EDITORIAL

The Etiologic Role of Radiation in the Development of Leukemia

By Eugene P. Cronkite

The evidence for radiation as an etiologic agent in the development of leukemia of certain types in animals and in man is unquestioned. The first indication of the induction of leukemia in man by x-ray was published in 1925 by Emile-Weil. Krebs and Furth demonstrated shortly thereafter the feasibility of inducing leukemia by irradiation of animals. Subsequently the abundant work of Furth, Kaplan and Mole on the development of leukemia in irradiated animals, the mechanism of the development of leukemia, and the evidence for a dose rate dependence and direct and indirect mediation have all been well established. Because of marked species differences in susceptibility, the experimental production of leukemia in animals by radiation and other etiologic factors, important as it is, may be of less value in trying to evaluate the relative hazard of radiation for man than a statistical analysis of the incidence of human leukemia.

Early in the century, cases of leukemia were described in x-ray technicians and other individuals working with radiation. Reputedly Mme. Curie died of leukemia or aplastic anemia. March, in a statistical study in the late 1930's, noted that the incidence of leukemia was higher in American radiologists than in physicians who had a limited exposure to radiation. Other reports followed. More recently, following the use of atomic bombs for military purposes in Japan, the Atomic Bomb Casualty Commission was established as a joint American and Japanese endeavor for the study of the exposed populations. The now classical studies of the American-Japanese groups have established that radiation was leukemogenic in Japan. There is some evidence from these studies in Japan that the incidence of leukemia increased as a linear function of the dose. However, there is a large error in the estimation of the dose. Cases of leukemia are still appearing in the exposed Japanese, although there is some uncertainty whether the rate is diminishing or perhaps, after certain low doses, even increasing. The results from Japan must be interpreted, with some reservations, as an incomplete study which is still in progress. Either revisions of the incidence or of the dose may conceivably alter the interpretation of the quantitative dose effect relationship in the future.

Court-Brown and Doll have reported on the occurrence of an increased incidence of leukemia in individuals given therapeutic x-ray irradiation of the spine for ankylosing spondylitis. Their data, between the observed points,
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Tended to show a linear relationship. However, when the highest dose is used, the relationship is curvilinear diverging from the apparent linearity at lower doses. Extrapolation of the linear portion of the curve downwards below the lowest observed dose of approximately 300 rad to the spinal marrow intercepts the coordinates at approximately 0 dose. However, the 95 per cent confidence limits of the statistical estimates of this intercept are 0-400 r. Therefore, it is statistically conceivable that there may be a threshold as high as 400—an unlikely event. It should be pointed out that the Japanese cases referred to above relate to whole-body irradiation, in contrast with the spinal irradiation of the patients with ankylosing spondylitis.

There are other sources of data that demonstrate the leukemogenic effects of radiation in human beings. For example, it has been shown by Simpson and Hempelmann that irradiation of the thymus in infancy results in an increased incidence of acute leukemia in the children irradiated, as compared to non-irradiated children who did not have enlarged thymuses. The authors very appropriately point out that the data are difficult to analyze because children who have enlarged thymuses in infancy may be more prone to later development of leukemia; hence there is no adequate control as yet. Furthermore, it is possible that some of these children may have had early mediastinal lymphoma.

Another source of debatable data is the assertion by Stewart and associates\(^2\) that the offspring of mothers who had pelvic diagnostic roentgen irradiation during pregnancy showed a higher incidence of leukemia than the siblings who were not irradiated in utero. All sources of data on the problem are discussed elsewhere.\(^2\) The findings of Stewart et al. in general are not supported by retrospective surveys in the United States. A recent prospective survey by Court-Brown et al.\(^3\) has shown that the incidence of leukemia in about 40,000 children whose mothers had diagnostic pelvic x-rays during pregnancy was not increased significantly. It is reassuring to know that doses of radiation in this range\(^4\) did not frankly increase the incidence of leukemia. If one assumes an average dose of one rad to the fetus and then computes the expected extra cases of leukemia in 40,000 children using the United Nations factors\(^5\) for computation, one would expect about one additional case, an increase from 9 to 10. Hence, these data are of no value in answering the question of threshold since a population nearer to \(4 \times 10^4\) would be needed to detect a leukemogenic effect at one rad exposure.

As the public became better informed about the sources of radiation in the modern environment and in particular about the contribution of fallout: radiation, considerable anxiety and numerous accusations of negligence were aimed at the Atomic Energy Commission and the administration in Washington. This is particularly so since fallout radiation involves the entire world and individuals have no freedom of choice regarding exposure. The public was unaware that the subject had been under constant study. For example, the Atomic Energy Commission has supported the Atomic Bomb Casualty Com-

\(^*\)From a fraction of a roentgen to about 5 r, depending upon equipment and technics.
mission in Japan through the United States National Academy of Sciences. In addition, since the early commencement of atomic bomb testing there have been studies of world wide atmospheric contamination together with assays of fallout throughout the world sponsored by the United States Atomic Energy Commission in addition to studies being carried on by other countries.

On March 1, 1954, an unpredictable fallout accident occurred following the experimental detonation of a large nuclear device in the Pacific Ocean. This incident, which emphasizes the potential hazards of radiation from the use of nuclear devices, resulted in the exposure of a large number of individuals to radiation from fallout. It was followed by considerable comment both from the press and diplomatic sources. During 1955, two extensive surveys on the effects of radiation on mankind were made in the United States and in the United Kingdom summarized in reports of the BEAR* Committees of the U. S. National Academy of Sciences and in the report of the British Medical Research Council for the United Kingdom. Both pointed out that the hazards to radiation in general and to leukemia in particular were realistic and definable. It had not been fully appreciated prior to these studies that in the western world the major exposure to ionizing radiation came from the medical and diagnostic uses of x-ray and radioisotopes and not from background, industrial uses or radioactive fallout. During 1957 and 1958, the Scientific Committee on the Effect of Atomic Radiations of the United Nations studied the problem exhaustively and published a comprehensive monograph on the effects of radiation on man. Again it was pointed out that the major source of exposure of human populations to radiation was the diagnostic and general medical uses of radiation rather than fallout, background or industrial uses of radiation.

The year following the classic survey by the National Academy of Sciences and the British Medical Research Council, Lewis in 1957 published a paper on radiation leukemogenesis in which he developed the hypothesis that there was a direct linear relation between the dose of radiation and the occurrence of leukemia and that there was no threshold dose of radiation for induction of leukemia. Brues has criticized the linear, "no threshold" concept and presented in a forceful fashion the available information indicating that a threshold may be operative. As to Lewis's hypothesis and Brues' attempt at refutation, one must conclude that neither case is proved. Burnet has considered critically the epidemiologic aspects of ionizing radiation and the development of leukemia. He has concluded that one must absolve radiation and viruses as being the major contributing causes to the increased incidence of leukemia in man in the last few decades. Admittedly his conclusions are highly speculative.

In addition to the external sources of radiation that have been shown to produce leukemia in man, it has also been shown that the therapeutic use of I may produce leukemia if the dosage has been sufficiently high (greater than 1 curie). This problem has been reviewed. Moloney also recently

*Biologic Effects of Atomic Radiation.
has presented a series of cases and in general outlined criteria that might be reasonable evidence for radiation-induced leukemia in man.

At the 1959 annual meeting of the American Society of Hematology, Dr. Jacob Furth, chairman of the symposium on leukemia, interrogated the assembled hematologists in respect to their own personal experience in observing cases of leukemia believed due to exposure to radiation, viruses, other carcinogens, etc. At least 28 cases were ascribed by the hematologists present as probably due to radiation. This is a startling observation, if true. Human experience to date, assembled and reviewed, shows that there are 12 reported cases due to occupational exposure, 55 from therapeutic irradiation of spondylitics, 18 from other therapeutic irradiation, 9 from $^{131}$I therapy, 9 ascribed but not proved due to Thorium, and 123 in survivors from the atomic bombs in Japan for a grand total of 226 cases. If one adds to these all of the questionable sources such as thymic irradiation, fetal exposure to diagnostic x-ray, etc., perhaps one can enlarge the group to about 300 cases. If at one annual meeting of the American Society of Hematology a number of cases equal to approximately 10 per cent of the total documented cases of the world's literature are claimed, the problem is one which must be carefully scrutinized. There will be an unquestioned increase in industrial and medical uses of radiation. Leukemia induction and other cancerogenesis by radiation is much too important a problem in the modern world to have physicians attribute some cases of observed leukemia to these agents without giving due consideration to minimal acceptable criteria for a radiation-induced leukemia and other possible leukemogenic factors in modern society.

The purely clinical problem of the relationship of $^{131}$I to therapy to later development of leukemia is one that is receiving intensive study. Pochin\textsuperscript{25} has recently analyzed the data in Great Britain. The observed incidence of leukemia in individuals treated with $^{131}$I for hyperthyroidism, and the expected incidence were very similar. Pochin points out that it is entirely conceivable in his study that there is a higher incidence because of under-reporting of cases. A questionnaire by S. Werner to thyroidologists has disclosed more cases of leukemia. Presently, the Bureau of State Services of the U. S. Public Health Service is sponsoring a nationwide retrospective and prospective cooperative followup study of patients who received therapeutic doses of $^{131}$I.\footnote{The Managing Secretary-Coordinator is Dr. A. Bertrand Brill, Johns Hopkins University, Baltimore, Md.}

One purpose of this editorial is to suggest minimal criteria for use of hematologists before considering radiation the most probable pathogenetic factor in any given case and discuss the problem of linear dose effect response and threshold. An analysis of this latter problem has been published.\textsuperscript{17} The latest analysis is from the U. S. National Academy of Sciences.\textsuperscript{29} Brues\textsuperscript{30} has pointed out that the doctor or health physicist is often asked by society to give an answer for guidance before adequate data are available and is expected to give an answer that will satisfy the human, social, ethical and economic requirements. The adjectives in the case of radiation that are used to modify
his answers are, "safe", "permissible" or "tolerable". This problem becomes extremely unscientific and confused when one gets into the area of low dose effects. At this time some scientists may take a low assumed but possible incidence and multiply it by the population of the world as has been done and come out with what appears to be an intolerable situation and thus ignore the eternally present concept of calculated risks in all endeavors.

If an increased incidence of leukemia is truly the end result of a non-threshold radiation effect then diagnostic x-rays and even background radiation itself are contributing their share to production of leukemia and presumably to other neoplastic diseases. With the assumption of linearity, no threshold and the best statistical estimate of the probability of leukemia/rad/individual at risk/year, the United Nations Scientific Committee computed the number of cases of leukemia due to the various sources per year in the United States and in the entire world. Any increase in the leukemia incidence is a tragic event. When the small possible increase from radiation is compared to the large positive life saving benefits of diagnostic and therapeutic x-ray, the small possible hazard dwindles into an acceptable and ethical possibility. For fallout, no brief can be given since it performs no useful purpose. For industrial development of nuclear power in the face of a diminishing fossil fuel supply, the benefits will unquestionably outweigh the small hazard which in good measure is avoidable by adequate design and protective measures.

It can be concluded that: (1) Data to predict the yield of leukemia per rad exposure per population at risk is adequate following a single acute exposure between the limits of exposure observed in Japan. Between these limits the yield appears to be roughly linear with doses above approximately 100 r. In the lowest dose group, data are inadequate to demonstrate if there is a threshold. (2) Evidence for a dose rate dependence in animal studies is good. Accordingly, it appears unlikely that the yield of leukemia for single doses and doses protracted over a lifetime would be the same. (3) It appears unlikely that the incidence of leukemia after exposure will continue at the same rate for the rest of life of the exposed population since the incidence in Japan appeared to go through a maximum in 1951. This is consistent with animal data. To assume that there will be no difference in the effectiveness between whole-body, thymic, spinal marrow or irradiation by radioisotopes deposited in the bone such as Sr or radium is not justified; this would be inconsistent with a large mass of animal data. (5) The dose of radiation in all human situations is not well known and in particular the exposure of American radiologists during their working lifetime has not been definitely established. To summarize the statement as the Subcommittee on Acute and Chronic Effects of Radiation on the Blood of the Committee on Pathologic Effects of Atomic Radiation of the National Academy of Sciences concluded: "It is recognized that the establishment of a threshold dose would be most

*After single large doses of external radiation, the best estimate is 1–2 cases of leukemia per million population at risk per year per rad averaged over at least 10 years. This value is used to estimate the hazard of acute exposure but has not been shown to apply after low doses, chronic or intermittent exposure.
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reassuring to those who have to be exposed and to those who must make policy decisions. However, data are not adequate to prove the existence of or the absence of a threshold for leukemia induction by radiation, nor is it possible to determine for all exposure conditions the shape of the dose effect curve even between the observed points.”

In view of the great importance of the problem, attempts at retrospective, prospective and animal experimentation on radiation leukemogenesis and carcinogenesis in general should be intensified.

There is no simple way of setting up criteria for radiation-induced leukemia of man. Chronic lymphocytic leukemia has not as yet been unequivocally connected with prior exposure. Since the incidence of chronic lymphocytic leukemia increases with age, one would expect more cases in aging radiologists. At the present time it is probable that this disease should not be considered radiation-induced. Acute or chronic exposure to radiation should be documented with dose estimates. It can only be hoped that the cytologic type of leukemia will be well established during life by appropriate clinical and laboratory studies. When single cases of leukemia develop after a cumulative exposure of less than 100 rad, it would not be logical to implicate radiation as the cause. To establish the leukemogenic capacity of the dose requires large numbers and an adequate statistical analysis. However, when leukemia develops one to fifteen years after larger single doses of radiation, it is now feasible to estimate the statistical probability that this leukemia was due to the prior radiation exposure. In conclusion, it appears desirable to establish a radiation leukemia registry in some organization within the U. S. with the purpose of evaluating the likelihood of radiation as the etiologic agent.

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