

Evidence for Radiation and Chemicals as Leukemogenic Agents

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Introduction

Modern society is replete with hazards of life on all hands. The hazards in the home, daily living, industry, and recreation *can* only be considered sensibly when divorced from politics, diplomacy, and emotions, and compared with the benefits to society at large or the personal satisfactions gained in particular. It is human for an individual to take a risk. It is reprehensible for individuals to be forced to submit to risks of which they have neither knowledge nor the opportunity to choose to accept the risk. For the public to accept a risk they must know what it is and the magnitude of this risk. Since the average citizen can neither understand nor equate the hazards, these must be performed by appropriate scientific groups and duly considered by legislative bodies for appropriate action. The heart of the problem in the induction of leukemia by industrial hazards rests upon quantitation of the agent **to** the yield of leukemia. Two agents used in industry have been correlated with an increased incidence of leukemia in human beings. The first, ionizing radiation, is unquestionably able to increase the incidence of leukemia. The second agent, benzol, probably can produce an increased incidence of leukemia, but the data are not as good as for the former. First, the finger of suspicion must be pointed at any agent which is able to produce an aplasia of the bone marrow, assuming it will probably be able to produce leukemia also. Second, there is no reason to doubt that any agent which will produce a cancer elsewhere in the body will not also be able to produce a leukemia if the offending agent is transported to the hemopoietic tissues. The types of radiation exposure of human beings that have resulted

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in an increased incidence of leukemia, the dose-effect relationships, and evidence for chemical leukemogens will be reviewed.

Induction of Leukemia by Ionizing Radiation in Man.—Historically, leukemia was correlated to overexposure to x-ray in the professional use of x-rays over 40 years ago.¹ Since the initial correlation there has been a continual procession of cases. Most of the earlier observations correlating radiation exposure in the practice of medicine or industrial use of radiation with the later development of leukemia only serves to demonstrate the fact that radiation can be leukemogenic, and does not answer the important problem of whether there is a threshold dose or the type of the dose-effect relationship. In discussing the leukemogenic action of radiation, it is necessary to recognize that this constitutes only a small fraction of the total problem of the radiation hazard, and that one is also concerned with carcinogenesis in other organs, life shortening, decreased fertility, cataracts, and genetic damage. There are 2 sets of data; one involves a single, relatively large exposure of human beings, and the other involves chronic exposure. The largest single amount of data is that which has been gleaned from the survivors of the Japanese atomic bomb explosion,^{2,3} which has been reviewed critically.* After the single large exposure as occurred in Japan, many of the individuals exposed had a severe temporary aplasia of the bone marrow. In those that recovered from this, there was a definite increase in the incidence of leukemia that seemed to commence about 1½ years after the bombings. However, in reality the minimum latent period may actually be shorter, since adequate clinical studies were not practical due to the chaotic conditions in the earlier period after the bombing. The largest number of cases of leukemia appeared in 1951 and 1952. Thereafter, the number apparently decreased, but cases of leukemia in excess of the expected incidence were still being found in 1960. Many observers have analyzed the incidence of leukemia in Japan.

The modal incubation time is approximately 5 years, and it has been deduced by et al.,⁵ on the basis of both the Japan—data and the incidence of leukemia in spondylitics given therapeutic spinal irradiation,⁴ that probably 90% of the cases will occur within approximately 10 years after exposure. In view of the various analyses and data published, it appears that an assumption that the incidence of leukemia will continue at a constant rate throughout the duration of life as has been assumed by Lewis⁷ is not justified. The most valuable published data for studying the dose-effect relationship of leukemia is that of Heyssel et al.⁸ Many investigators have plotted the incidence of leukemia against the computed dose of radiation in Japan. Burch⁸ has shown that the data can be treated as a curvilinear relationship. Heyssel et al.⁸ have chosen to interpret it as best fitting a linear no-threshold relationship. When one treats the data as if the incidence versus dose were linear, fully recognizing that the slope of the line is not known with precision, one can make a general estimate that the incidence of leukemia per rad, measured outside Japanese homes per million people at risk per year following a single exposure, is about 1 case per 10⁶ population at risk for at least the first 10 to 15 years after the exposure. Since neither the dose within the homes nor the absorbed dose is known adequately, it is not yet possible to estimate the incidence per unit of absorbed dose, the entity in which one is interested. However, the incidence would be greater for absorbed dose than that listed above. Another set of data is the incidence of leukemia in persons with spondylitis who were exposed to therapeutic spinal radiation. These data have been extensively analyzed by Court-Brown and Doll.⁶ These investigators indicate that the relationship of dose to leukemia may be linear. They conclude in the analysis of the data that there may not be a threshold dose, and that the dose which would double the incidence of leukemia is of the order of 40 rads. They deduce the probability of developing leukemia per year per rad averaged over the whole red bone

marrow system to be approximately that which was deduced for the Japanese. In passing, it is of interest to note that the confidence limits of their threshold dose varies between 0 and approximately 400 rads.

A very critical study from the standpoint of determining the relative magnitude of a minimal threshold dose for leukemogenesis is the asserted correlation of in utero exposure from pelvic diagnostic x-rays to the later development of leukemia in the offspring. Stewart et al.⁹ have reported a higher incidence of leukemia in children exposed in utero to diagnostic radiation than in the control population. It is imperative to establish whether diagnostic x-rays of the pelvis in pregnancy will induce leukemia. Obviously, if this small dose (1-4 rads) is leukemogenic it indicates a very low threshold or that the fetus is extremely sensitive to later development of leukemia. However, this is a very difficult problem to analyze statistically. Court-Brown and Doll¹⁰ have recently published the 10-year incidence of leukemia in 40,000 children who received in utero irradiation. The incidence of leukemia in these 40,000 children who had received x-ray in utero was essentially the same as the incidence in the control population of children. Whereas this is reassuring, it does not answer satisfactorily the question either of sensitivity of the fetus or of a threshold. If one assumes the same sensitivity of the fetus and the adult and computes the increased incidence of leukemia in the children in the first 10 years after birth, one would have a difference of only one case,* assuming a 4 rad exposure and using the doubling time of radiation suggested by Court-Brown and Doll.¹¹ Thus, to answer this question, not 40,000 children would be needed, but, more nearly, 4,000,000 births would have to be analyzed.

Irradiation of the thymic area alone has been correlated with a later development of leukemia¹² and reviewed.¹ A large number

of children have been irradiated shortly after birth for a presumed enlarged thymus. This set of data indicates that the type of therapy resulted in an increase in the incidence of leukemia. However, because of uncertainties in dose, the port size, the precise area radiated, and the absence of an adequate control population, it is not feasible to deduce any realistic yield of leukemia per rad of exposure to this area.

A series of observations on x-ray therapy, repetitive diagnostic x-rays, radiothorium, and I¹³¹ therapy for cancer indicates that all of these situations can be leukemogenic, but it is not practical to deduce any realistic dose-effect relationship.¹³ Since I¹³¹ may be used under various industrial conditions a further discussion of the hazard of this isotope appears in order. Thousands of people have been treated with multimillicurie amounts of I¹³¹ for hyperthyroidism. However, there is no well-documented case of leukemia in these individuals that could be reasonably associated with the prior treatment with I¹³¹ for hyperthyroidism.¹⁴ However, following a case of the treatment of thyroid cancer with doses of I¹³¹ totaling in excess of 1 curie the incidence of leukemia is greater than would be expected.¹⁵

Lastly, one comes to the consideration of occupational exposure in radiologists, nurses, technicians, and physicists, and what might be expected to occur in the chemical processing of radioisotopes and the utilization of radioactive sources and isotopes in industry. The incidence of leukemia in American physicians is about 1.7 times what it is in the population at large.¹⁵ The incidence of leukemia is higher in radiologists than in nonradiologists.¹⁶ In Great Britain the incidence of leukemia is not higher in radiologists than in nonradiologists. This is probably ascribable to the fact that almost all x-rays in Great Britain were taken in hospitals by radiological technicians in contrast to the United States, where a high fraction are taken in private offices by the radiologist, and because x-rays were used more widely in the United States than Great Britain. The existence of an increased in-

*This method of analysis suggested by Dr. Leonard Hamilton, Sloan Kettering Institute for Cancer Research.

cidence of leukemia in these individuals chronically exposed to radiation is unquestioned. However, it is not feasible to deduce any realistic dose-effect relationship.

Radium was administered to many individuals for therapeutic purposes before its hazard was well appreciated, and a larger number of individuals were exposed in industry utilizing radium and mesothorium for watch dials. The incidence of osteosarcoma, cancer of the nasal sinuses, and aplastic anemia was high in these individuals. In the watch dial painters, Martland's descriptions "of an intense replacement of the normal fatty marrow by a red actively regenerating bone marrow with numerous primitive red and white cell precursors is classic. However, the conclusion of Martland, "it would seem very likely that a myeloid leukemia could easily develop" has not been realized except in one case report. The reason for the relatively small yield of leukemia with radium poisoning is not clear.

The industrial problem becomes then one of ability to predict the hazard and make calculated risk decisions. The problem of the dose rate dependence is therefore critical. For the single dose, the Japanese data are reasonably good and give one a reasonable estimate of the excess leukemia to be expected in a population receiving doses in excess of 100 rad in a single exposure. For doses less than 100 rad it is not as reliable because of the few observations between no dose and the lowest, well-documented dose. None of the human sets of data provide a satisfactory dose-effect relationship below 100-rad exposure or for chronic radiation. However, one can lean in part upon the animal observations of Mole,¹⁸ who has shown that animal leukemogenesis is dependent upon dose rate. However, in his experiments, the dose rate was also relatively high compared with background, diagnostic, fall-out, and industrial exposure. It is hazardous to make quantitative extrapolations from animals to man; however, it is equally hazardous to set up assumptions for man that are in a variance with the wealth of animal experimentation available. If one

assumes a dose rate dependence for man, then the hazards from chronic exposure are less than with the acute exposure.

Another important medical legal compensation and industrial problem is the estimation of the probability of cause and effect relationship when a case of leukemia (other than chronic lymphocytic) develops in an individual who has had prior exposure to radiation. If the leukemia develops 15 to 15 years after exposure, and if one uses the unproved linear no-threshold hypothesis with a yield of 2 extra cases per 10^6 persons at risk per year per rad exposure, for 15 years, a probability can be computed at any age, using the expected incidence of leukemia at that age. After single doses less than 100 rads and with chronic exposure, these estimates will have little reliability. It is well known that development of many of the late effects of radiation is a statistical process, and it is impossible to predict what is going to happen to any one individual. However, after the leukemia has developed, one can compute the probability of cause and effect relationship to prior exposure, as Bonner has done:

As an example, one can take a case of leukemia in a 30-year-old man exposed previously to 10 rad. The natural incidence of leukemia at this age is about 25 cases per million, per year. Applying Lewis' figures literally, 10 rad may result in 20 leukemias per million per year, or the chances of getting leukemia any one year from 10 rad are approximately 20 in a million. In the first 2 years following exposure. The total chances are 20 plus 25, or approximately 45,000,000. The chances that the 10 rad are responsible for this leukemia are approximately 20 out of 45. Because of the increasing natural incidence of leukemia with age, the chances of the 10 rad being responsible are approximately 20 out of 54 if he develops leukemia at age 40, 20 out of 169 at age 60, and 20 out of 296 at age 70. These computations of probability can be made for any dose and any age, but are never proof of causal effect. The leukemia may still have been spontaneous.

Before leaving radiation hazards, a comment on the maximum permissible dosage is in order. It is common knowledge that these have been reduced regularly since 1934 from 100 rem per year to the current 5 rem

per year. It is mistakenly believed that the reductions have been recommended by the National Commission of Radiation Protection and the International Commission of Radiation Protection because evidence shows somatic injuries at the earlier levels of 100 rem. This is not the case. There is not a single case of proved personal injury to an individual exposed in the so-called maximum permissible dose range. The maximum permissible dose ranges have been reduced purely because of genetic considerations—possible but not proved harm to generations yet unborn. The atomic energy industry has a remarkable record of safety in respect to radiation injury, and the planners are to be commended.

Philosophically, in respect to somatic and genetic hazards, Brues²⁰ has pointed out that "the doctor or the health physicist is asked practical questions and, since progress does not or cannot wait for the scientific answers, is expected to give an answer before adequate data are present. In the case of radiation he is forced to employ such adjectives as, "safe," "permissible," or "tolerable," in order to satisfy the human, social, or ethical requirements. This problem becomes extremely unscientific when one becomes involved in the area of low dose effects. In this area the theoretical scientist may take a low incidence and multiply it by the population of the world and come out with what appears to be an intolerable situation, ignoring the calculated risks in all human endeavors. When death, disease, or injury is being produced by a factor in society it can only be considered in relation to the benefit obtained. An interesting comment which helps to place the problem in humorous if not correct perspective is an article that appeared in the London Times, Sept. 9, 1959. Professor Mayneord (a distinguished x-ray physicist) and associates analyzed carefully elements of the British diet and concluded that a typical high carbohydrate British diet contains amounts of radium and thorium equivalent in effect to some 300 times the present intake of Sr^{90} in nuclear explosions. It was pointed out

that 4 ounces of Brazil nuts contains 3 times as much radium and thorium as the entire bone and soft tissues of a normal adult. In typical British irony, "If the level of Sr^{90} in food in this country represents a radiation hazard, and apparently does to the arm-chair calculator, then the whole process of eating food must be regarded as highly dangerous."

Chemicals as Leukemogenic Agents in Man.—The case for radiation being leukemogenic can be considered air tight. However, the case for chemical leukemogenic agents in man is not nearly so good. As stated in the introduction, any agent capable of producing an aplasia of the bone marrow should be considered as potentially leukemogenic. The chemical substances that have been accused of being responsible for the later development of leukemia in animals are legion. However, to date only benzol has been investigated sufficiently well to make it appear a serious contender for the part of a chemical leukemogen in man.²¹ A much better sound statistical examination of the danger to industrial porkers of benzol is needed comparable to the extensive retrospective and prospective studies with sources of radiation.

Apparently the first case of leukemia in a benzol worker²¹ was published in 1928, and the second²¹ in 1932. The typical history is that of prolonged exposure to benzol vapors in rubber or other industry for many years, with ultimate development of fatigue, anemia, leukocytosis, immature cells in the peripheral blood, and death. Cause of death in some instances was ascribed to aplastic anemia, and in others, to leukemia. The autopsy studies of Mallory et al.²² and others implicate leukemia in some cases and aplastic anemia in others. When the correlation between an exposure to a toxic substance and the later development of disease is questionable in man, one naturally turns to animal experimentation to implicate the agent as being potentially leukemogenic. In this case the numerous animal studies remain equivocal. The published human studies in respect to the relationship of

benzol to leukemia and other blood dyscrasias is akin to the situation with radium. Martland,¹⁷ in his classical series of studies on the late pathologic effects of radium poisoning, described the cases which developed osteosarcoma, carcinoma of the nasal sinuses, and aplastic anemia. No mention was made of the hundreds or thousands of individuals who did not develop an obvious late effect. It was only in 1959 that a study was commenced in New Jersey of the total population of those exposed to radium in 1914-1919 and still alive, to try to obtain a better evaluation of the hazard in a statistical sense. In the industries using benzol, extensive studies have been made on obvious hemopoietic diseases that developed in these workers in Massachusetts by Bowditch and Elkin,²² Hunter,²³ and Mallory et al.²⁴ Eighty-nine individuals were found with hematologic abnormalities who had been exposed to benzol. Ten died, one from acute leukemia. Additional cases were studied by Mallory, and from 19 cases, autopsies or marrow punctures, cases with aplasia and normal cellularity, hyperplasia of the marrow, and acute leukemia were observed. The spleen in many instances showed more or less widespread foci of hematopoiesis which, in advance cases, became extremely large and undifferentiated. The transition to leukemia thus appeared to be gradual in this material. In addition, in some cases, fibrosis of the marrow accompanied extramedullary hematopoiesis, and this fact has been interpreted as signifying that benzol can cause a syndrome of myelofibrosis and myeloid metaplasia as well as leukemia with aplasia of the marrow as a third possibility. The relation between leukemia and myelofibrosis is one which has been discussed in great detail by Dameshek and Gunz.²¹ There can be no doubt that there have been "epidemics" of blood dyscrasias in industries using benzol, which certainly incriminates benzol as being a hemopoietic toxin. In these epidemics the cases of leukemia and myelofibrosis have been few indeed. As with radiation, one must consider individual susceptibility,

length of exposure, concentration of the benzol vapor, and whether the exposure is continuous or intermittent. Again, as in the case of radiation, individual susceptibility cannot be measured experimentally. The length of exposure has nearly always been very considerable, varying from several years to several decades, and the disease has appeared many months after the exposure has ceased. A few exceptions have been noted (the shortest duration of exposure being 8 months). The degree of exposure also needs to be marked, and must lead to high concentrations of benzol in the blood and hemopoietic organs.

Summary and Conclusions

Both single and prolonged exposure to x-ray and γ -rays has been demonstrated to produce an increase in the incidence of leukemia in man.

There is no reason to question the leukemogenic capacity of all types and energies of radiation irrespective of the source, providing that the hemopoietic tissues are irradiated.

After single doses of penetrating x-ray or gamma rays, reasonable estimates of the increased incidence of leukemia to be expected can be made. Comparable estimates after chronic exposure, intermittent exposure, and deposition of radioisotopes in bone cannot be made.

Many chemicals and drugs have been shown to be capable of inducing leukemia in animals. Of all the toxic agents to which man is exposed in industry, a reasonable cause and effect relationship has been established only for benzol.

The absence of a positive correlation of leukemia induction with other agents does not give these other toxic agents a "clean bill of health," since all carcinogenic processes are statistical, and the unequivocal demonstration of a small effect may necessitate a sample size in excess of 10^5 . Such an exposed group is a rarity, even in huge industries. When a positive effect is demonstrated in a small group the hazard is relatively great. The leukemia burden from

toxic influences in industry remains unknown, but its sum throughout industry could be significant. Continuous surveillance for an effect and increasing protection against all known leukemogens is essential.

Any drug or chemical capable of inducing bone marrow damage must be assumed to be potentially a leukemogen. The calculated risk concept is ever present in all facets of modern society—recreation, industry, the home, and the practice of medicine. To calculate and weigh the risk demands quantitation often lacking or not evaluated because of an assumed exorbitant cost in dollars. In the evaluation of the radiation hazard, the Atomic Energy Commission is to be commended for its efforts to obtain adequate quantitation of the risk by supporting a wide spectrum of human and animal experimentation, notably absent in respect to most industrial "toxins."

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