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Leukemia in Hiroshima City Atomic Bomb Survivors

It has become generally accepted that an increased incidence of leukemia follows the acute or chronic exposure of various experimental animals and of man to ionizing radiation (*1*). Recently an attempt has been made to establish a quantitative relation beween the probability of radiation-induced leukemia and the unit-dose of radiation received, on the basis of data from studies of various groups of radiation-exposed human beings (*2*).

The survivors of the atomic bombings in Hiroshima and Nagasaki, Japan, comprise two such groups. Reports concerning the occurrence of leukemia in these populations over a period, through June 1956, have been published at intervals by various staff members (*3*) of the Atomic Bomb Casualty Commission (*4*). In addition, an unpublished compilation of certain specific detailed information requested by the British Medical Research Council was prepared in September 1955 (*5*). An analysis of these data appeared in a publication of the Medical Research Council (*6*), and a portion was also published in a report of the National Research Council (*7*).

Since that time a review has been made of all the leukemia cases known to the Atomic Bomb Casualty Commission, and a master list has been compiled. Some of the cases on the September 1955 listing have been dropped for various reasons, and many cases have been added. No detailed official report has been published recently, in the hope that more adequate dosimetry data might become available. This wish is nearing fulfillment because of the joint initiation of a large program of dosimetry studies in 1955 by the Atomic Bomb Casualty Commission and a group of interested organizations, including the Atomic Energy Commission's Division of Biology and Medicine, the National Academy of Sciences–National Research Council, the U.S. Air Force School of Aviation Medicine, Los Alamos Scientific Laboratory, and Oak Ridge National Laboratory. The program is designed to make possible the assignment of a specific neutron or gamma ray dose, or both, in rads to the record of each survivor in the Atomic Bomb Casualty Commission's files for whom sufficient pertinent information is available.

A detailed interim report on leukemia in the Hiroshima atomic bomb survivors is presently being prepared by various staff members of the Atomic Bomb Casualty Commission and the National Research Council. It will include the best currently available dosimetry information resulting from the afore-mentioned collaborative effort. However, because of the present interest in data pertinent to radiation leukemogenesis and the desirability of making available current information obtained by the Atomic Bomb Casualty Commission, Table 1, summarizing results of the leukemia survey in Hiroshima as of December 1957, is presented at this time.

Certain limitations of these data should be pointed out. The program was initiated in 1947, but the present level of intensity of effort was not achieved until about 1950. Therefore, while it may be assumed that the numbers of cases shown for the years 1950 through 1956 are fairly accurate, the numbers that arose in the preceding years may be understated rather seriously. With respect to 1957, it is probable that additional cases remain to be discovered with onset in that year.

The denominators of the incidence rates are estimates, subject to errors of presently unknown magnitude. The 3 June 1953 residential census of Hiroshima was conducted by the Hiroshima Census Bureau and was presumably of a reasonable degree of accuracy. The categorization by distance from the hypocenter was made on the basis of Atomic Bomb Casualty Commission investigations of 50.8 percent of the males and 44.6 percent of the females who reported themselves exposed to the bomb. However, it was found that 3.1 percent of those reportedly exposed were in fact not in the city at the exact time of the bombing.

Apart from the uncertainties regarding the population on 3 June 1953, it may be incorrect to assume that migration in and out of the city during the period from 1950 to the present was the same for persons exposed in different distance categories. However, despite the current lack of pertinent information, the simple expedient of multiplying the June 1953 population values by eight to obtain estimates of person-years at risk has been adopted, since the census date is roughly near the mid-point of the interval under study. This procedure seems reasonable at present, although the magnitude of any resultant error is hard to estimate.

In addition to the above-mentioned points, which have to do with the in-

Table 1. Leukemia in Hiroshima atomic bomb survivors who were residents of Hiroshima City at the time of diagnosis (diagnoses verified by the Atomic Bomb Casualty Commission), as of December 1957.

Year of onset	Total	Distance from hypocenter (meters)				
		Under 1000	1000–1499	1500–1999	2000–2999	3000 and over
1945						
1946						
1947	3		1		2	
1948	7	2	4		1	
1949	5	1	1	1	1	1
1950	9	3	5			1
1951	11	3	7	1		
1952	11	3	5	1		2
1953	12	2	6	2	1	1
1954	6	2	2	1	1	
1955	8	1	4	2		1
1956	6		1	1	1	3
1957	5	1	3			1
Total	83	18	39	9	7	10
		*Estimated population**				
	95,819	1,241	8,810	20,113	32,692	32,963
		Number of cases with onset in 1950–1957				
	68	15	33	8	3	9
		Estimated person–years at risk				
	766,552	9,928	70,480	160,904	261,536	263,704
		Annual incidence of leukemia per 100,000				
	8.9	151.1	46.8	5.0	1.1	3.4

* Based on Hiroshima Census Bureau's daytime population census of Hiroshima City, 3 June 1953.

trinsic accuracy of the data presented, a further caution should be strongly emphasized. The uncertainties involved in inferring radiation dose from distance alone are too large to support conclusions beyond the previously reported qualitative one that those survivors who received large doses of radiation—that is, who were within 1500 meters of the hypocenter—had a significantly higher incidence of leukemia than those beyond that distance, who received relatively little or none (*3*). The relationship of incidence to distance as presented in Table 1 cannot be given a more quantitative interpretation because there are too many variables, as yet unresolved, which cannot be ignored.

For example, the presently available estimates of the air dose in Hiroshima have a large uncertainty, the magnitude of which is itself not yet definite. Also, experimental dosimetry studies at Oak Ridge National Laboratory emphasize the need for detailed information, such as is being collected by the Atomic Bomb Casualty Commission, concerning the shielding situation of any particular survivor at any distance. It is conceivable that the radiation received within a light frame house (the most common shielding situation) may vary from an amount almost equaling the outside air dose to one equal to the outside air dose attenuated by perhaps a factor of two, depending on the position of the person in the house.

In determining the relationship of radiation exposure to the incidence of leukemia, such detailed data must be examined not only for each leukemic survivor but also for enough of the population at risk to permit calculation of statistically significant incidence rates. Until this information becomes available from the dosimetry program, it is premature to attempt precise quantitation of dose-effect relationships in radiation leukemogenesis on the basis of the Hiroshima and Nagasaki radiation-exposed populations (*8*).

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8. Grateful acknowledgement is made for the biostatistical assistance of Mr. Seymour Jablon, National Research Council, and also for the aid of Dr. Lowell Woodbury, head of the Biostatistics Department of the Atomic Bomb Casualty Commission, and his staff. Appreciation is also expressed for the help of Dr. Robert M. Heyssel, who provided the hematological data for 1957, and for the cooperation of the physicians of both the Atomic Bomb Casualty Commission and the city of Hiroshima, who make the long-term Hiroshima leukemia study possible.
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Stimulating Action of Soluble Antigen-Antibody Complexes on Normal Guinea-Pig Smooth Muscle

During the course of a study on the disappearance of soluble antigen-antibody complexes in rabbits, it was observed that normal rabbits exhibited moderate-to-severe shock following the intravenous injection of solutions containing soluble antigen-antibody complexes prepared by dissolving precipitates in excess antigen. The significance of these observations was not fully appreciated until Germuth and McKinnon (*1*) reported their work on the production of shock in guinea pigs following the injection of soluble antigen-antibody complexes formed in excess antigen.

In view of these findings, the investigation described in this report (*2*) was made to determine the effect of such soluble complexes on isolated strips of smooth muscle from the intestine of normal guinea pigs. The Schultz-Dale technique of in vitro tissue anaphylaxis provides a more sensitive measure of the irritability of soluble antigen-antibody complexes than other techniques, and it was thought that this technique might indicate whether nontoxic soluble complexes could be obtained that would permit continuation of the in vivo studies on the disappearance and fate of soluble complexes in rabbits.

The antigen used in this study was recrystallized bovine serum albumin (BSA) (*3*). A pool of antiserum was obtained from rabbits following 12 intravenous injections (of 10 mg each) given over a period of about 4 weeks. Quantitative precipitin curves were obtained by the method described by Lanni and Campbell (*4*). Each tube contained 3 ml of the antigen dilution and 3 ml of undiluted antiserum. The diluent used was saline-borate buffer (pH 8.4; μ = 0.006 borate and μ = 0.16 NaCl). After the tubes had been kept 48 hours at 4°C, they were centrifuged for 45 minutes at 3000 rev/min (1600 *g*) in a refrigerated centrifuge, and the clear supernates were decanted into a separate set of tubes. The precipitates were washed and then analyzed for total nitrogen by Nesslerization (*4*). The guinea pigs used for this work were normal nonsensitized animals, each weighing between 400–500 g. Each animal was killed by a blow on the head, and 30 to 40 cm of the lower portion of the small intestine was carefully removed and kept moistened at all times with warm modified Tyrode solution (*5*). The intestinal contents were carefully removed by flushing the intestine with three or four 25-ml portions of fresh Tyrode solution.

Each supernate was tested, by the method of Campbell and McCasland (*6*), on fresh duplicate strips of guinea-pig ileum (3 to 4 cm in length) from two different animals. The strips were immersed in a 120-ml muscle bath containing Tyrode solution at 37°C, and a stream of O_2 (90 percent) plus CO_2 (10 percent) was used to aerate and stir the bath. The experimental procedure was to allow the muscle strips to equilibrate in the bath for 15 minutes, add 2 ml of the supernate to be tested, and record the subsequent contraction of the muscle strip for a 10-minute period. Five micrograms of histamine was then added to the bath as a means of obtaining a value for maximal contraction. The stimulating effect of soluble complex was expressed as a percentage of the maximal contraction obtained with histamine.

Control tests were made with solutions containing only antiserum or normal rabbit serums, varying in amounts from 0.08 to 3.64 times the amount of protein in

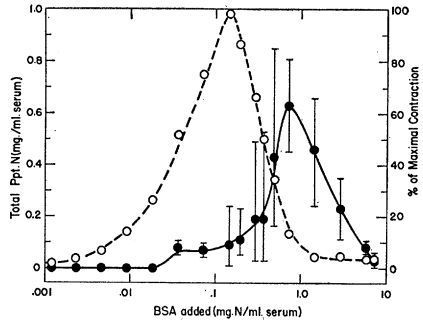

Fig. 1. Relationship between the precipitin curve (open circles) and smooth-muscle contraction (closed circles). The contraction of the guinea-pig ileum is expressed as a percentage of the maximal response obtained with histamine and is the average for six intestinal strips. The range is indicated by the vertical lines.