LEUKEMIA IN RADIOLOGISTS IN A 20 YEAR PERIOD

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Some experimental evidence has been presented to show that exposure to ionizing high energy irradiation (by Roentgen irradiation) can produce leukemia. Heineke[10], Ziegler[21], and Fischer-Wasels[3] reported that the general irradiation of mice with Roentgen rays caused a myeloid transformation of the tissues of the spleen. Calò[1] observed the appearance of large histocytic infiltrations in the organs of white mice which had been exposed to small doses of Roentgen rays. Krebs, Rask-Nielson, and Wagner[16] found that among 10,500 normal mice there occurred 6 cases of the leukemic state (0.058%), while among 5550 subjected to Roentgen rays, there were 19 cases (0.36%). These authors do not attempt to distinguish between a true leukemia with peripheral blood changes, an aleukemic lymphadenosis, a lymphosarcoma, or a leukosarcomatosis, because of the various gradations that may exist between these different forms. Furth, Seibold, and Rathbone[8,9] found that most, if not all, resistant strains of mice can be made susceptible to transmissible leukemia through exposures to single or repeated doses of Roentgen rays. Furth[4] further showed that myeloid leukemia rarely occurred in his mice unless they were irradiated. Of 481 controls, 2 died of myeloid leukemia; of 385 irradiated mice, 21 died with myeloid leukemia, a 13-fold increase. In a subsequent study, Furth and Furth[7], using 1290 controls and 775 irradiated mice, found that irradiation produced 8 times the incidence of myelosis (6.8% as against 0.9%). In the majority of cases there was a conspicuous invasion of the circulating blood by immature myeloid cells (leukemia). Generalized lymphomatosis with or without blood involvement likewise occurred more often after irradiation in all of the 3 stocks that they used, but this increase was only 2-fold.

Hueper[13] found that total irradiation of a highly susceptible strain of cancer mice with small doses of Roentgen rays resulted in a marked increase in the incidence of leukemia that normally occurred (74% as against 19%) in animals of the strain used. He thought that hyperplastic myeloid or lymphoid proliferations were transformed into leukemic ones by the effect of Roentgen rays upon the regenerative activity of these tissues. Henshaw[11] gave repeated moderate single doses at 4 week intervals and found more than a 4-fold increase in incidence of leukemia (in its broader sense) in a moderately susceptible strain of mice. Furth and Boon[6] found that the leukemogenic action of methylcholanthrene was greatly enhanced by preirradiation with doses of Roentgen rays (175 r), which alone rarely produces leukemia, and the onset of leukemia occurred in a shorter interval. Kirschbaum and Kaplan[15] point out that the problem of leukemogenesis in mice is very complex: 1, multiple agents (Roentgen rays, carcinogens and other chemical agents, estrogens) can produce leukemia; 2, mice of only certain genetic constitution are sus-

ceptible to only certain agents; 3, genetic susceptibility to one agent, or to the spontaneous disease, cannot necessarily be correlated with susceptibility to other leukemogenic agents. Furth[5], in a comprehensive review, states that from a survey of the literature it appears that Roentgen rays are weak leukemogens (relative to other experimental agents) and act after a relatively long incubation period. In all of the above experimental procedures, the Roentgen rays initially exert a destructive influence on the leukopoietic foci, following which there is a period of regeneration in which frequent mitotic figures are seen and abnormal forms are produced. Persistence and multiplication of the latter produces the leukemic state.

In a more recent study, Lorenz *et al.*[17] have investigated the effect of prolonged low-dosage irradiation on mice, guinea pigs, and rabbits in an attempt to determine tolerance ranges. They found in mice that the time in which leukemia (lymphoma) appears is approximately the same for those animals receiving up to 2.2 r per 8 hours per day as in the controls, and the percentage incidence was also the same. With somewhat larger doses there was an earlier onset of leukemia, and with 8.8 r per 8 hours per day not only was the onset much earlier but there was a 70% incidence instead of a 45% incidence. The authors prefer to explain this higher incidence on the basis of the earlier onset, thinking that otherwise susceptible mice in the less irradiated group might have died of other causes before the onset of leukemia. Exception might be taken to this interpretation. The results in guinea pigs and rabbits are not given, but in a subsequent paper Lorenz[18] states that no increase of leukemia incidence was observed in the guinea pigs or rabbits. He notes, however, that the number of animals used in these latter experiments is small. From his experiments Lorenz[18] concludes that "in spite of the statistical evidence (of the increased incidence of leukemia in radiologists) reported, the data obtained in (my and my associates') experimental animals do not seem to support the view that chronic irradiation (of the amounts to which I believe radiologists are exposed) will induce leukemia in man unless one is willing to assume differences in the susceptibility and the mechanism of leukemia induction in humans." That such an assumption may not be entirely out of order is indicated by the known differences in susceptibility found in different strains of mice, and the species difference in susceptibility demonstrated in the varying results obtained in mice, guinea pigs and rabbits in these experiments.

In a companion study to the preceding, on the same animals, Jacobson and Marks[14] studied the peripheral blood findings in these animals and found no peripheral lymphocytosis occurring in any of the 3 species. A lymphopenia as the result of chronic low-grade irradiation was the consistent finding and the earliest abnormality noted.

What might be regarded as a form of clinical corroboration of the relationship between Roentgen ray exposure and increased incidence of leukemia in humans was presented several years ago when this writer[19] pointed out that the incidence of leukemia (in its narrower sense) was more than 10 times as great in radiologists as in non-radiological physicians. This difference was shown to be statistically significant. The present report is a continuation of the previous study and includes the ensuing 5 year period, 1944 to 1948, inclusive. The same method was followed as in the previous paper, extreme care being

taken to obtain as complete figures as possible and to avoid any duplication or the inclusion of any non-pertinent subjects. For a more detailed discussion of the method, reference can be made to the previous paper. It is probable that a very few of those listed as radiologists (but none of the leukemia cases) were in reality surgeons or other specialists who were members of one of the national radiological societies. This factor would tend to dilute slightly the actual incidence rate for bona fide radiologists.

During this 5 year period, the deaths of 15,762 United States physicians were reported in the Journal of the American Medical Association. During this same period, the Directory fluoroscopy very extensively in physiological research from the earlier days of these modalities. He developed leukemia cutis (mycosis fungoides) for which he received Roentgen therapy over a period of 15 years. In the obituary notice appearing in the Journal of the American Medical Association, he is reported to have died of leukemia, but in the one appearing in the American Journal of Roentgenology and Radium Therapy, the cause of death is said to have been a malignant lymphoma, apparently from more positive information. Since it has been the policy in this study to include only positive leukemia cases, this case was excluded. Likewise, no other case of lymphosarcoma was included.

TABLE 1.—RADIOLOGISTS DYING OF LEUKEMIA

Initials	*Date of Death*	*Type of Leukemia Recorded*	*Age*	*Location*
N. J. N.	July 2, 1948	Acute	67	Sioux Falls, S. D.
L. G. A.	May 28, 1948	Myelogenous	57	Kansas City, Ka.
R. H. S.	May 16, 1946	Acute	78	Detroit, Mich.
E. R. B.	June 16, 1946	Chronic Myelogenous	58	Cincinnati, Ohio
C. W.	May 29, 1945	"Leukemia"	68	Boston, Mass.
A. W. J.	Aug. 8, 1945	"Leukemia"	52	New York, N. Y.

Report Service of the American Medical Association listed 19,529 deaths, the discrepancy resulting from the fact that the Journal does not publish an obituary for every physician who dies. Since, however, our present interest is in causes of death, the Journal's figures are being used. Leukemia was reported as the cause of death in 119 of these. During the same period, 124 radiologists died; in this group (all of whom had the cause of death recorded) 6 were reported as dying of leukemia, as indicated in Table 1.

In Table 1 might have been included Dr. W. B. C., who was not strictly a radiologist but a renowned physiologist. However, he was a member of the American Roentgen Ray Society and had used Roentgen rays and

It is seen from these figures that the incidence of leukemia in non-radiological physicians for this 5-year period is 113 in 15,637 (0.72%). The incidence of leukemia in radiologists during this period is 6 in 124 (4.84%). These percentages approximate those reported for the preceding 15-year period in both non-radiological physicians (0.44%) and radiologists (4.57%). This serves as some additional confirmation of the validity of the claim that the figures previously presented were statistically significant. The combined figures for the 2 decades 1929 to 1948 inclusive become: 65,922 non-radiological physicians died, of whom 334 died of leukemia. During this same 20-year period, 299 radiologists died, of whom 14 had leukemia. The over-

all incidence for non-radiological physicians is 0.51% and for radiologists 4.68%.

It is thus seen that the incidence of leukemia in radiologists is over 9 times as great as in non-radiological physicians. This order of increase is larger than was obtained in most of the experimental work on mice. In spite of the relatively low incidence rate in man, both groups under consideration, the non-radiological physicians and the radiologists, are now sufficiently large and the statistics cover a sufficient number of years for this difference in incidence rate to bear the stamp of validity. Moreover, by applying the same statistical analytical evaluation as in the previous paper (expansion of the binomial $(p + q)^n$ to the appropriate term) it is found that this term equals 1×10^{-9}, indicating that there is only 1 chance in a billion of the observed increased incidence rate of leukemia in radiologists being coincidental.

It has been observed[2,12] that the incidence of leukemia is almost twice as great in physicians as a whole as in the general adult male white population. The writer[20] has pointed out that the bulk of this increase was due to the inclusion of radiologists in the statistics for physicians, and that when only non-radiological physicians were considered, the increased incidence is only slight and might perhaps be accounted for by the rather considerable number of non-radiological physicians who use fluoroscopes, Roentgen-ray machines, radium, and now radioactive isotopes in their clinical or investigative work.

This occupational hazard of radiology indicates that: 1, the hazard was not sufficiently appreciated, and insufficient care was exercised to employ standard means of protection against ionizing radiation; or 2, these standard means of protection are insufficient protection; or 3, they are too difficult to employ correctly in routine work. In this connection, the work of Archer at the University of Virginia is interesting. He has lately developed and exhibited a gown made of spun lead glass that affords much more complete protection to the body than conventional lead apron and gloves.

Summary. 1. The experimental work showing an increased incidence of leukemia in mice exposed to Roentgen irradiation has been reviewed.

2. The study of the incidence of leukemia in radiologists has been extended to cover a 20 year period.

3. It has been shown that during this time leukemia has occurred more than 9 times as frequently in radiologists as in non-radiological physicians.

4. This difference has statistical significance.

5. It is suggested that the increased incidence of leukemia in physicians as a whole (compared with the adult male white population) might be due to the same factor of exposure to ionizing radiation.

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