The Incidence of Leukemia and Related Diseases in Patients with Rheumatoid (Ankylosing) Spondylitis Treated with X-ray Therapy

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In a series of 496 rheumatoid spondylitis patients treated with x-ray, the authors have reported an incidence of leukemia over 17 times greater than expected in a comparable population. No conclusion can be drawn with respect to the exact nature of dose-response relationship in leukemogenesis. Four of the reported leukemias arose from myeloid reticular elements of the bone marrow; the fifth case is of undetermined origin. Since the chief use of x-ray therapy under these circumstances is as an analgesic, it would seem unwise to compound the risk of developing leukemia in these patients by its continued use unless all other forms of symptomatic treatment have failed and the patient and the physician mutually accept the possibility of this increased hazard.

Super le base de 496 patientes tractate con radios X pro spondylitis rheumatoide, le autores reporta un incidentia de leucemia plus que 17 vices plus alte que illo expectate in un comparabile population de controlo. Nulle conclusion pote esser derivate con respecto al exacte natura del relation de dosage a responsa in le leucemiogenese. In quatro del reportate casos, le leucemia habeva su origine in elementos reticular myeloide del medulla ossee; in le quinte, le origine es indeterminate. Viste que le uso principal del radiotherapia sub iste conditiones es illo de un analgesico, il pare pauco sage currer le risco del disveloppamento de leucemia in le patientes rheumatoide per le continue uso de radiotherapia, excepte quando omne altere forma de tractamento symptomatic se ha provate van e quando tante le medico como etiam le patiente es conscie del hasardo inherente e accepta lo.

LEUKEMIA occurring in persons previously exposed to x-ray radiation either accidentally or for benign medical disorders has been reported with rising frequency during the past several years.[1] An increased incidence of leukemia has been reported among radiologists[2-5]; among the survivors of the atomic bomb explosions in Japan[6,7,8]; in patients who had been treated with x-ray therapy for thymic enlargement as infants[9]; and in children whose mothers had diagnostic x-ray examinations during pregnancy.[10] In addition, numerous well controlled experiments in which leukemia has been induced with x-ray in laboratory animals support the human epidemiologic data.[11]

Kahlmeter,[12] in England, in 1930, was the first to report that x-ray therapy is of symptomatic benefit in rheumatoid (ankylosing) spondylitis. His early

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experience was followed by widespread trial of the new treatment, with good results being reported elsewhere.[13] Among the first controlled observations of larger series of patients were those of Freyberg, Smyth, Lampe and Peck at the University of Michigan Hospital, who started using x-ray therapy for the treatment of rheumatoid spondylitis in the late 1930's.[14,15] The results, as reported by these workers in 1941, and by Robinson and Lampe in 1948,[16] were sufficiently gratifying to warrant the continued use of x-ray therapy in this disease at Michigan as well as at other medical centers.[17]

In 1948 the development of two cases of leukemia was reported by W. Graham[18] in a group of patients with rheumatoid spondylitis treated with x-ray. Van Swaay in 1955 collected seven such cases from Holland, as isolated case reports,[19] and similar cases have been reported by others.[20,21,28] In 1957 Court-Brown and Doll reported an intensive British investigation of this problem.[22] They found a significantly increased incidence of leukemia and allied disorders among irradiated rheumatoid spondylitics in England and Wales. In 1958 D. Graham reported that, in Toronto, 4 of 146 irradiated rheumatoid spondylitis patients developed leukemia.[30]

Materials and Methods

In this study the authors have assessed the incidence of leukemia and related disorders in patients with rheumatoid spondylitis treated with x-ray at the University of Michigan Hospital from 1938 through 1954. These patients satisfied the clinical and x-ray criteria for the diagnosis of rheumatoid spondylitis. Active disease and appropriate symptomatology were considered minimum requirements for acceptance for treatment by the Radiation Therapy Unit. A small percentage of patients (4 per cent) were treated elsewhere using standards suggested by the Radiation Therapy Unit. The technic used and suggested by the University of Michigan Radiation Therapy Unit was as follows[23]: Kilovolts (kv.)—200; Filter—0.5 mm.Cu + 1.0 mm.Al; Focal Skin Distance (FSD)—50.0 cm.; Half Value Layer (HVL)—0.9 mm.Cu; Average Field Width—15 cm.; r/min (AIR), approx—48.

During the period of 1938 to 1955, 527 selected patients with rheumatoid spondylitis received x-ray therapy to their spines, and/or hips and shoulders. For the purpose of this study letters were written to all patients except those seen at University Hospital after January 1, 1956, and those known to be dead, in order to obtain follow-up information. These individuals were asked specific questions regarding their health, whether they had seen their local physician recently and, if so, for what reason; for obvious reasons no specific questions were asked regarding blood dyscrasias. For the purpose of this study it was assumed that description of a satisfactory general state of health was an acceptable basis for concluding that the patient did not have leukemia. Limiting factors in the study did not permit us to recall these individuals for a physical examination. Since it was not feasible to obtain films of peripheral blood, it is possible, therefore, that there are patients in this series with undiagnosed leukemia. In those patients who had died during this period, the cause of death was determined by correspondence with the patient's local physician, their next of kin, by information on the death certificate and when possible by examination of pathologic material by the Department of Pathology and the staff of the Simpson Memorial Institute at the University Hospital.

Follow-up information was obtained on 496 of the 527 patients for a percentage of 94 per cent.* Only those patients who were followed were used in the statistical compilations.

Credit for the success of the follow-up in this study is gladly paid to Mrs. Jean K. Waters and Mrs. Patricia J. Suggitt of the Follow-Up Unit, University Hospital and to a commercial follow-up concern. Without the efforts of the various individuals involved, the study could not have been completed.

Results

This series consisted of 430 males and 66 females for a sex ratio of 6.5:1 (see table 1). This is similar to previously reported ratios of the incidence of rheumatoid spondylitis.[24,25] The average age at which patients were first irradiated was 33 years with no significant difference between sexes. The ages ranged from 14 to 78 years with the median age being 32 years. Most patients, however, had symptoms of spondylitis for several years before they received x-ray therapy.

A course of irradiation was defined as any irradiation received within a period of one week. In general, the shortest period of time elapsing between two courses of irradiation was one month. The number of courses ranged from 1 to 13; the average was 2.7 in males, it was slightly higher in females.

Treatment was usually given to five spinal ports: cervical, upper dorsal, lower dorsal, lumbar and sacroiliac, and in some individuals to the hips and shoulders. The number of roentgens received by the entire body, by the spine ports alone, to the hips and shoulders and by the most heavily irradiated spine port was calculated. The extremes were quite widely separated with the smallest total dose of x-ray being 300 r and the largest being 11,150 r, as measured in air. Of the 496 patients in the series, 349 received x-ray therapy to the spine only. The average total dose received by patients was 2,520 r while the average dose to the spine ports was 2,314 r with males receiving slightly more than females. The median values were slightly lower. There was also considerable variability in regard to the total x-ray received by the most heavily irradiated port, the extremes ranging from 150 r to 4,200 r. The average was 731 r with the median being 500 r. (see table 2).

Table 1.—*Total Number of Man-Years Follow-Up; 5339 Man-Years*

	# Patients in series (1938-1955)	Age at onset of irradiation Average	Average follow-up
Total	496	33.2 yrs.	10.8 yrs.
Male	430	33.2 yrs.	10.7 yrs.
Female	66	32.9 yrs.	11 3 yrs.

Table 2.—*Average and Median Roentgens Received*

	Average number courses of irradiation	Average Roentgens Received			
		all ports	spine ports	other ports*	most heavily irradiated spine port
Total	2.7	2520	2314	1021	731
Male	2.7	2547	2357	1012	737
Female	2.9	2392	2037	1088	694

*includes shoulders & hips.

	Median Roentgens Received	
	all ports	Most heavily irradiated spine port
Total	2000	500r
Male	2000	500r
Female	2000	500r

Follow-up study ranged from one to twenty-one years. The total number of "man-years" of follow-up was 5,330 man-years. The average follow-up period was 10.8 years; this value was slightly higher in females than in males.

Leukemia—Five patients in this series (of 496 patients), all males, developed leukemia (cases 1 to 5) during a period of from 2 and one-half to 10 years following the initial dose of irradiation. These included two monocytic, one myelo-monocytic, one erythroleukemia, and one acute leukemia of undetermined type. In addition, another patient developed Hodgkin's disease (case 6) (see table 3).

Case Histories

Patient 1.—N. W. UMH Reg. #564642. This 28 year old male presented at the University of Michigan Hospital on 2/6/45 with a four year history of increasing pain and stiffness of the back and shoulders. There was limited motion of the entire spine; the peripheral joints were not involved. X-ray demonstrated advanced sclerosis of the sacroiliac joints; definite calcification of the interspinous ligaments was absent. X-ray therapy was administered totaling 3,000 roentgens as follows: as of 3/10/45 he received 250 r to each of five ports; as of 4/20/45 he received an additional 250 r to each of four ports; the third course, completed on 12/27/46, consisted of 250 r to each of three ports. Each course of x-ray therapy was associated with moderate symptomatic relief. During this period, laboratory tests were normal with the exception of an elevated sedimentation rate. No knowledge of the patient's condition is available except that he was apparently quite well until 4/5/48 when there was the acute onset of fever, chills, myalgia, anorexia and diarrhea. He was treated with sulfadiazine and penicillin without marked relief of symptoms. On 4/15/48 he developed "rapid respirations and a questionable soft spleen." The next morning there was gross hematuria; the respirations increased markedly; there was a fall in blood pressure and the appearance of a few petechial lesions over the skin of the abdomen. Shortly thereafter, on 4/16/48, he expired. Blood was taken the morning of his death for examination; postmortem attempt at sternal puncture was not successful. The peripheral blood film was interpreted by Dr. Frank Bethell, University of Michigan, as representive of an acute fulminating type of leukemia. "The cells in the blood were almost exclusively blast forms of variable size. They appeared, however, to be of the same type and probably represented undifferentiated hemocytoblasts. They possessed some of the features of monoblasts. The neutrophils were less than 1 per cent of the total white cells and the film contained a large amount of cytoplasmic fragments. Mitotic figures were present. This condition might be described as malignant reticuloendotheliosis with acute monocytic leukemia."

*We are indebted to Dr. James W. Hall, Traverse City, Michigan for information concerning the terminal illness and the opportunity to review the blood obtained at that time.

Patient 2.—T. B. UMH Reg. #548492. This 25 year old Negro male was first seen at

Table 3

Case	Disease	Sex	Age first irrad.	No.	Total r	r to most heavily irrad. port	Interval time
1, N. W.	Monocytic leukemia	M	28 yrs.	3	3,000	750	3 yr.
2, T. B.	Monocytic leukemia	M	25 yrs.	1	2,000	400	9 yr.
3, A. K.	Myelomonocytic leukemia	M	41 yrs.	7	6,125	1,825	10 yr.
4, C. D.	Erythroleukemia	M	63 yrs.	1	1,250	250	2½ yr.
5, J. P.	Acute leukemia type undetermined	M	46 yrs.	3	6,000	1,600	5 yr.
6, E. M.	Hodgkin's disease	M	39 yrs.	3	2,700	450	15 yr.

the University of Michigan Hospital on 5/29/44 with a history of pain in the low back and sacroiliac regions present for two years. Examination demonstrated limitation of chest expansion, and decrease in flexion and extension of the spine. X-ray examination of the spine showed extensive bilateral sacroiliac arthritis and beginning calcification of the longitudinal spinal ligaments; except for minimal sclerosis of the roof of each acetabulum, the hips, shoulders and peripheral joints were not involved. In August of 1944, x-ray therapy was administered as follows: "The entire spine was treated in three sittings, on August 18, 19 and 21; the dosage of each area was 400 roentgens air." At that time "the hemoglobin was 13.6 grams, the red blood cell count 4,500,000, and the white blood cell count 7,100 with 65 per cent polymorphonuclear leukocytes, 3 per cent eosinophils and 32 per cent lymphocytes."*

Subsequently, the patient was apparently well until he was admitted to the University of Michigan Hospital on September 11, 1953, with the complaint of headache, nausea and vomiting of sudden onset; he was pale and acutely ill; petechiae and small purpuric areas were found in abundance. The hemoglobin was 4.0 Gm., the red blood cell count 1,700,000 and the white blood cell count 1,075; the Rumpel-Leeds test was positive. Iliac crest marrow aspiration was reported as follows: megakaryocytes were present in approximately normal numbers; granulopoiesis was markedly depressed and toxic in appearance. There were a large number of degenerated and broken cells which could not be identified. Concerning the hypoplastic anemia, it was commented, "Whether or not the marrow will show recovery with time remains to be seen; the possibility of an aleukemic leukemia exists." Blood transfusions were administered until the hemoglobin reached 13.2 Gm.

The patient was readmitted on June 16, 1954 with maxillary, ethmoid and frontal sinusitis. His hemoglobin at this time was 10.6 Gm., the white blood cell count was 4,200 and the differential count was normal. Repeat bone marrow aspiration was refused by the patient. He was discharged after 12 days but re-entered the hospital on May 12, 1954 with anorexia, abdominal bloating, weakness, fever and epistaxis. There were palpable cervical and axillary lymph nodes; splenomegaly was now observed. The hemoglobin had dropped to 7.8 Gm., the white blood cell count was now 53,100 with 1 per cent polymorphonuclear cells, 8 per cent lymphocytes, 2 per cent promonocytes and 89 per cent blast cells. The platelets were decreased in normal. Repeat sternal aspiration was reported to show infiltration of the marrow with primitive cells which appeared to be differentiating as monocytes. This diganosis was reported as subacute monocytic leukemia of the histiomonocytic type. The patient's condition deteriorated rapidly, and he died on May 31, 1954 at the age of 34; permission for autopsy was not granted.

Patient 3.—A. K. UMH Reg. #581631. This 41 year old white male, at the time of his first visit to the University of Michigan Hospital on 12/15/45, stated that he had experienced back pain for 10 years. Examination demonstrated marked limitation of movement of the entire spine; the x-rays (1943 and 1945) showed progressive obliteration of the sacroiliac joints and extensive calcification of the longitudinal ligaments of the entire spine. The hips, shoulders and peripheral joints were not involved. X-ray therapy totaling 6125 r was administered to this patient, at his local hospital, as follows: as of March 1, 1946 he received 250 r to each of five ports; in November, 1950 he received 300 r to each of five ports; in December, 1950 he received 300 r to each of five ports; in March of 1951 he received 300 r to a single cervical port; in August of 1951 he received 225 r to a single cervical port; in January, 1953 he received 225 r to each of three ports; in March of 1953 he received 225 r to each of three ports. This treatment was associated with moderate symptomatic relief. In June of 1956 a complete blood count was reported to be normal. In July, 1956, however, there was the development of fatigue and weakness. By August, 1956, the hemoglobin was reported to be 7.3 Gm. with a red blood cell count of 2,010,000. Sternal marrow biopsy at this time "revealed marked activity of the erythrocytic series." There were many large hyperchromic red blood cells seen in the peripheral blood. These findings, with achlorhydria, were thought compatible

We are indebted to Dr. Dwight Ensign, Henry Ford Hospital, Detroit, Mich., for treatment details in this patient.

with the diagnosis of pernicious anemia or some other type of macrocytic anemia. He was given blood transfusions and started on intramuscular vitamin B_{12}. Because of persistent anemia and melena and in the face of negative gastrointestinal x-ray examinations, a laporatomy was performed on 9/11/56. No explanation was found for the melena. Postoperatively the patient deteriorated progressively. Difficulty in maintaining adequate hemoglobin levels led to repeat marrow examination on 9/11/56, at which time monocytic hyperplasia was reported—"A finding certainly changed from the megaloblastic features previously reported. The monocytes seen are young forms; no diagnosis of leukemia can be made." The terminal hospital course was marked by wound infection and purpura; the platelet count, however, remained normal; lymphadenopathy was never prominent. He died on 11/9/56. A complete autopsy was performed. Hepatosplenomegaly was observed. This material was reviewed by Dr. Frank Bethell, University of Michigan, in whose opinion the final diagnosis was aleukemic myelomonocytic leukemia.*

Patient 4.—C. D. UMH Reg. #792781. This white male patient first experienced back pain when 23 years of age; this had its onset in the lumbar area and at first occurred only upon movement. He received no treatment at this time. There was no progression of this complaint until the age of 59, when stiffness of the spine and pain in the neck occurred and persisted, leading eventually to his admission to the University of Michigan Hospital on 9/7/54, at which time he was 63 years of age. Comparison of x-rays obtained at the age of 59 with those upon admission revealed progressive calcification of the anterior and lateral ligaments of the dorsolumbar spine to present a typical bamboo configuration. Sclerotic changes and obliteration of the sacroiliac joint spaces, typical of those seen in rheumatoid spondylitis, were also present; peripheral involvement was absent. By October 5, 1954 the patient had received, over a period of seven days, 250 r to each of five spinal ports. X-ray therapy was not repeated thereafter; he was not seen in this hospital again. Information was provided by his referring physician,† however, to the effect that two and one-half years later he was noted to have "marked anemia, congestive failure, splenomegaly and hepatomegaly." During the following year numerous red blood cell transfusions were given, but there was continual "red blood cell failure." Material obtained from the sternal marrow in February, 1957, was interpreted by the referring physician as Di Guglielmo's disease. During the following year there was a decrease in the platelet count and an increase in hepatomegaly. In February, 1958 the patient was admitted to his local hospital because of circulatory failure; he died there on February 14, 1958. Material obtained at autopsy from the bone marrow and liver was interpreted by Dr. Frank Bethell, of the University of Michigan, as follows: "Bone marrow smears show disturbance of development involving all myeloid elements. There are bizarre, primitive, erythroblasts with many forms, showing multiple nuclear divisions. Some of the more differentiated nuclear erythrocytes have megaloblastoid nuclei but with scanty cytoplasm. Tiny micronormoblasts are present. There are also micromyeloblasts and atypical progranulocytes. Platelets are reduced in number, but giant forms are present. The findings are indicative of erythroleukemia. This is an example of Di Guglielmo's mixed type of erythremia and granulocytic leukemia."

Patient 5.—J. P. UMH Reg. #462289. This 46 year old white male was first seen at the University of Michigan Hospital on June 4, 1940 with a 3 year history of back pain and limitation of motion. The physical findings were those of ankylosing spondylitis with peripheral joint involvement. The x-ray changes consisted of definite disease of the sacroiliac joints; only osteoporosis was evident in the peripheral joints. A complete blood count was normal with the exception of an elevated sedimentation rate. In a period of approximately two months he received a total of 6,000 r to the spine as follows: as of June 15, 1940 he had received 600 r each to four ports; this dose had been repeated to the same

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*We are indebted to the generosity and cooperation of Dr. Gerald Beal and Dr. John Manning, St. Joseph, Mich., for details of the clinical course of this patient and the privilege to review the pathologic material.

Clinical information and pathologic material relevant to this case was obtained with the kind assistance and cooperation of Dr. Phillip C. Stiff, Toledo, Ohio.

areas by July 18, 1940; by August 19, 1940 he had received an additional 200 r to each of two ports and 400 r to each of two ports. His white blood cell counts were as follows in this period: 6,500 as of July 14; 4,100 as of July 18; and 1,900 as of August 22. Examination was made of the peripheral blood on this same date at the Simpson Memorial Institute. Hemoglobin was 9.6 Gm., the RBC 3,400,000; WBC 1,150; there were 31 per cent polymorphonuclear cells, 31 per cent large and 13 per cent small lymphocytes, 18 per cent monocytes, 4 per cent eosinophils and 3 per cent basophils; the platelets were adequate. Upon examination of the bone marrow it was observed that the cells did not appear altered qualitatively; the majority of the red cells were normoblasts; only occasional megakaryocytes were observed. There were very few immature white blood cells; the mature polymorphonuclear cells appeared to be normal in quantity. In view of the decreased elements in the peripheral blood, it was felt that there was slight to moderate depression of the activity of the marrow. The prognosis was thought to be, however, good. The total white blood cell count persisted in this range for about 9 days. At the time of discharge on September 11, 1940 the total white blood cell count was 3,700. When he was next seen on June 27, 1941 there was evidence of relief of the back symptomatology and almost complete subsidence of the active synovitis in the peripheral joints. The total white blood cell count at this time was 6,000. The subsequent history of this patient (made available to us by his referring physician*) was as follows: In the fall of 1944 he experienced fatigue and dizziness. On January 29, 1945 he entered his local hospital with a 6 week history of weight loss, severe epistaxis and generalized muscular soreness. Upon physical examination multiple petechiae and hematomas were observed; the spleen and liver were palpable; rib tenderness was present; the temperature was elevated to 105 F. The red blood cell count was 1,120,000; hemoglobin 24 per cent; white blood cell count 4800, with 3 per cent polymorphonuclear cells, 68 per cent small and 25 per cent large lymphocyte and 4 lymphoblasts; gross hematuria was present. The patient expired on February 22, 1945. Autopsy was not performed. The final diagnosis appearing upon the death certificate was: "lymphatic leukemia, aleukemic phase." On review of this clinical information, Dr. Frank Bethell, The University of Michigan, stated that in his opinion, such an acute course in a patient of this age (51 years) was not consistent with the diagnosis of lymphatic leukemia; he preferred the diagnosis of acute leukemia, type undetermined.

Patient 6.—E. M. UMH Reg. #492076 This white male was first seen at the University of Michigan Hospital, on October 24, 1941, at the age of 39, with the chief complaint of intermittent back pain of 10 years duration. X-rays showed definite bilateral sacroiliac arthritis; the spine above, the hips, shoulders and peripheral joints were not involved. In a period of 14 months, he received a total of 2700 roentgens as follows: by November 1, 1941, he had received 450 roentgens to each of two ports covering the lumbar and sacroiliac regions; exactly the same dose was repeated to the same areas as of December 22, 1941 and February 13, 1942. His response to this therapy was excellent and he remained essentially well for 13 years. A careful checkup examination was made in February, 1955 which included a complete physical examination, repeat chest x-ray examination and laboratory evaluation; no particular change from normal was observed; the appearance of the sacroiliac joints was unchanged. The patient was well until January, 1957 when there was the onset of a persistent cough. Two weeks before his admission on June 14, 1957 this had grown worse. Physical examination now revealed pharyngeal lymphoid hypertrophy, supraclavicular adenopathy, splenomegaly and a nontender mass in the left lower abdominal quadrant. Hilar adenopathy and parenchymal infiltration in the left midlung was evident in the chest x-ray; an intra-abdominal mass was observed in gastrointestinal x-rays. Biopsy of a supraclavicular lymphnode was reported as follows: "Many atypical neoplastic cells are seen in the dilated sinuses of the lymph nodes and in the surrounding adipose tissue. These are large cells with moderately abundant eosinophilic cytoplasm and large, pale vesicular nuclei containing large eosinophilic nucleoli. Some of the atypical cells

*We are indebted to Dr. Earl Rhind and Mr. Ward A. Stoddard of Sault Ste. Marie, Mich., for technical information concerning this case.

are in vascular channels; in some areas these cells have a spindle shape." It was the pathologists' impression that these findings probably represented a reticuloendothelial cell sarcoma type of lymphoblastoma or Hodgkin's Disease. Upon this basis, the patient was treated with x-ray therapy to the chest and supraclavicular areas. Prior to discharge on July 16, 1957, there was evidence of bilateral pleural effusion, and bilateral extensive pulmonary infiltration. The patient died at home on August 5, 1957; an autopsy was not performed.

Discussion

The expected incidence of leukemia in this series was derived from figures released by the United States Public Health Service for the year 1947, (the midyear in this series) by constructing a population identical in size, age and sex to that of this series of spondylitis patients (see table 4). Since the average follow-up per patient was about ten years, the average age at risk of developing leukemia was the age at first irradiation plus half the average follow-up period, or five years (see table 5). The expected incidence of leukemia in this group would be 0.291 cases or 5.4 cases per 100,000 man-years. Our findings of five cases in 5339 man-years establishes our incidence as being 94 cases per 100,000 man-years, or an increase of 17.3 times. The probability that these results could have been obtained by random sampling alone, is 0.00045 or less than one chance in 2000. (This figure was obtained by the expansion of the binomial formula in which "a" is the probability of "not developing leukemia in this population," and "b" the probability of developing leukemia, and "n" is the number of man- years of follow up.)

The case of Hodgkin's disease was not used in determining the leukemia incidence rate in this series since its relationship to the leukemias remains unclear, but its reporting appears justified by the possibility of a close relationship.

In previous reports the question of a linear versus threshold radiation dose response in leukemogenesis has been discussed.[8,22] Court-Brown and Doll concluded that with low and moderate dosage of radiation (up to 2000 r), there exists a linear response between the amount of x-ray received and the risk of developing leukemia. At high doses of radiation, the actual incidence exceeded the expected incidence, if the relationship were considered entirely linear in nature. Interpretation of the incidence of leukemia following the atomic bombings in Japan indicates a similar linear relationship at the lower levels of radiation.

In this series, the average dose of radiation received by the patients developing leukemia and related disorders is not significantly higher than that received by the average patient in the series, but the number of cases is not large enough to justify any conclusions with regard to the nature of the dose response in leukemogenesis.

There have been many reports concerning the histologic types of leukemia occurring following irradiation.[6,8,9,11,19,22] Court-Brown and Doll found that the incidence of myelogenous leukemia disproportionately increased with respect to other cell types when compared to leukemia incidence figures by histologic type in the British Isles. According to Lange et al.,[8] the distribution of histologic types of leukemia occurring among survivors of the atomic ir-

Table 4.—*Age Incidence Rates of Leukemia/100,000 Population (1947)*[26]

Age	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84
White Male	4.2	2.7	3.3	1.5	4.5	3.7	4.6	7.9	10.6	19.3	19.1	32.3	40.5	58.7	46.6
White Female	3.3	1.2	1.3	2.4	2.0	4.0	3.4	6.5	11.6	13.6	18.0	20.5	17.7	15.7	22.4

Table 5.—*Age Distribution of Patients at Time of First Irradiation (496 Patients)*

Age	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
Male	2	23	67	93	72	56	56	29	15	10	4	1	1	1
Female	0	3	11	12	15	12	6	6	0	0	0	1	0	0

radiation in Japan was more nearly proportional to the distribution of the expected cell types in the population-at-large in Japan.

Four of the leukemias in this series are of a similar nature, arising from myeloid reticular elements of the bone marrow. They vary from a less well differentiated myelomonocytic leukemia to well differentiated monocytic and erythroleukemias. These results are in general agreement with those of Van Swaay[19] and Court-Brown and Doll,[22] who reported an increase in the proportion of myelogenous leukemia in irradiated patients with spondylitis.

In order for our data to have statistical significance, a control group is required by which all variables are eliminated except the radiation received. A satisfactory control group could not be obtained at the University of Michigan Hospital because since 1938 almost all rheumatoid spondylitis patients have been treated with x-ray therapy. It is believed that a control group composed of patients with peripheral classical rheumatoid arthritis would be of questionable value since many other variables would then be introduced. Consequently, it cannot be said that rheumatoid spondylitis patients do not have an increased susceptibility to the leukemogenic effects of radiation, or that there is no primary relationship between the two diseases. Abbatt and Lea[27] found no leukemia in a group of 399 nonirradiated spondylitics. This group was used as a control series in their original report which showed 7 cases of leukemia and 1 of aplastic anemia in a group of 1627 irradiated patients with spondylitis. However, two years later the same investigators reported that statistical analysis of 679 cases of leukemia revealed a definite association between leukemia and the rheumatic diseases.[29] No division into types of rheumatic diseases was made. It was pointed out that although the evidence for an association between the rheumatic diseases and leukemia is valid, the data does not permit the exact determination of this relationship.

Hence, it is possible that patients with rheumatoid spondylitis have an increased incidence of leukemia associated with their disease alone. X-ray therapy and incidental exposure to x-rays have been shown elsewhere to cause an increased incidence of leukemia in people other than patients with rheumatoid spondylitis.[1-10] Since the chief use of x-ray therapy in rheumatoid spondylitis is as an analgesic,[12,16] it would seem unwise to compound the risk of developing leukemia in these patients by its continued use, unless all other forms of symptomatic treatment have failed, and the patient and the physician mutually accept the possibility of this increased hazard. If the increased incidence of leukemia in this study is due to the x-ray exposure alone the same conclusion would hold.

Summary

In a series of 496 rheumatoid spondylitis patients treated with x-ray ,the authors have reported an incidence of leukemia over 17 times greater than expected in a comparable population. No conclusion can be drawn with respect to the exact nature of dose response relationship in leukemogenesis. Four of the reported leukemias arose from myeloid reticular elements of the bone marrow; the fifth case is of undetermined origin.

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REFERENCES

1. Voll, A., and Tveit, J.: Leukemia following roentgen / radium therapy. Nord. med. *58:*114, 1957.
2. March, H.: Leukemia in radiologists, Radiology *43:*275, 1944.
3. —: Leukemia in radiologists in a 20 year period, Am.J.M.Sc. *220:*282, 1950.
4. Warren, S.: Longevity and causes of death from irradiation in physicians, J.A.M.A. *162:*464, 1956.
5. Ulrich, F. F. A.: The incidence of leukemia in radiologists, New England J.Med. *234:*45, 1946.
6. Folley, J. H., Borges, W., Yamawaki, T.: Incidence of leukemia in survivors of the atomic bomb in Hiroshima and Nagasaki, Japan. Am.J.Med. *13:* 311, 1952.
7. Wald, N.: Leukemia in Hiroshima A-bomb survivors, Science *127:*699, 1958.
8. Lange, R. D., Moloney, W., and Yamawaki, T.: Leukemia in Hiroshima and Nagasaki, Blood *9:*574, 1954.
9. Simpson, C. L., Hempelmann, L. H., and Fuller, L. M.: Neoplasia in children treated with x-rays in infancy for thymic enlargement, Radiology *64:*840, 1955.
10. Stewart, A., Webb, J., Giles, D., and Hewitt, D.: Malignant disease in childhood and diagnostic irradiation in utero, Lancet *2:*447, 1956.
11. Henshaw, P. S.: Leukemia in mice following exposure to x-rays, Radiology *43:*279, 1944.
12. Kahlmeter, G.: The roentgen treatment of arthritis, Brit.J. Actinotherapy *5:* 93, 1930.
13. Scott, S. G.: X-ray in chronic rheumatic arthritis; diagnosis, prognosis and treatment, Brit.J.Phys.Med. *10:*127, 1935.
14. Smyth, C. J., Freyberg, R. H., and Peck, W. S.: Roentgen therapy for rheumatic disease, J.A.M.A. *116:*1995, 1941.
15. —, —, and Lampe, I.: Roentgen therapy for rheumatoid arthritis of the spine, J.A.M.A. *117:*826, 1941.
16. Robinson, W. D., and Lampe, I.: Long range evaluation of radiotherapy in rheumatoid spondylitis. Ann.Rheumat. Dis. *7:*245, 1948.
17. Coste, F., and Faure, C.: Effects et mode d'action de la radiotherapie des affections rheumatismales, Semaine des Hopitaux de Paris *32:* 2491, 1956.
18. Graham, W.: Ann.Rheumat.Dis. *7:*245, 1948.
19. Van Swaay, J.: Aplastic anemia and myeloid leukemia after irradiation of the vertebral column, Lancet *2:* 225, July 30, 1955.
20. Windeyer, B. W.: Proc.Roy.Soc.Med. *45:*548, 1952.
21. Goodman, G. B.: Radiation leucopenia in ankylosing spondylitis, J.Facul. of Radiologists, *7:*167, 1956.
22. Court-Brown, and Doll, R.: Leukemia and aplastic anaemia in patients irradiated for ankylosing spondylitis; Privy Council, Medical Research Council Special Report Series, No. 295, London, Her Majesty's Stationery Office, 1957.

*Deceased.

23. Personal communication, I. Lampe, University of Michigan Hospital, Ann Arbor, Mich. Radiation Therapy Unit.
24. Boland, E. W.: *In* Lea, and Febiger, Eds.: Comroe's Arthritis and Allied Conditions, Philadelphia, 1953, pp. 550.
25. Short, C. L., Bauer, W., and Reynolds, W. E.: Rheumatoid arthritis; a definition of the disease and a clinical description based on a numerical study of 293 patients and controls, Cambridge, Mass., Harvard Univ. Press, 1957, pp. 105.
26. Morbidity from cancer in the United States; U.S.P.H.S. Monograph 29, P.H.S. Pub. 418, U. S. Government Printing Office, Washington, D. C., 1955.
27. Abbatt, J. D., and Lea, C. J.: Leukemia in ankylosing spondylitis treated with x-rays, Lancet 6957:1317, Dec. 29, 1956.
28. Penfold, J. B., and Rhys-Lewis, D. S.: Leukemia, amyloidosis and renal vein thrombosis in irradiated ankylosing spondylitis, Brit.M.J. 5052:1034, Nov. 2, 1957.
29. Abbatt, J. D., and Lea, A. J.: Leukaemogens, Lancet 2:880, Oct. 25, 1958.
30. Graham, Donald.: Arth. & Rheumat. 2: 35, Feb. 1959.

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