Epidemiological Studies of Leukemia in Persons Exposed to Ionizing Radiation

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SUMMARY

After reviewing the epidemiological studies of persons exposed to ionizing radiation, the author concludes that there is no question that radiation exposure in man is associated with an increased incidence of leukemia and that a cause-and-effect relationship must be accepted. Such an association holds in the higher dose range regardless of (a) sex and age, (b) the amount of body exposed (provided a substantial amount of blood-forming tissue is irradiated), and (c) whether or not the radiation was administered as a single dose or intermittently over a long period of time. In two studies which have an adequate sample size and a sufficient number of cases in each of several exposure groups to permit analysis, there is a proportionality between leukemia incidence and dosage in the middle dose range. Probably because of the small number of cases studied, such a relationship was not observed in children treated for thymic enlargement in infancy.

The author believes that the available data are insufficient to permit conclusions to be drawn concerning the relationship between leukemia incidence and exposure to low doses of radiation. Thus, in the British series of spondylitics, only one case of leukemia (excluding a second case with extraspinal radiation) occurred in the relatively few patients receiving less than 500 roentgens to the spinal marrow. In the Japanese, uncertainties regarding actual dose values as well as the small number of cases in the exposure zones between 1,600 and 2,000 meters preclude extrapolation of the curve of dose-versus-incidence to the low dose range. The other studies reviewed in this paper do not lend themselves to analysis in the low dose range either because of the small number of cases or dose uncertainties or, in the case of prenatal exposures, because the role of radiation in the development of the disease has not been established.

Although there is some suggestion that children are more sensitive to the leukemogenic effects of radiation than adults, the author concludes that the present retrospective studies of prenatal exposure of children dying of leukemia or cancer do not establish exposure to diagnostic doses of radiation as an etiologic factor.

The difficulties of carrying out epidemiological studies in man to show an increase in a rare event such as leukemia have been pointed out. The size of the group needed for study, the long latent period between exposure and study and the choice of proper control groups present serious problems, especially in the low dose range. In view of our need for information about radiation hazards in the low dose range, it is emphasized that restraint must be exercised to avoid reading more significance into the available data than is justifiable. This does not mean that the possibility of radiation hazards existing at low doses should not be recognized. Clearly, unnecessary exposure of large groups of people should be reduced to a minimum.

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An accurate evaluation of the risk in man's exposure to small doses of ionizing radiation can be based only on the study of large groups of persons known to have had such exposures. The vast amount of data from experiments with irradiated animals and with simpler biological systems has provided important information concerning the manifestations of radiation injury and the mechanisms by which such injury occurs; as has been pointed out repeatedly, most recently by Mole (21), such information cannot be extrapolated directly to man, at least insofar as the quantitative response to given doses of radiation is concerned. Because of our great need for information about the hazards of exposing man to the increasing and widespread levels of radiation throughout the world, it is important to consider carefully the data now available from studies of irradiated human beings to assess the state of knowledge in this field. It is hoped that careful analysis can help to clarify some of the confusing and conflicting opinions that now appear in the medical literature and lay press. Similar critiques have been published previously by the United Nations Scientific Committee on The Effects of Atomic Radiation (33), Brues (9), Kaplan (11), and Loutit (14).

Before considering the epidemiological studies of groups of people exposed to radiation, it is well to point out the limitations involved in this type of investigation. Three serious limitations should be mentioned. The first is concerned with the size of the sample needed for study. Obviously, the number of subjects needed depends upon the magnitude of the effect to be detected. If one wishes to demonstrate an increase in a rare, spontaneously occurring event, such as the development of leukemia, or to show a possible shortening of life by a small fraction of the total life span, it is obvious that large numbers of people with known exposures must be surveyed. Invariably, such large groups of people, usually numbering thousands, present serious problems for study. The second limitation depends upon the long interval between exposure and time of study. The procedure usually employed in these studies is to survey a group of people exposed to radiation many years before. Because of the elapsed time, a certain fraction of the group inevitably will be difficult or impossible to locate. Also, certain of the persons contacted may provide medical information which will be difficult to confirm at the time of the study, and others will have had additional uncontrolled exposure to radiation.

The final limitation is concerned with the planning of the epidemiological studies. Because groups of exposed persons satisfactory for study are uncommon, the investigator has no choice but to accept the experimental design offered by the situation. This is usually far from ideal in many respects. For example, the exposure data may be inadequately documented or impossible to calculate accurately. Also, the exposed individuals usually constitute a selected group for which there is no available control group comparable in all respects except for radiation exposure. In this case, the selection of appropriate controls will be a matter of judgment, and this will be greatly influenced by practical considerations. The use of more than one group to control different characteristics of the exposed sample is often desirable, but this adds to the time and expense of an already expensive and tedious study. Thus, it is apparent that, in the case of epidemiological studies of irradiated persons, it is impossible to reach the precise conclusions which can be deduced from well planned animal experiments.

With these limitations in mind, the author will now consider data from the five groups of irradiated individuals most intensively studied from the point of view of leukemia incidence and radiation dosage. The studies in children will be discussed in detail, because they contain new data only recently available.

EPIDEMIOLOGICAL STUDIES
CHILDREN RECEIVING PARTIAL-BODY EXPOSURE TO X-RAYS

Infants treated with x-rays for thymic enlargement.—In 1955, Simpson, Hempelmann, and Fuller (30) published the preliminary results of a study of the incidence of neoplasia in a group of children mainly from Rochester, New York. This series of 1,722 children had been treated in infancy with x-rays for enlargement of the thymus gland during the period 1926-1951. In their last report, Simpson and Hempelmann (29) showed that many more cases of malignant disease including leukemia occurred in the treated group than would have been expected on the basis of the number of children studied and the age-specific cancer incidence rates in upstate New York. Recently, Simpson (28) has studied 671 additional children treated for thymic enlargement in Buffalo, New York. In the 87 per cent of children traced from the composite group of 2,393, 81 cases of cancer were found instead of the 3.6 cases expected to occur in the total group. Nine and possibly ten (one case unconfirmed) children had died of leukemia, whereas one death was expected. Thyroid carcinoma accounted for most of the other excess cases of cancer. There was not a significant difference between the expected and observed number of cases of can-
cancer or leukemia in 2,732 untreated siblings of the study children. When the cases were divided according to the method of treatment, the children with leukemia seemed to be randomly distributed among the subgroups. More than half of the cases of other types of cancer occurred in one subgroup of 268 children. These children had been treated with 110–150 roentgens of 140 kvP x-rays through a 9-cm. circular port to the front as well as to the back of the chest. The treatment was repeated once and sometimes twice at biweekly intervals. The radiation factors used in treating the children in the other subgroups varied considerably during the 25-year period during which treatments were given, but, in general, the doses and port size became smaller in the later years. The smallest dose and port size used in any subgroup was 50–75 r through a 6 X 8 cm. port, usually to the anterior chest.

The doses in roentgens as measured in air were known or were calculated from the radiation factors for all but 299 children. Four of the known cases of leukemia occurred in 1,050 children receiving a cumulative dose of less than 200 r, whereas five cases were found in 1,025 children given more than 200 and usually less than 600 r. In contrast, all cases of other malignant neoplasia occurred in children receiving 200 r or more. The average time between exposure and death from leukemia was 5.3 years.

In addition to the study just reported, other similar prospective surveys of children treated with x-rays for thymic enlargement are now being carried out in this country. In a preliminary report of a survey of 1,131 children so treated in a Boston hospital (31), Snegireff states that he observed no cases of leukemia in 148 treated children or in 185 untreated controls. In discussing Simpson’s paper (28), Maloney mentions a follow-up of 125 of 700 children treated in Boston. He did not find any cases of leukemia in this group but observed seven cases of thyroid neoplasia including two malignancies. Retrospective studies of a questionnaire type designed to obtain, among other information, the history of prior x-ray exposure of children with leukemia showed that only a very small percentage had been treated for thymic enlargement. In Great Britain, where the practice of treating thymus glands was abandoned many years ago, Stewart and her colleagues (32) obtained a history of therapeutic irradiation (none for thymic enlargement) in only five of 677 children dying of leukemia. Snegireff (31) quotes Farber as having obtained a history of thymic irradiation in only five of 856 children with leukemia seen at the Tumor Clinic at the Children’s Cancer Center in Boston.

Polhemus and Koch (25) report a history of x-ray treatment to the thymus in 4.3 per cent of 261 children with leukemia seen at the Los Angeles Children’s Hospital, in comparison with 0.8 per cent of children so treated in a comparable group of controls without malignant disease. Murray and colleagues (22) reported that eight of 65 children dying of leukemia in Rochester, New York, had a history of x-ray treatment (five for thymic enlargement), whereas none of 65 matched dead controls and only two of 175 living siblings had such a history.

In evaluating these observations, it seems clear that further studies of a prospective nature must be undertaken to establish the true incidence of leukemia in children given thymic irradiation, particularly as far as the relation of the incidence to dose and port size is concerned. In the survey in upstate New York, the number of leukemia deaths, although not large in absolute terms, is unquestionably greater than that in their untreated siblings or in children of the general population. Since the state of the thymus gland is unknown for the sibling group and is, for the most part, normal by definition in children of the general population, it is clear that this study does not differentiate between the association of leukemia and (a) prior exposure to x-rays or (b) the medical condition diagnosed as thymic enlargement. Because it is impractical, if not impossible, to obtain an ideal group, i.e., a series of children diagnosed as having thymic enlargement at birth not treated with x-rays, it has been necessary to initiate studies of children irradiated for other medical conditions in an effort to distinguish between the associated and, possibly, leukemogenic factors.

**Infants with normal-sized thymus glands given x-ray treatments.** —A group of 1,564 children treated with x-rays in Pittsburgh was studied in 1948 by Conti and his colleagues (3). Ninety-six per cent of these children were shown to have thymus glands of normal size at birth. The radiation factors were uniform in the entire group, being: 140 kvP x-rays; 3 mm. Al filtration; STD, 8–9 cm.; port size, 4 X 4 cm.; dose increments of 50–75 r at 1– to 2-day intervals. Eighty-eight per cent of the children received 75–900 r (usually 150 r) to the region of the manubrium; the remainder received 200–450 r.

Ninety per cent of the children were contacted again 11–18 years after therapy by Conti and his colleagues (4). The names of those not located were searched for carefully in the death records of the Pennsylvania State Department of Health. Four cases of malignant disease were expected to occur in this group, but not one was found; the one
expected case of leukemia was not observed. There
was not a significant difference between the num-
ber of expected and observed cases of cancer and
leukemia in the untreated siblings.

The failure to observe any cases of neoplasia
when only four (including one leukemia) were ex-
pected is not significant, particularly since one-
tenth of the group was not located. In view of the
negative observations, one can only conclude that
there is no evidence for an increase (a doubling,
perhaps) in the cancer rate in the treated children
or a greatly enhanced leukemia frequency, i.e.,
5–10 times that in the general population. Such
increases probably would have been detected in
this study. It is interesting, however, to compare
the findings in the traced children of this series
with those reported in the New York study. Such
a comparison can be made directly without being
concerned about the 10–13 per cent untraced chil-
dren in each group. The difference in the number
of cases of leukemia in children receiving less than
200 r (none in 1,375 children of the Pittsburgh
series and four in 1,050 children of the New York
series) is significant at less than the 5 per cent
level. One cannot say whether the absence of ex-
cess cases of leukemia in the Pittsburgh children
is due to (a) their normal-sized thymus glands
which, conceivably, did not predispose them to
develop leukemia, or (b) the smaller port size used
in treatment. Although the first possibility cannot
be excluded, it is entirely possible that the small
port size could be responsible for the difference in
findings. A simple calculation shows that the vol-
ume of tissue irradiated in the case of the Pitts-
burgh children was one-third that of the New
York State children treated with the smallest
ports. The exposed tissues include the blood-form-
ing cells of the sternum and anterior portions of
the ribs as well as those of the thymus gland and
mediastinal lymph nodes.

Children given x-ray treatments for benign condi-
tions.—To avoid complications introduced by con-
sidering only children given x-ray therapy to the
mediastinal region, a study was made of 6,473 chil-
dren in Rochester treated with x-rays for various
benign conditions (22). This group of children is
believed to represent the vast majority of children
so treated in Monroe County in the past 25 years.
The only cases known to have been missed are the
patients of one radiologist who destroyed his ther-
apy records upon retiring in 1944. The number of
cases of leukemia in this group was determined by
checking these names against the cancer records
in the Division of Vital Statistics of the New York
State Department of Health. In addition, the
families of all children dying of leukemia in this
county since 1940 were interviewed to obtain a
history of previous radiation exposure.

Considerable bias was introduced deliberately
into the study to raise the number of expected
cases of leukemia and to lower the observed num-
ber. Nevertheless, the difference between the eight
observed and two expected cases is significant
(P < 0.001). Five leukemia deaths occurred in
2,750 children treated for thymic enlargement, two
occurred in 75 children treated for pertussis, and
one in 1,073 children given x-ray treatments to the
head and neck region, mainly for lymphoid hyper-
plasia of the nasopharynx. No deaths of leukemia
were found in 2,460 children treated with superfici-
(al x-rays for benign skin lesions. The fact that
the number of observed cases exceed the expected
number in three categories representing unrelated
medical conditions including two cases in 75 chil-
dren treated with x-rays for pertussis would seem
to suggest that the high voltage x-rays used in
treatment were the etiologic factor in the subse-
quent development of leukemia.

Discussion.—In evaluating the data obtained in
these three studies, it seems clear that an associa-
tion has been established between radiation ex-
posure and subsequent leukemia in certain children
treated with x-rays for thymic enlargement but
not in the case of infants with normal-sized glands
given small doses of x-rays through a small port.
The occurrence of two cases of leukemia in 75 chil-
dren treated with x-rays for pertussis and one case
in about 1000 children given x-ray treatments to the
head is not significant in itself but fits the pattern
of an increased incidence of leukemia in irradiated
children. The occurrence of only twelve cases in
approximately 9,000 children studied emphasizes
the scope of the studies needed to establish a pos-
sible quantitative relationship between exposure
and leukemia incidence, especially since port size,
as well as dose, may be an important factor. In the
nine cases observed in children treated for thymic
enlargement, there was no obvious correlation be-
tween dose and incidence.

It should be emphasized that the doses of x-rays
associated with the considerable increase in leuke-
emia frequency in these children is far less than the
thousands of roentgens formerly believed to be
necessary to induce malignant change.

Patients with Ankylosing Spondylitis Given
X-Ray Treatments to the Spine

Court-Brown and Doll (5) have published a
thorough study of the cases of leukemia and
aplastic anemia in 13,200 patients treated with
x-rays for ankylosing spondylitis. They reviewed
the death certificates and studied the clinical and
pathological data of all patients suspected of dying of leukemia or aplastic anemia. In addition, they obtained dosage records from which they calculated the mean dose to the spinal marrow and the whole-body integral dose of a large sample of the cases. They concluded that 32 proved and five probable cases of leukemia occurred in this group of patients as well as four cases of aplastic anemia. When the cases are divided according to the mean dose to the spinal marrow or to the integral dose, there is a definite relationship between dose and leukemia incidence. The exact shape of the curve of incidence vs. dosage plotted on an arithmetic scale depends upon whether the mean spinal marrow dose or the integral dose is used and upon whether or not the cases receiving extraspinal radiation are excluded. The curve is clearly linear in the middle three dose groups expressed either in terms of mean spinal marrow dose or integral dose. In the higher dose range, the curve departs sharply from linearity unless the incidence in all cases receiving more than 1,250 roentgens is averaged as a single point. There has been considerable discussion of how the curve should be drawn below 500 r or 7.5 megagram r, particularly with regard to whether or not there is a threshold dose below which there is no increase in the leukemia incidence. The most favorable plot for the interpretation of linearity is found when the leukemia incidence of 35 cases of leukemia, excluding two coexistent cases, is plotted against mean spinal marrow dose. It should be emphasized that the only point below 500 roentgens is based on two cases of lymphocytic leukemia. One of these patients developed chronic lymphocytic leukemia after receiving a mean marrow dose of 471 r; the other developed lymphocytic leukemia after a series of treatments which delivered 118 r to the spine. The total integral dose including that given extraspinally to the second patient exceeded that given to the first patient, i.e., 12.2 vs. 18.8 megagram r.

It is interesting to note that, of the 50 cases of leukemia in patients treated with x-rays for spondylitis, including those in Court-Brown and Doll’s series, 38 have been examples of the acute disease (7). Only one of the eight cases of chronic leukemia, presumably the patient mentioned above, has been lymphocytic in type.

This report is clearly one of the most valuable published to date, with the dosage factors being particularly useful. The linearity of the curve in the middle dosage range is unquestionable, as is the curvilinearity in the higher dose region under most conditions of plotting. However, there has been considerable criticism of the attempts to extrapolate the data to the low dose region. This includes the author’s own mention of the dissimilarity of the curves obtained when the leukemia incidence is plotted against the integral dose or against the marrow dose. Also criticized are the small number of cases below 500 r (2), the use of the spontaneous leukemia incidence in general population as a point on the curve at dose zero (24), and the unknown role of age-susceptibility in the development of leukemia (19). In connection with the attempted extrapolation of the incidence data to low doses, a word should be said about the non-irradiated controls available for comparison with the study group. Since there appears to be a strong hereditary factor in ankylosing spondylitis (23), the leukemia rate in the population-at-large cannot be accepted as the rate for the untreated patients. This is illustrated by the report of Abbatt and Lea showing an association between untreated rheumatism and leukemia. The only available control group of 599 spondylitic patients not treated with x-rays is too small to be of use in determining the leukemia rate, since the absence of any cases when less than 0.2 case is expected is not meaningful.

In view of the limited data in the lower dose range and the lack of an appropriate control group, it seems reasonable to conclude that this study does not provide evidence (a) to determine the true leukemia incidence in the dose range below 500 roentgens or (b) to ascertain whether or not a threshold dose for leukemia induction exists. It is interesting to note that almost all cases occurred in patients receiving more than 500 roentgens to the spinal marrow in contrast to the findings in leukemic children, almost all of whom received less than this dose when measured in air. One cannot determine whether this difference is due to the small number of patients receiving lower doses (about 3,000 receiving less than 500 r), age-susceptibility, treatment technique, i.e., protracted vs. one or two treatments, or to the volume of blood-forming tissues exposed.

**Japanese Populations Receiving Total-Body Radiation from Atomic Bomb Explosions**

A number of reports published since 1951 by the Atomic Bomb Casualty Commission have dealt with the increased incidence of leukemia in the Japanese survivors of the atomic bomb explosions in 1945. The results of these studies have been summarized by Heyssel and his colleagues. The number of cases below 500 r (2), the use of the spontaneous leukemia incidence in general population as a point on the curve at dose zero (24), and the unknown role of age-susceptibility in the development of leukemia (19). In connection with the attempted extrapolation of the incidence data to low doses, a word should be said about the non-irradiated controls available for comparison with the study group. Since there appears to be a strong hereditary factor in ankylosing spondylitis (23), the leukemia rate in the population-at-large cannot be accepted as the rate for the untreated patients. This is illustrated by the report of Abbatt and Lea showing an association between untreated rheumatism and leukemia. The only available control group of 599 spondylitic patients not treated with x-rays is too small to be of use in determining the leukemia rate, since the absence of any cases when less than 0.2 case is expected is not meaningful.

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the incidence increases as an inverse function of the distance of the population groups from the hypocenter is well established. The study of Maloney and Kastenbaum (16) published in 1955 indicated that the ratio of observed to expected cases even in the lowest exposure zone (2,000–2,999 meters from the hypocenter) at Hiroshima was greater than that expected (1.5:1). In the most recent report from Hiroshima, Heyssel and colleagues2 discuss fully the meaning of the values for leukemia incidence in terms of the bias introduced by attempts to estimate retrospectively the number of persons in each exposure zone. In their Table II, they show the leukemia incidence in each zone according to the number of exposed persons in each zone estimated on the basis of three census reports and of one other selected group of survivors. Only in the case of the so-called “reserve” group of the 1950 census, a small and highly biased group (whose official and actual residences were not identical) does the leukemia incidence in the persons between 2,000 and 2,900 meters exceed that in two unexposed groups. These control groups are composed of 24,091 persons with a total of 168,119 years-at-risk.

Heyssel and his colleagues also present data showing the leukemia frequency according to additive gamma rays and neutron dose in the open air at various distances from the hypocenter. In these calculations, the latest dosage data obtained from recent tests were used, and a relative biological efficiency (RBE) of one was used for the neutrons. The authors estimate that 60 per cent of the people were indoors at the time of the explosion and state that this would reduce the air dose by 30–70 per cent. They consider smaller dose increments (about a factor of two) per group than those used formerly. Using only leukemia cases diagnosed between the years 1950 and 1958, they observed a linear relationship between incidence and the calculated open air dose of 177 rads or above. The point representing the leukemia incidence of 3,605 persons receiving a mean dose of 77 rads falls almost exactly on the line drawn through the points at higher dosage. Although twice the spontaneous incidence, the increase at this dosage is not significant. No cases of leukemia were observed in 3,512 and in 1,305 people receiving an average dose of 34 and 19 rads, respectively. They state that there is insufficient data to permit a definitive analysis of the dose-response curve in the region below 77 rads, a conclusion that seems well justified.

In addition to the studies on leukemia incidence as a function of distance and dose, Heyssel and his colleagues present evidence showing that the latent period between exposure and development of the disease is a function of the size of the dose. Their data also indicate that radiation exposure causes an excess number of cases rather than an acceleration of the time of appearance of cases which would occur spontaneously. They also report that practically all cases in either the exposed or nonexposed persons were acute in nature or, if chronic, then of the myelocytic type; chronic lymphocytic leukemia was rare in either group.

The recent report of the Japanese survivors of the atomic explosions appears to provide the most reliable data to date on the subject, even though the leukemia cases occurring before 1950 are excluded. Although errors have undoubtedly been introduced by establishing the so-called “closed” population so long after the event, it is probably impossible to improve upon the samples. By rigorous definition of the sample in each exposure zone, the number of cases of leukemia is reduced, particularly in the zones more than 1,500 meters from the hypocenter. This makes the estimates of leukemia incidence at these distances subject to considerable error. Future data on leukemia in Hiroshima and perhaps information from Nagasaki now being compiled and analyzed may help to clarify the question of the leukemogenic action of radiation exposure at these distances.

The dose estimates, based on recent tests simulating the nuclear detonations during the war, would seem to have more basis in fact than any formerly made. The authors point out, however, that there is still uncertainty in the estimates due to errors in the precise location and shielding of each individual. For a number of other reasons, it is evident that there must be a considerable margin of error associated with the individual dose values. It has been pointed out by Bond3 that at least 200 people survived in the exposure zone where the mean open air dose was calculated to be 2,620 rads. Even allowing for shielding and assuming that these persons were located at the periphery of the exposure zone, the doses received by these survivors according to these calculations must have been well in excess of that generally considered to be 100 per cent lethal. In the low dose region, a question may also be raised about the exactness of the calculated doses. Many persons in the zone 2,000–2,499 meters where the average estimated dose was 6 rads reported a history of severe radiation symptoms (epilation, oropharyngeal lesions, and purpura) (15). This dose is far below that associated with radiation sickness after total-body exposure (18). Since persons even farther away were said to have similar symptoms, it is the consensus of a number of observers4 present.

1 V. C. Bond, personal communication.
ent at the time of the interviews with the patients that these symptoms are probably due to factors other than radiation. Finally, it has been suggested by Mole (31) that the use of the dose at the midpoint of the exposure zones as the mean dose of the people in that zone is misleading for reasons of geometry.

Since a number of assumptions is involved in these calculations, e.g., the RBE for neutrons, the applicability of data from the simulated tests to the exposure conditions at Hiroshima, etc., it is perhaps best to accept even these latest dose estimates with reservation. It is obvious that the leukemia incidence regresses with diminishing dose, but how far down the dosage scale this regression holds is not certain. Taking shielding into account, Heyssel and his colleagues believe that 50–100 rads is the probable actual dose received by persons in the outermost zones showing an increased leukemia incidence. They admit, however, that there may be a considerable error in their estimates.

**Radiologists Receiving Partial-Body Radiation (X-Rays) over Many Years**

Since 1944, a number of studies have shown the increased frequency of deaths from leukemia in American radiologists (10, 17, 27). Most of these reports are based on analyses of the obituaries appearing in the *Journal of The American Medical Association*, a method of epidemiological study open to criticism. Nevertheless, it is clear from these studies that the incidence of leukemia deaths in American radiologists exceeds by far that expected in the general male population or that in other medical specialties. In contrast, excess cases of leukemia have not occurred in British radiologists who began to practice after 1921, and only two cases occurred in radiologists in practice before this time (6). The absolute number of published cases of persons developing leukemia among the many thousands of x-ray workers exposed to radiation since the turn of the century is not large, only 87 well documented cases having been reported in the literature (15).

Although the fact that repeated irradiation with small doses of x-rays over a period of many years can be associated with a high leukemia incidence is of great interest, it is almost impossible to make any sensible statements about the relationship of dose and leukemia frequency. Braestrup (1) estimates that a radiologist working with old-type x-ray equipment and few protective measures was exposed to as much as 100 roentgens of x-rays per year. He believes that exposure of individuals before 1930 was considerably higher than this, whereas, at the present time, it averages considerably less than 5 r per year. His estimate of the cumulative total exposure of a radiologist using old-type x-ray units was of the order of 2,000 r during 40 years of practice. In the study to be mentioned later, Lewis (12) estimated the average exposure of all radiologists to be 50 rad per year or 1,200 r in 40 years.

Although it is apparent that a relatively few old-time radiologists received large doses of radiation over a period of many years, the estimates of the average dose for all radiologists obviously are subject to great error. In any given period, the exposure varied with the practice of each individual, his concern for safety, the type of equipment used, and his work load. How the gradual improvement in safety standards and the rapid increase in the number of radiologists influenced the average individual exposures can only be a matter of speculation. It is clear, however, that the scattered radiation from the low-voltage diagnostic equipment responsible for most of the exposure was poorly penetrating in nature. The energy of this soft radiation was dissipated mainly in the tissues of the hands and hands of the radiologists. The abdomen and chest or head and upper chest received the next highest dose depending upon protective measures used. The exposures were intermittent, and the dose rate was low compared with those in the previous three studies.

Aside from showing that repeated intermittent partial-body exposure over many years is associated with an increased incidence of leukemia, study of American radiologists adds little to our knowledge of the quantitative aspects of the relationship between x-ray exposure and the disease. The difference in leukemia frequency in British and American radiologists could be due to the high British standards of radiation protection introduced in the early days of radiology (6).

**Prenatal Exposure to Diagnostic Doses of X-Rays in Children with Leukemia and Cancer**

Recently, Stewart and her colleagues (32) published an extensive survey of the retrospective interview type of 1,399 children dying of leukemia or cancer. These children died before the age of 10 in England and Wales during a 3-year period, 1954–1956. One of their significant findings with respect to radiation exposure was the frequency of diagnostic x-ray examinations (13.7 per cent) of the mothers of children with malignant disease. This was almost double the per cent (7.2) of such examinations in the case of mothers of the
control children. The control children in this study were matched with the study child for age, sex, and locality but were otherwise randomly chosen from the official registers of births. The average number of films taken was 2.37 per child and the exposure has been calculated to be of the order of 86-600 milliroentgens per film measured at the gonads of the fetus (38). If one assumes that radiation was the etiologic factor in the 6-7 per cent excess of the leukemia children receiving prenatal exposure, as the authors proposed, then sixteen to eighteen cases of leukemia per year would have resulted from this diagnostic practice.

Four other retrospective studies in different sections of this country have attempted to obtain the same information from the mothers of children dying of leukemia and cancer. That of Ford and her colleagues in New Orleans (8) is concerned with 78 leukemic children and 74 children with other malignant disease compared with 306 dead controls matched for color, age, and place of death. The findings of this study confirm the observations mentioned above. Thus, 26.0 and 28.4 per cent of the children with leukemia and with other forms of cancer, respectively, had been irradiated in utero, whereas only 18.3 per cent of the control children had been so exposed.

The three following reports using other methods for selecting controls do not show the same excess of fetal irradiation in leukemic children. Polhemus and Koch (25) found no difference in the history of prenatal irradiation in 251 children diagnosed as having leukemia in the Children's Hospital of Los Angeles and in the same number of matched control children with nonorthopedic diseases on the surgical service of the same hospital. In a current study of childhood leukemia in California, Kaplan and Moses (11) found that the number of children with leukemia having a history of prenatal irradiation exceeded that of the untreated siblings. However, such an excess was not observed when the leukemic children were compared with healthy playmates. Murray and colleagues (22) found no difference in the history of prenatal exposure of 65 children with leukemia, 65 matched dead controls, and the 175 living siblings of both groups.

In retrospective studies of this kind, the choice of the control group may be crucial in reaching definitive conclusions. Questions can always be raised about the strict comparability of controls even when selected with great care and forethought. It would seem that the studies as presented do not differentiate clearly between the association of leukemia and (a) the effect of the medical condition which justified the diagnostic examination or (b) the effect of x-rays. Clearly, more studies, preferably prospective in type with more than one control group, are needed to determine whether small doses of x-rays of the magnitude used in radiology are leukemogenic to the human fetus.

INDIVIDUAL CASE REPORTS OF LEUKEMIA IN PERSONS EXPOSED TO RADIATION

There are a number of individual case reports of leukemia occurring in persons who have been exposed to the radiations from internally deposited radioactive materials. For example, four cases of leukemia (18) have been reported in patients given thorotrast parenterally. Similarly, six cases of leukemia have been recorded in persons given therapeutic doses of I\(^{131}\) for hyperthyroidism (34). Since the total number of persons so treated is not known, one cannot be certain that this represents more than the expected number. In a recent report (34), it has been estimated that this is not an excessive number of cases assuming that all have been reported. It is interesting to note, however, that five of the six cases occurred within 2 years after treatment with the radioactive iodine. This is a much shorter latent period than that usually observed when leukemia develops in persons exposed to ionizing radiation.

In a report on the frequency of diagnostic radiographic procedures in 888 cases of leukemia, Faber (8) states that adults with chronic myelogenous and acute leukemia have a history of having more frequent diagnostic x-ray procedures than persons with chronic lymphocytic leukemia. He believes that the exposure of the body to diagnostic doses of x-rays must be partly responsible for causing these forms of leukemia.

THE LEWIS' STUDY OF FOUR IRRADIATED POPULATIONS

In a stimulating and highly provocative article published in Science, Lewis (12) compared the available data on leukemia incidence and radiation doses in four of the irradiated groups mentioned above. He attempted to assess the probability of developing leukemia on the basis of the calculated dose of radiation absorbed in the blood-forming tissues of each individual of the four groups. Using a number of assumptions concerning dosages and correcting for the amount of tissue exposed, Lewis found that his "best" estimate of the probability of developing leukemia/individual/roentgen/year is essentially the same in all groups, namely, \(1-2 \times 10^{-4}\). Even for the different exposure groups of the patients with ankylosing spondylitis and of the survivors of the atomic bomb-
ings, his calculation of the probability of developing leukemia per roentgen was approximately the same. Because each roentgen appears to be equally effective in inducing leukemia, regardless of race, sex, age, and period of exposure, Lewis concluded that the cases of leukemia in irradiated individuals could be regarded as the somatic counterpart to a radiation-induced gene mutation in germ plasm.

Reconsidering his calculations in the light of more recent information, the values for the probability for the different groups do not seem quite as close as Lewis found. Using the new estimates of leukemia frequency in Hiroshima, the probability varies from 0.3 to $1.2 \times 10^{-4}$ in the different exposure zones (83). The negative probability in the 2,000-2,999-meter zone does not seem meaningful in view of the small size of the group and the absence of cases. Lewis' probability value calculated for children with thymic enlargement and for American radiologists should be modified, because his estimates of the average dose to the entire blood-forming tissues are incorrect. Since the average dose administered to each child was 250 roentgens and since less than a fourth or fifth of the body was exposed, the probability in their cases should be at least $4-5 \times 10^{-4}$ rather than $1 \times 10^{-4}$. According to Lewis' estimates of the average exposure for the radiologists, but with the assumption that the soft x-rays irradiated only one-half to one-third of the blood-forming tissues, the probability becomes at least $4-6 \times 10^{-4}$. In the case of the children irradiated prenatally, which Lewis did not consider, the probability turns out to be of the order of $10^{-11} \times 10^{-6}$.

The minor corrections of Lewis' calculation do not alter the fact that dividing the leukemia frequency by the estimated dose results in a remarkably constant number. Whether it is justifiable to include the radiologists in this study is debatable since the dose estimates represent nothing more reliable than a guess. The recent finding of Russell (26) that the frequency of genetic mutations varies with the dose rate raises the question whether or not a constant probability of producing leukemia per roentgen absorbed in the blood-forming tissue should be considered as evidence for a somatic mutation being responsible for the development of the disease. This may be unimportant in the present studies because the dose rate is relatively high in all cases. The lowest dose rate presumably occurred in the radiologists who were exposed to scattered x-ray mainly during fluoroscopic examinations. Even in these cases, the exposure rate was probably high compared with background radiation. A final point to be considered is that the number of persons receiving less than 500 roentgens is relatively small in the case of the spondylitic series and the radiologists, and, in the latter series, the dose is highly uncertain. Therefore, it would seem that Lewis' probability values do not apply to persons exposed to less than 500 roentgens except for children and for some of the Japanese.

ADDENDUM

Since this article was submitted for publication, the results of two other studies of a similar nature have been brought to the attention of the author. Latourette and Hodes (Am. J. Roentgenol., 82:667, 1959) studied 867 out of 935 patients treated for thymic enlargement at the University Hospital in Ann Arbor, Michigan, mostly before 1942. Seven hundred and eighty-three received less than 200 roentgens, usually through a 10 x 10 cm. port. One of the children of the families contacted had died of leukemia and another of lymphosarcoma. In another, as yet unpublished, study, Saenger, Silverman, Sterling and Turner (personal communication) interviewed the families of 1,644 of 3,230 children treated with x-rays for various benign conditions in Cincinnati, Ohio. One of the traced group had died of leukemia, ten had cancer of the thyroid, five had other types of malignant disease, and a number of others had benign neoplasia. Forty per cent of the children had received less than 400 roentgens, 65 per cent less than 400 roentgens, and 90 per cent had an unknown dose. In 81 per cent of the cases, the port size was less than 75 sq. cm., and in almost all others with known exposure factors, the port was less than 100 sq. cm. Approximately one-third of the patients were treated for thymic enlargement, and another third received treatment to the head and neck.

REFERENCES

Epidemiological Studies of Leukemia in Persons Exposed to Ionizing Radiation

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