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HUMAN RADIATION INJURY - A CORRELATION OF LEUKOCYTE DEPRESSION WITH
MORTALITY IN THE JAPANESE EXPOSED TO THE ATOMIC BOMBS.*

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INTRODUCTION:

The method of collection and the subsequent analysis of the hematological data accumulated by the Joint Commission of the Investigation of the Early Effects of the Atomic Bomb in Japan, have been described.⁽¹⁻³⁾ In the present investigations, an additional analysis of the hematological data was made to investigate a possible relationship between leukopenia and the mortality rate within the first nine weeks following the bombings.

It has been frequently observed in laboratory animals exposed to ionizing radiation⁴⁻⁹ that the extent of the fall in the white blood count reflects the dose of radiation received. Smith et al⁵ have demonstrated that in mice survival can be related to the depression of the granulocyte count at various times following radiation. Cronkite and Brecher⁷ and Cronkite, Bond and Dunham¹⁰ inferred that the hematological response could be used as a biologic dosimeter for exposed human beings. This report is concerned with the study of the response of the white blood cells to ionizing radiation resulting from the atomic bomb detonation in Japan.

METHODS:

The data presented here were collected by the Joint Commission for the Investigation of the "Early" Effects of the Atomic Bomb in Japan. The IBM cards and medical charts which are repositied at the Armed Forces Institute of Pathology, Washington, D. C. and the IBM cards at the Atomic Bomb Casualty Commission, Hiroshima, Japan, were used for the present study. This investigation includes data from Hiroshima and Nagasaki, and is limited to the first nine weeks following the bombings. The nine week period was chosen because the incidence of "acute" deaths from radiation decreased

after that time. The leukocyte counts used in this study were made initially by the Japanese. An American medical team arrived in the seventh week and worked thereafter with the Japanese.¹⁻³ In Hiroshima 3116 leukocyte counts and in Nagasaki 2303 counts for a total of 5419 counts were performed. These counts were made on individuals who had been within 3000 meters of the hypocenter. Included in this are 287 counts made on 201 patients in Hiroshima and 73 counts on 59 patients in Nagasaki, all of whom died during the first nine weeks. It is possible that death was not recorded in some medical charts. In this case the data would be included with that of the survivors. The casualties in Nagasaki had more medical attention than those in Hiroshima. However, even in Nagasaki medical treatment was grossly inadequate. It is felt that the treatment received in both cities had no effect on blood cell level and probably did not influence significantly the survival rate although it is conceivable that some benefit accrued in Nagasaki.

Some casualties had single leukocyte counts and others serial counts. When more than one count was performed during a single week, the average was used. Although all casualties were not studied, it is felt that an insight into the relationship of the leukocyte counts to mortality in the first nine weeks following exposure to ionizing radiation can be gained.

A control population was constructed from the leukocyte counts performed on people who were in Hiroshima on August 6, 1945 but who were further than 2550 meters from the hypocenter and who showed no signs of either radiation or other injury. The control leukocyte values are: mean: 7,050/mm³; median: 6,300/mm³; and range: 2,100-17,800/mm³.

RESULTS:

Table 1 lists the total number of leukocyte counts performed in Hiroshima and Nagasaki for the first nine weeks for survivors and non-survivors. The total number of leukocyte counts is greater than the number of people since in some cases more than one count was performed on an individual during the nine week period. The survivors may include a few individuals whose death was not recorded in the medical record. Most of the counts on survivors were done during the fifth and sixth postirradiation weeks. The majority of counts on people who did not survive the nine week period were done in the third, fourth and fifth post irradiation weeks.

Table 2 shows the mean, median and confidence limits of the median leukocyte levels of those people who survived for at least nine weeks in Hiroshima and Nagasaki. The greatest mean and median depression of leukocytes occurred in the fourth week in both cities. Figures 1 to 3 show the percent mortality within nine weeks of those people represented by these counts. For example, in the third week in Hiroshima, people with counts falling into the 1,000-1,999 WBC class interval, 62.5% died in the nine week period. Hiroshima and Nagasaki data are plotted separately and combined (Figure 3). The quantitative difference between Hiroshima and Nagasaki (Figures 1 and 2) is evident. Table 3 shows a compilation of

* The data upon which these figures are based can be obtained in Jacobs, G. J. et al., Human radiation injury. The correlation of leukocyte depression with mortality of re-evaluation of the early effects of the atomic bombs on the Japanese. Technical Report 09-59. ABCC.

data from Hiroshima and Nagasaki of the median leukocyte count and median survival time of those who died within the nine week test period. Data for each week are given as well as the number of leukocyte counts performed on those who died within the nine weeks.

The above data suggest that the white blood count prognosticates the probability of survival after irradiation. The greater the leukopenia during the first five and six weeks after exposure, the higher the probability of death, as would be expected. The relationship of nine-week mortality to the leukocyte level was not constant from week to week. Figure 1 suggests that the best correlation was possible in the third week. However, the characteristics of the curves for the third, fourth and fifth weeks may be distorted by inaccuracies in the data recorded and by imbalance of the number of cases in each category.

To consolidate these data, the nine-week mortality was correlated with the lowest white blood count obtained for each patient in the first five weeks after the bombs. The results are shown in Table 4 and Figure 4. It can be seen that, except for the 2001-2500 white cell interval in the Hiroshima data, the higher the leukocytes, the better the prognosis. It is emphasized that the patients were not examined regularly; many had only one leukocyte determination.

Tables 5 and 8 and Figures 5 to 9 show the trend of leukocytic response as a function of the leukocytic depression for a particular week from the third to the sixth. Data for both cities have been compiled jointly. Only those cases in which serial counts were available were used. In some cases, insufficient data precluded tabular and graphic presentation.

There are not enough data on non-survivors to tabulate time trends. In general, the curves of these non-survivors when plotted, show no upward trend. This is especially true for those counts falling in the lowest class interval. In the case of survivors, the curves show probable leukopoietic recovery after four to five weeks. The steep recovery slopes of the curves in these cases may reflect the effect of infection or other injuries. Among the non-survivors, the data for the lower leukocyte intervals show no tendency towards recovery after the fifth week. For the higher class intervals of non-survivors, there is an increase in leukocytes before death. The cause of the pre-mortal increase is not clear.

DISCUSSION:

Under the conditions of the above study of the Hiroshima and Nagasaki casualties, it has been shown that of those whose leukocyte levels are known to have fallen to $500/\text{mm}^3$ or below, 72 percent died within nine weeks of the explosion. With lesser degrees of neutropenia, the mortality rate is correspondingly less. The relationship between the degree of neutropenia and mortality varied with the time of the blood count. In the Hiroshima data, a correlation was obtained over a wider range of blood counts if the blood values for the third week were used; rather than fourth or fifth week data. This this did not hold in the Nagasaki data. Further, the quantitative relationship between blood count and mortality rate was markedly different in the Hiroshima and Nagasaki data, and for a given degree of neutropenia, fewer individuals died in Nagasaki than in Hiroshima. This difference appears to be real, and most marked in the severely neutropenic. The reason is not known. However, it is known that

the fast neutron contribution to the total dose in Hiroshima was considerably greater than that for Nagasaki, and the relative neutron contribution increases with decreasing distance from the hypocenter. It is possible that with neutrons, additional damage might be incurred that may not be reflected in the bone marrow and thus in the blood counts. It is well known that mice die between the third and sixth day with severe gastrointestinal symptoms presumably due to a relatively greater injury of the mucosa than the marrow.¹¹⁻¹³ However, larger animals such as the dog do not behave similarly.¹⁴

Circumstances did not allow more than token therapy to the exposed Japanese. After the first week the commonest causes of death were infection and hemorrhage. On clinical grounds, one would think that the combined use of antibiotics, fresh whole blood infusions and platelet transfusions, when needed, would increase the survival rate. It was shown by Miller et al¹⁵ that antibiotics would increase the survival rate in mice. The Rochester group¹⁶ obtained no marked benefit from antibiotic and transfusion therapy initially. In latter studies¹⁷ successive use of antibiotics reduced a 50% mortality to 10% but after an LD₈₀ dose, no benefit was obtained. Since then, however, Sorensen et al¹⁸ and Perman et al¹⁹ have consistently reduced mortality from a near 100% fatal dose to about 10% mortality in dogs by the combined use of high dosage of successive antibiotics and fresh whole blood transfusions supplemented by platelet-rich plasma when red cells were not needed.

It has often been stated that the lymphocyte count is the most sensitive hematologic index of exposure to radiation. While this may be true,

the depression of lymphocytes becomes nearly maximal after sublethal doses of radiation, and therefore of almost no prognostic value in the lethal range proper. However, the granulocyte count correlates more closely with survival in mice⁵ and dogs⁷. Since it has been established in man that the total white count after the first 48 hours reflects changes in the granulocyte levels¹⁰, the total white count is a simple and effective means of estimating the biologic injury. The work reported here, with all the deficiencies in data, indicates that WBC has considerable prognostic value.

In the event of radiation casualties, it would appear that a study of the leukocyte counts would be of considerable aid in selecting those individuals in whom the available supplies of antibiotics and fresh blood would be of the most benefit. It appears that the chance of spontaneous survival is very remote in individuals in whom the leukocyte count is below 1000 in the third and fourth weeks. It is probably unwise to select leukocyte levels at which one would deny therapy on the basis of these data. However, with cell counting devices, mass leukocyte counts could be performed and would be very useful.

SUMMARY AND CONCLUSIONS:

1. The Joint Commission and the Japanese data of 1945 have been re-evaluated to see if the leukocyte count at various time intervals reliably prognosticates death survival.
2. There is a good correlation between death and depression of the leukocyte count taken during the third to fifth week after exposure.
3. The correlation is perhaps best for counts taken during the third week.

4. Leukocyte counts less than 3000 are not as hazardous in the fourth and fifth week as in the third week.

5. It is believed that the leukocyte count is the best single indicator of severe radiation injury, and that electronic methods of counting leukocytes should be made available to assist in casualty sorting and direction of therapy.

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TABLE 1
NUMBER OF LEUKOCYTE DETERMINATIONS OF PEOPLE IN HIROSHIMA AND NAGASAKI
IRRESPECTIVE OF WHETHER RADIATION OR
COMBINED INJURIES OCCURRED

WEEK	NUMBER OF DETERMINATIONS ON SURVIVORS AND NON-SURVIVORS				
	SURVIVED FOR 9 WEEKS		DIED WITHIN 9 WEEKS		TOTAL Σ
	HIROSHIMA	NAGASAKI	HIROSHIMA	NAGASAKI	
1	50	12	26	1	89
2	44	13	30	1	88
3	77	115	52	15	259
4	181	290	89	26	586
5	553	516	59	11	1139
6	1085	386	12	11	1494
7	418	224	11	2	655
8	231	270	7	3	511
9	190	404	1	3	598
TOTAL	2829	2230	287	73	5419

TABLE 2
MEAN MEDIAN AND CONFIDENCE LIMITS OF THE MEDIAN OF LEUKOCYTE LEVEL OF EXPOSED
PEOPLE SURVIVING FOR 9 WEEKS (HIROSHIMA AND NAGASAKI)

WEEK	MEAN WBC X 10 ⁻²		MEDIAN WBC X 10 ⁻²		CONFIDENCE LIMITS OF MEDIAN (95% OR BETTER)		CONFIDENCE LIMITS OF MEDIAN (95% OR BETTER)	
	HIROSHIMA	NAGASAKI	HIROSHIMA	NAGASAKI	HIROSHIMA		NAGASAKI	
					LOWER LIMIT	UPPER LIMIT	LOWER LIMIT	UPPER LIMIT
1	45.0	41.0	43.0	44.0	23.0	55.0	19.0	52.0
2	63.0	43.0	61.0	43.0	48.0	80.0	32.0	56.0
3	60.0	40.0	56.0	33.0	20.0	103.0	17.0	54.0
4	49.0	37.0	34.0	32.0	17.0	55.0	17.0	52.0
5	44.0	47.0	42.0	43.0	33.0	51.0	32.0	52.0
6	34.0	49.0	33.0	45.0	33.0	74.0	32.0	55.0
7	53.0	54.0	50.0	52.0	42.0	57.0	40.0	62.0
8	55.0	67.0	54.0	63.0	44.0	66.0	45.0	75.0
9	67.0	74.0	66.0	69.0	50.0	81.0	56.0	81.0

TABLE 3
LEUKOCYTE LEVEL OF EXPOSED INDIVIDUALS WHO DIED
WITHIN 9 WEEKS (HIROSHIMA AND NAGASAKI)

WEEK	MEDIAN WBC	MEDIAN SURVIVAL TIME (WEEKS)	NUMBER OF COUNTS
1	500	2.0	27
2	600	2.0	31
3	1000	4.0	57
4	2000	4.0	115
5	700	5.0	70
6	2200	6.0	23
7	4500	8.0	13
8	5200	8.0	10
9	7500	9.0	4

TABLE 4
9 WEEK MORTALITY AS RELATED TO THE LOWEST WBC IN THE FIRST
5 WEEKS AFTER EXPOSURE TO THE ATOMIC BOMB

LOWEST WBC WITHIN 35 DAYS	HIROSHIMA			NAGASAKI			BOTH CITIES COMBINED		
	NUMBER IN RANGE	DIED WITHIN 9 WKS. OF EXPOSURE		NUMBER IN RANGE	DIED WITHIN 9 WKS. OF EXPOSURE		NUMBER IN RANGE	DIED WITHIN 9 WKS. OF EXPOSURE	
		NUMBER	%		NUMBER	%		NUMBER	%
0- 500	106	80	75.5	36	22	61.1	142	102	72
501- 1000	87	43	49.4	60	12	20.0	147	55	37
1001- 1500	73	24	32.9	45	5	11.1	118	29	24
1501- 2000	51	10	19.6	38	3	7.9	89	13	15
2001- 2500	52	13	25.0	47	2	4.3	99	15	15
2501- 3000	42	1	2.4	42	0	0	84	1	1
3001 & OVER	464	18	3.9	444	7	1.6	908	25	3
TOTAL	875	189	-	712	51	-	1587	240	-

TABLE 5.
TREND OF LEUKOCYTIC RESPONSE AS A FUNCTION OF DEGREE OF DEPRESSION DURING WEEK 3
(SURVIVORS - HIROSHIMA AND NAGASAKI)

WEEK	WBC INTERVAL									
	0 - 1199		1200 - 1999		2000 - 2999		3000 - 5999		6000 & OVER	
	NO. OF COUNTS	MEDIAN COUNT WBC X 10^{-2}	NO. OF COUNTS	MEDIAN COUNT WBC X 10^{-2}	NO. OF COUNTS	MEDIAN COUNT WBC X 10^{-2}	NO. OF COUNTS	MEDIAN COUNT WBC X 10^{-2}	NO. OF COUNTS	MEDIAN COUNT WBC X 10^{-2}
1	-	-	-	-	-	-	6	64.5	10	64.0
2	-	-	-	-	-	-	5	59.0	9	63.0
3	9	9.0	13	16.0	10	25.5	32	48.0	39	60.0
4	5	10.0	5	53.0	-	-	13	48.0	25	57.0
5	4	21.0	11	31.0	6	20.5	16	43.0	16	59.5
6	-	-	-	-	-	-	11	45.0	8	64.0
7	4	66.5	6	49.0	7	36.0	11	44.0	7	49.0
8	5	73.0	5	76.0	5	66.0	9	56.0	6	62.0
9	5	47.0	-	-	5	85.0	6	49.5	5	55.0

TABLE 6.
TREND OF LEUKOCYTIC RESPONSE AS A FUNCTION OF DEGREE OF DEPRESSION DURING WEEK 4
(SURVIVORS - HIROSHIMA AND NAGASAKI)

WEEK	WBC INTERVAL											
	0-599		600-999		1000-1599		1600-2699		2700-3999		4000 AND OVER	
	NO. OF COUNTS	MEDIAN COUNT WBC X 10^{-2}	NO. OF COUNTS	MEDIAN COUNT WBC X 10^{-2}	NO. OF COUNTS	MEDIAN COUNT WBC X 10^{-2}	NO. OF COUNTS	MEDIAN COUNT WBC X 10^{-2}	NO. OF COUNTS	MEDIAN COUNT WBC X 10^{-2}	NO. OF COUNTS	MEDIAN COUNT WBC X 10^{-2}
1	-	-	-	-	-	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-	-	-	-	5	83.0
3	-	-	-	-	4	17.0	-	-	7	64.0	33	63.0
4	9	4.0	24	7.0	35	12.0	40	21.0	40	33.0	76	58.0
5	7	11.0	18	17.5	32	25.0	25	24.0	25	28.0	46	51.5
6	6	21.0	17	33.0	23	50.0	25	42.0	20	36.0	27	55.0
7	6	48.5	15	44.0	27	54.0	24	44.0	20	40.0	15	64.0
8	5	53.0	13	51.0	17	67.0	19	69.0	19	52.0	24	72.0
9	4	62.0	7	50.0	17	65.0	12	59.0	12	58.5	15	60.0

TABLE 7.
TREND OF LEUKOCYTIC RESPONSE AS A FUNCTION OF DEGREE OF DEPRESSION DURING WEEK 5
(SURVIVORS - HIROSHIMA AND NAGASAKI)

WEEK	WBC INTERVAL							
	0 - 999		1000 - 1299		1300 - 1499		1500 - 1899	
	NO. OF COUNTS	MEDIAN COUNT WBC x 10 ⁻²	NO. OF COUNTS	MEDIAN COUNT WBC x 10 ⁻²	NO. OF COUNTS	MEDIAN COUNT WBC x 10 ⁻²	NO. OF COUNTS	MEDIAN COUNT WBC x 10 ⁻²
1	-	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-	-
4	9	8.0	15	12.0	-	-	14	15.0
5	33	7.0	36	11.0	11	14.0	23	17.0
6	29	17.0	23	24.0	10	22.5	17	36.0
7	22	27.0	24	38.5	6	29.0	21	51.0
8	19	48.0	13	48.5	5	42.0	14	65.0
9	15	57.0	14	49.5	4	58.5	6	76.5

TABLE 8.
TREND OF LEUKOCYTIC RESPONSE AS A FUNCTION OF DEGREE OF DEPRESSION DURING WEEK 6
(SURVIVORS - NAGASAKI)

WEEK	WBC INTERVAL							
	0 - 1999		2000 - 2999		3000 - 4099		4100 - 9999	
	NO. OF COUNTS	MEDIAN COUNT WBC x 10 ⁻²	NO. OF COUNTS	MEDIAN COUNT WBC x 10 ⁻²	NO. OF COUNTS	MEDIAN COUNT WBC x 10 ⁻²	NO. OF COUNTS	MEDIAN COUNT WBC x 10 ⁻²
1	-	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-	-
4	4	13.5	6	19.0	9	7.0	26	35.5
5	17	9.0	12	16.5	19	26.0	43	44.0
6	24	14.5	24	24.0	23	35.0	74	53.0
7	11	26.0	9	43.0	15	40.0	29	66.0
8	11	36.0	11	52.0	10	66.5	26	72.0
9	11	44.0	11	72.0	7	64.0	22	65.5

FIG. 1 MORTALITY (DIED WITHIN 9 WEEKS)
RELATED TO WBC LEVEL HIROSHIMA

FIG. 2 MORTALITY (DIED WITHIN 9 WEEKS)
RELATED TO WBC LEVEL NAGASAKI

FIG.3 MORTALITY(DIED WITHIN 9 WEEKS)RELATED
TO WBC LEVEL HIROSHIMA & NAGASAKI

FIG. 4 MORTALITY(DIED WITHIN 9 WEEKS)RELATED
TO LOWEST WBC IN FIRST FIVE WEEKS

FIG.5 SUBSEQUENT WBC RESPONSE IN RELATION TO WBC LEVEL AT WEEK 3 (HIROSHIMA & NAGASAKI SURVIVORS)

FIG.6 SUBSEQUENT WBC RESPONSE IN RELATION TO WBC LEVEL AT WEEK 4 (HIROSHIMA & NAGASAKI SURVIVORS)

FIG. 7 SUBSEQUENT WBC RESPONSE IN RELATION TO WBC LEVEL AT WEEK 5 (HIROSHIMA & NAGASAKI SURVIVORS)

FIG. 8 SUBSEQUENT WBC RESPONSE IN RELATION TO WBC LEVEL AT WEEK 5 (HIROSHIMA & NAGASAKI SURVIVORS)

FIG.9 SUBSEQUENT WBC RESPONSE IN RELATION TO
WBC LEVEL AT WEEK 6 (NAGASAKI SURVIVORS)