

procedures described (2) and contained a blue fluorescent material having the properties of aflatoxin. Thus, it appears that an aflatoxin-producing strain of *A. flavus* has been isolated from domestic peanuts (7).

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### Leukemia, Multiple Myeloma, and Aplastic Anemia in American Radiologists

**Abstract.** A survey of 425 death certificates of radiologists dying between the ages of 35 and 74 during the years 1948 to 1961 reveals a statistically highly significant excess of deaths from leukemia, multiple myeloma, and aplastic anemia. That this excess is due to radiation exposure (or to some factor acting in a similar manner), rather than to an artifact of diagnosis is suggested by the absence of deaths ascribed to chronic lymphatic leukemia.

It has never been excluded that the excessive number of deaths from leukemia in American radiologists (1-3) is largely or wholly an artifact of diagnosis. For example, leukemia might have the same probability of occurrence in a radiologist as in a member of the general male population, but have a higher probability of being accurately diagnosed in a radiologist owing to such factors as his more ready access to medical facilities. A way of testing such a possibility became evident when Court Brown and Doll (4) discovered that one form of the disease, namely, chronic lymphatic leukemia (CLL), is apparently either not induced by ionizing radiation, or is much less readily induced than are the forms of this

disease in which other types of cells are affected. Their finding was based on leukemia deaths arising in a group of adult British males who had received x-ray therapy for an arthritic condition (ankylosing spondylitis). Among 28 such deaths only one was reported as due to CLL; yet, as will be discussed below, this type of leukemia is one of the commonest forms of the disease in adult white males. More recently, Pochin (5) cites only one death reported as being due to lymphatic leukemia (subchronic) among 17 deaths from leukemia arising in a group of adults who had received radioiodine therapy for hyperthyroidism.

Evidently, if radiation (or some other agent acting in a similar manner) is responsible for a rise in the death rates for leukemia in a given population, the death rate for chronic lymphatic leukemia in that population should rise little, if at all. On the other hand, if diagnosis is responsible, the death rate for CLL should rise proportionately, since diagnosis ought not to affect classification by histological cell type differentially.

This report presents the principal findings of a study designed to answer three interrelated questions. (i) Do excessive numbers of deaths from leukemia continue to occur in American radiologists in recent years? (ii) If so, does the number of deaths from CLL occur in accord with expectation based on radiation or on diagnosis as the responsible factor? (iii) Do excessive numbers of deaths occur in this group from diseases related to leukemia?

To assess the significance of an observed number of deaths from a given cause it is first necessary to determine the composition, with respect to age and size, of the living population that produces such deaths, and then to compute the number of deaths expected in that population had it been subject to the mortality of some standard reference population. The living population of radiologists chosen for study is restricted to those physicians who are listed in the biennial editions of the *Directory of Medical Specialists* (DMS) (6) as being certified by the American Board of Radiology. Punched cards showing name, year of Board-certification, and year of birth were prepared for all such individuals residing in the continental United States and having entries in the 1950 and 1960 editions of these directories (7). Similar cards, showing also year of death, were pre-

pared for Board-certified radiologists who were known to have died in the study period and whose names appeared in one or more of the DMS editions spanning the years 1948 to 1960, inclusive. The resulting deck of cards, after elimination of duplicates and of cards bearing female names, provided the basic data for computing the composition, with respect to age, of the living male population as of July 1 of each year of the 14-year period, and for each year of age from 35 to 74, inclusive (8). The results, by 5-year age groups, for representative years, 1950, 1955, and 1960, are shown in Table 1. The estimated number of male radiologists aged 35 to 74 years, inclusive, increased from 2167 in 1948 to 4713.5 in 1961; for the entire 14-year period the number of man years at risk at these ages was 47,348.

The U.S. white male population was the standard chosen for the present study. It is the ultimate population from which the radiologists are drawn and it is the only relevant population for which sufficient data are available to calculate death rates for the rather rare diseases here under study.

Death rates for leukemia and related diseases categories in the U.S. white

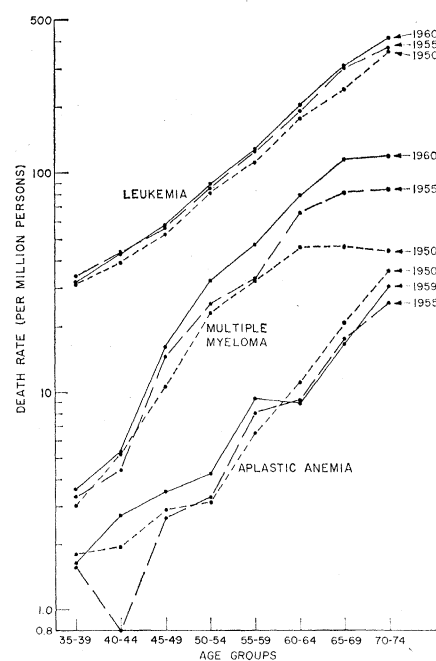


Fig. 1. Death rates, with respect to specific age and cause, in the U.S. white male population (deaths per million living persons per year) for selected years of the study period (semi-log plot) (11). Death rates for aplastic anemia for each age group below age 50, and for multiple myeloma for each group below age 40, are based upon 20, or fewer, deaths.

male population were computed for each 5-year age group between 35 and 74, inclusive, and for as many years of the study period as the data permitted (9) (Fig. 1).

The population of deceased radiologists was identified by two methods: by scanning the death notices in the *Journal of the American Medical Association* for any reference to radiology, and by matching all the names of radiologists entered in the 1950 or 1954 DMS editions with all such names in the 1960 edition (10). The first method yielded the names of 426 individuals who were listed as Board-certified radiologists in one or more of the DMS editions from 1948 to 1960, inclusive, and whose deaths could be substantiated by means of death certificate sources as having occurred between the ages of 35 and 74, inclusive. The second method yielded the names of two more such individuals; for one, the name appeared in the death notices of the *Journal* without mention of radiology; for the other, no death notice could be found but a death certificate was located.

Certified copies of death certificates were obtained for all but three of the 428 deaths located in the population under study (11). Selection of the main cause of death from the group of causes usually listed on the death certificate was then made by following the international rules for coding the cause of death (12).

In Table 2, the observed number of deaths for which the main cause was leukemia or a related disease is compared with the corresponding expected numbers calculated by applying the death rates (with respect to specific age and year of death) in the U.S. white male population for the disease category in question to the number of living radiologists at risk (13). Also shown are values of the "mortality ratio," defined in the usual way as the ratio of the observed number of deaths from a given cause to the number expected had the population at risk been subject to the mortality experience of the standard (14).

It is evident that the observed 12 deaths from leukemia greatly exceeds the expected number of 4.02. The probability of observing 12 or more deaths under these circumstances can be obtained from the Poisson distribution and has a value of 0.001. The mortality ratio for leukemia is 3.0 (12:4.02); however, the limits for

Table 1. The percentage composition, according to age, of the population of male radiologists for selected years. The estimated total number of living radiologists between the ages of 35 and 74, inclusive, for these years were: (1950) 2542.0; (1955) 3353.0; (1960) 4571.5 (7).

Age	1 July 1950	1 July 1955	1 July 1960
35-39	27.0	22.8	26.8
40-44	21.2	24.3	19.9
45-49	15.6	17.8	18.6
50-54	11.3	12.1	13.3
55-59	10.3	8.4	8.8
60-64	7.4	6.9	5.6
65-69	5.0	4.8	4.3
70-74	2.2	2.8	2.8

such a ratio are wide. The 95 percent Poisson confidence limits for the 12 observed deaths are 6.2 and 21.0 deaths; it follows that the true mortality ratio for leukemia is not likely to be lower than 1.5 (6.2:4.02) nor higher than 5.2 (21.0:4.02).

It becomes important, as already noted, to compare observed and expected numbers of deaths from chronic lymphatic leukemia in the present study population. On the basis of the death rates for lymphatic leukemia in the U.S. white male population for the years 1949 (15), 1951, and 1956 (9), the only years for which data are available, roughly 4.4 deaths among the 12 leukemia deaths in the population under study are expected to be of the lymphatic type (16). Although death rates for CLL as such are not tabulated, it is known from studies of MacMahon and Clarke (17) that among adult white males (in Brooklyn) the vast majority of cases of lymphatic leukemia are of the chronic rather than of the acute type. Among the 12 deaths from leukemia in the present study, only one was reported as being due to the lymphatic type and this case was further specified (on the death certificate) to

be acute rather than chronic. The failure of any of these 12 deaths to be ascribed to CLL suggests that radiation exposure rather than diagnosis is the principal factor responsible for the excessive number of deaths from leukemia in this population (18). It is, of course, possible that some other factor (or factors) which acts in the same manner as radiation, is responsible.

For certain lymphomas such as Hodgkin's disease, lymphosarcoma, and lymphoblastoma, the observed numbers of deaths in the population under study occur in reasonable agreement with the expected numbers (Table 2). On the other hand, for both multiple myeloma and aplastic anemia the observed numbers of deaths exceed the expected numbers at levels which, statistically, are highly significant (19).

The excessive number of deaths from aplastic anemia in radiologists (4 observed as opposed to 0.2 expected) parallels a similar finding in the study of Court Brown and Doll (4); namely, that an excessive number of deaths from aplastic anemia (12 observed as opposed to 0.3 expected) occurred among patients receiving large doses of x-rays to the spine. Although aplastic anemia is not classified as a cancer (12), some cases of the disease are believed to be identical with aleukemic leukemia—a form of leukemia in which there is an excessive number of white cells in the bone marrow but not in the peripheral blood. Upon review of the 12 deaths ascribed to aplastic anemia in their series, Court Brown and Doll concluded that one-half had been certain or probable cases of aleukemic leukemia.

The excessive number of deaths from multiple myeloma (5 observed as opposed to 1.01 expected) in the population under study has no parallel in other studies of irradiated adults with

Table 2. Mortality among radiologists: deaths attributed to cancers of the lymphatic and blood-forming tissues and from aplastic anemia. Only deaths occurring between the ages of 35 and 74, inclusive, in the 14-year period, 1948 to 1961, are included (12-14, 18).

International code rubric	Principal disease	Number of deaths		P*	Mortality ratio (M.R.)	95% Confidence M.R.
		Observed	Expected			
200	Lymphosarcoma	4†	2.4	>.05	1.7	0.5 to 4.3
201	Hodgkin's disease	1	1.6	>.05	0.6	0.02 to 3.5
202, 205	Lymphoblastoma	1	0.38	>.05	2.6	0.07 to 14.6
203	Multiple myeloma	5	1.01	.004	5.0	1.6 to 11.6
204	Leukemia	12	4.02	.001	3.0	1.5 to 5.2
292.4	Aplastic anemia	4	0.23	.0001	17.0	4.7 to 44.5

\* Probability that the observed number of deaths, or a larger number, would occur by chance. † Includes two deaths from lymphosarcoma, one from reticulum cell sarcoma, and one from malignant lymphoma.

one exception (20). That there may be a real association between radiation and an increased risk of multiple myeloma is supported by the similarity of this disease to aleukemic leukemia. Thus, multiple myeloma is characterized by an excessive proliferation of immature plasma cells in the bone marrow without an excessive count of these cells in the peripheral blood; hence, it is sometimes classified as an aleukemic phase of plasma cell leukemia (21).

It is important to consider why, if radiation increases the risk of multiple myeloma, other studies of irradiated groups have not detected such an increase. Reports of multiple myeloma being a cause of death in individuals under the age of 30 are so rare (22) that only studies of adult individuals are likely to yield significant numbers of cases of this disease. Studies of atom-bomb survivors (23) fail to mention multiple myeloma.

However, deaths from this disease are so rarely reported in Japan (24), that few or no deaths would be expected among such survivors even if their death rate from this disease were many times the normal Japanese rate. The failure of Court Brown and Doll (4) to mention this disease in their series of spondylitic patients may or may not represent a real discrepancy with the present findings; it can be inferred that roughly only four or five deaths from multiple myeloma would be expected in their spondylitic series if the age-specific death rates for this disease had increased to the same proportionate extent as did the age-specific death rates for leukemia in that series (25).

Although an association between radiation exposure and increased risk of multiple myeloma is suggested by the present study, it is not established. Additional studies are needed of the incidence of multiple myeloma in other groups of irradiated adults, such as hyperthyroid patients who have received radioiodine therapy (5). It would also be of value to conduct retrospective studies, along the lines of the ingenious ones of Faber and of Stewart *et al.* (26); that is, the histories of exposure to radiation experienced by multiple myeloma patients would be compared with such histories obtained from various "control" groups such as CLL patients (27).

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6. *Directory of Medical Specialists* (Marquis, Chicago, 1950-1960).
7. When year of birth was not stated, it was readily found in the case of every male radiologist by reference to editions of the *American Medical Directory* (American Medical Association, Chicago).
8. Dates of births were punched to the nearest half-year for the deceased group. For the living population it was necessary to assume that a birth was equally likely to have occurred in the first as in the second half of a year. This accounts for the presence of "half-individuals" (Table 1). Any errors due to wrong assignment to sex are likely to be negligible since only 2.8 percent of the names of Board-certified radiologists in the 1950 and 1960 editions of the *Directory of Medical Specialists* are estimated to be of females.
9. Death rates were computed by dividing the number of deaths in each 5-year age group (obtained from *Vital Statistics of the United States*, U.S. Govt. Printing Office, Washington, D.C. 1948-59) by the latest mid-year census estimates of the living population of U.S. white males (obtained from *Current Population Reports*, Series P-25, Nos. 98, 246, and 265, U.S. Bureau of the Census, Washington, D.C.). The National Vital Statistics Division of the U.S. Public Health Service kindly provided the following unpublished data: deaths of U.S. white males (by 5-year age groups) from leukemia for 1960-1961, from multiple myeloma for 1949-1961, from aplastic anemia for 1950 and for 1953-1959; and deaths of U.S. white males (by 10-year age groups) from lymphatic leukemia for 1951 and 1956.
10. A third method was used, but yielded no additional names. This involved checking the death notices in unpublished annual bulletins of the American College of Radiology, the majority of whose members are Board-certified radiologists. It remains possible that a few deaths occurred that were not detected by any of the three methods.
11. In two cases, death certificates were unobtainable because the place of death could not be traced; in the third case, death occurred outside the U.S. Among the 425 death certificates obtained, four were for deaths occurring outside the continental U.S.; in none of these four cases, however, was death ascribed to causes under discussion in this report.
12. *Manual of the International Statistical Classification of Disease, Injuries and Causes of Death*. Fifth, Sixth and Seventh Revisions. (World Health Organization, Geneva, 1938, 1948, 1955).
13. In this computation the terms of an  $8 \times 14$  matrix of white male death rates (eight 5-year age groups for 14 years of the study period) were identically multiplied by the terms of a similar matrix of the numbers of living radiologists, and then summed over all 112 products. Death rates were calculated for leukemia for the years 1948-1961 inclusive and for multiple myeloma for the years 1949-1961, inclusive. For all other diseases shown in Table 2, the necessary data were lacking for 1948 and for 1960-1961. For these two time periods, death rates for such diseases were assumed to be the same as the corresponding rates for 1949 and for 1959, respectively. The over-all systematic error introduced by using such substituted rates in computing the expected number of deaths of radiologists is believed to be, at the most, a 3 percent under- or over-estimation of the true expected numbers.
14. The value of the mortality ratio for deaths from all causes in the present study population is 0.8. This agrees well with Dublin and Spiegelman's (2) findings for the years 1938-1942, that the class of full-time medical specialists, and the subclasses thereof, including radiologists, each enjoyed lower death rates from all causes of death combined than did the class of all physicians (or of all white males). (See also reference 3). For the present study population, it should be remembered that the value of the mortality ratio for any given cause of death is expected to be less than 1.0 if the radiologists were to enjoy as low a mortality rate for that cause as they do for all causes of death combined.
15. A. G. Gilliam, *Blood* **8**, 698 (1953).
16. In this computation the 1949 rates were applied to the years 1948-1949, the 1951 rates to the years 1950-1954 and the 1956 rates to the years 1955-1961.
17. B. MacMahon and D. W. Clarke, *Blood* **11**, 871 (1956).
18. For four additional deaths in the study population, the death certificates reported leukemia as a contributory rather than as the underlying or main cause of death; among these four, one was listed as lymphatic (chronicity unspecified) and the other as CLL. With these four deaths added to the 12 valid deaths, the ratio stands at one death with mention of CLL to 15 deaths without mention of this type. For still another death in the study population, the Journal death notice listed the cause as "myelogenous leukemia"; however, a certified copy of the death certificate failed to mention leukemia and ascribed death in this case to another cause.
19. An analysis (in preparation) of the distribution of deaths in the study population from leukemia, multiple myeloma, and aplastic anemia by age at death and year of death shows (i) that the observed number of deaths in each age group tends to exceed the expected number to the same proportionate extent that the observed total number of deaths in all age groups exceeds the corresponding expected total number, and (ii) that there is no tendency for the death rates for leukemia and multiple myeloma to decline during the 14-year period; however, for aplastic anemia, all four observed deaths occurred between 1948 and 1953, inclusive.
20. W. Pohl [*Med. Klin. Munich* **55**, 1839 (1960)] reports three cases of multiple myeloma among German medical technicians with long histories of occupational exposure to radiation; however, the statistical significance of such a finding cannot be assessed because no information was provided on composition, in terms of size and age, of the living population of technicians from which the three cases were drawn.
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24. *Deaths from Multiple Myeloma (Plasmocytoma) in Selected Countries by Sex and Age*, Epidemiology and Vital Statistics Rept. No. 8 (World Health Organization, Geneva, 1955), p. 24.
25. In this computation it was assumed that for each 5-year age group in which leukemia deaths occurred in the Court Brown and Doll study, the ratio of leukemia deaths to multiple myeloma deaths would be the same as the corresponding ratios for British males for the years 1950-1952, the only years for which published data (see reference 24) are available.
26. M. Faber, in *Transactions of the 6th Congress of the European Society of Haematology* (Karger, New York, 1957), p. S-211; A. Stewart, W. Pennybacker, R. Barber, *Brit. Med. J.* **II**, 882 (1962).
27. I thank R. Giesen, M. Hershey and S. Hillyard and especially my wife for technical assistance. I thank F. Lawler for writing the programs used to calculate the age composition of, and the expected numbers of deaths in, the study population. This work was supported in part by an institutional grant from the American Cancer Society (IN-39).

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