the American Medical Association, from the mortality reports of the United States Bureau of the Census, and an unpublished compilation of the United States Public Health Service.

Comparisons were made on the basis of (1) the ratio of deaths from leukemia

to deaths from cancer, (2) ratio of deaths from leukemia to total death rates, and (3) death rates from leukemia.

Leukemia was recognized approximately 1.7 times more frequently among physicians than among white males in the general population.

Possible discrepancies in the data were discussed.

While these observations furnish no direct proof that radiation acts to incite leukemia in human beings, they are, nevertheless, in accord with the findings on experimental animals in which exposure to X-rays has been found to increase the incidence of leukemia.

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