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HEMATOLOGICAL CHANGES IN HUMANS CHRONICALLY EXPOSED TO LOW-LEVEL GAMMA RADIATION

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HEMATOLOGICAL CHANGES IN HUMANS CHRONICALLY EXPOSED TO LOW-LEVEL GAMMA RADIATION

At the Los Alamos Scientific Laboratory, a number of individuals are exposed continually to small amounts of ionizing radiation. Although it is well known that small doses of whole-body radiation (0.1 to 10 r) in single acute exposures cause no change in the peripheral blood picture, it is possible that if a large enough group of individuals, chronically exposed to low-level gamma radiation, is studied over a long enough period of time, statistically significant hematological changes might be observed.

Ten individuals at the Los Alamos Scientific Laboratory were considered satisfactory for such a study, both from the point of view of the duration and average level of their exposures, and because of the complete records available in each case. This paper reports the analysis of the blood counts done on these ten men, together with suitable control cases, over a three-year period from December 12, 1946 through December 11, 1949. This time interval has been divided into four consecutive nine-month periods, designated Periods I - IV.

A. INDIVIDUALS STUDIED

1. Exposed Group

These ten individuals, all males, whose ages ranged from 25 to 36, had resided at the altitude of Los Alamos, New Mexico (7100 feet) for an average of three months before blood counts were done for purposes of analysis. From pre-employment physical examinations and hematological observations during their early weeks at the Project, the individuals were presumed to be in good health. During the study period, the ten men carried out essentially similar work involving materials that emit beta and gamma rays. Radiation exposure was whole-body in nature. The beta radiation received by these men was roughly 5 rep for every one roentgen of gamma radiation. It is felt that this beta exposure probably did not contribute to any hematological changes, since doses of 5000 rep to the hands of individuals have been shown to have no effect on the circulating lymphocytes.[1] The gamma-ray spectrum may be considered essentially that of radium.

During the course of the three-year period reported, periodic physical examinations showed the ten men to be in good health. No increase in upper respiratory infections or incidence of any diseases known to effect the peripheral blood picture for an appreciable length of time was recorded.

2. Control Groups

a. Forty-six individuals, selected because their work involved no exposure to beta, gamma, or x-irradiation, were used for one series of control cases. These individuals, all males, had resided at the altitude of Los Alamos at least as long as the exposed group and were presumed to be in good health because of periodic and pre-employment physical examinations. Ages ranged between 20 and 42 years of age. Their occupational hazards included exposure to alpha emitters but, due to the slight penetration of alpha particles in tissue (50 microns) and the slight possibility of ingestion of the active substances, they were considered satisfactory for control purposes. As in the case of the exposed group, no known exposure to other toxic agents (dusts, organic solvent vapors, etc.) existed. During the course of the three-year period, 10 individuals from the control group left the Project, and the number of control samples for Period IV was, therefore, reduced to 36 individuals.

b. Since it was felt that unconscious "selection" of favorable cases might have occured in choosing the original control cases (the investigators were familiar with the general hematological pictures of all individuals at the Project), or that only 46 individuals did not represent a sufficiently large cross section of the general Los

Alamos population, an additional control group was drawn from the Laboratory files. A blindfolded individual, unfamiliar with the records, was allowed to select at random from all the active files (over 2000) 46 individual cases. (The records of the ten men in the exposed group were not available for selection.) Those records with fewer than ten counts (i.e., those individuals who had resided at the elevation of Los Alamos for less than approximately two years) were excluded, and the drawing was continued until the full complement of 46 was attained. Of the 46 males chosen, all had been exposed to various types and amounts of ionizing radiation and to other toxic agents known to occasionally produce hematological changes. Exposures were extremely erratic, however, and the average weekly exposure of any individual in this control group was at least a factor of 10 below those of the exposed group individuals. This "random" control group is marked with an asterisk in all data tabulations.

B. METHOD OF COLLECTION OF DATA

Blood counts were uniformly obtained between 8 and 10 in the morning. Capillary blood was used, and diluting pipettes and counting chambers, calibrated by the National Bureau of Standards, were employed. One side of a chamber and one pipette were used for each determination. Smears were made on cover slips, and 100 cells were examined routinely on each differential count. For the majority of the three-year period, each member of the exposed group received a blood count weekly. Variations in this schedule occured, however, and a tabulation of the number of counts done on each individual is given in Table II. Control cases received counts much less frequently than did the exposed individuals. Of the 92 control records considered in this report, the average number of counts for one individual for any nine-month period was three to four.

Ionizing-radiation exposure was measured with film badges and with pocket ionization chambers. Total figures for the dose received by each man by the two methods agreed closely. The figures reported in Table I are for body film badges.

C. METHOD OF STATISTICAL ANALYSIS OF DATA*

The average total white count, absolute neutrophil count, and absolute lymphocyte count for each individual in the study was determined for each nine-month period. The mean values for each group were then calculated using the means for the individual members of each group. Thus, the group-period averages reported are made up of 10 samples in the case of the exposed group, and of 36 to 46 samples in the cases of the control groups. The significance of the difference of suitable means was calculated and is expressed in this report in terms of the index of abmodality. (2) The index of abmodality represents the number of standard deviations of the difference of two means separating the two means. An index of abmodality of 3.0 or greater, representing three standard deviations separating the two means, was taken as the lower limit of statistical significance. Such a result could occur once in 3.7×10^2 times through chance alone. An index of abmodality of 4.0 represents one chance in 1.6×10^4 that the observed result was due to chance alone.

In addition to the analysis of the data from the point of view of the significance of the difference of comparable means, an additional study of the lymphocyte values for each individual in the exposed group was carried out. The best line of fit for the points representing the lymphocyte values for each individual for the four periods was calculated by the method of least squares. The regression coefficients of the formulae for the exposed individuals were averaged and the significance of the depression of lymphocytes studied by this means. (3) The regression coefficients were studied for

*The assistance of Mrs. Verda Strang and Miss Elizabeth Busch in the compilation and analysis of data is gratefully acknowledged.

internal homogeneity and were found to be homogeneous at the 10 percent level.

As has been stated, the time during which the study was continued was divided into four consecutive nine-month periods designated as Periods I - IV respectively.

D. EXPERIMENTAL RESULTS

Table I gives the total and average exposure of the 10 individuals in the exposed group. The mean total white count, absolute neutrophil value and absolute lymphocyte value for each individual and for the group as a whole is presented in Table II. Similar values for the control groups are given in Table III. The significance of differences of means within the control and exposed groups themselves are presented in Table IV. Table V gives the significances of differences between exposed and control-group means for comparable periods. Table VI gives the data on the lymphocyte depression in the exposed group as studied by the means of regression coefficients, and the significance of the findings.

It is seen that positive findings are limited to Tables V and VI. Whether compared to the selected control group or to a totally random cross section of the Laboratory population, the exposed individuals showed a significant deviation from the "normal" groups in Periods III and IV. In Table VI, it is seen that the linear relationship representing the progressive depression of lymphocytes of the exposed group, noted in all four periods of study, carries a probability of less than 2 percent that it is due to chance alone.

E. DISCUSSION

In the authors' opinion, to prove that an average weekly radiation dosage of the level reported causes a significant depression of lymphocytes, several criteria must be met. A significant difference between the exposed individuals and suitable control cases must be shown to exist. The depression of circulating lymphocytes from initial pre-exposure levels in the group selected for study must be significant. No other possible explanation for hematological variation can be present. Finally, other groups at similar exposure levels should demonstrate essentially similar findings.

Clearly, only the first two requirements have been strictly met in this study. So few counts were done on the individuals in the exposed group prior to the start of Period I that no suitable statistical figure for pre-exposure lymphocyte values are available for this group. Hence, it was necessary to take the average lymphocyte value for Period I as the initial value for the exposed group from which the significance of later depressions within the group was calculated. These data, given in Table VI, show that there is a less than a 2 percent chance that the observed depression within the exposed group itself could be due to chance alone. In view of the fact that heavy exposures occurred during the first period, this lymphocyte value is in all probability low, and the significance of depressions within the exposed group also slightly low for this reason. The majority of the decrease in the lymphocytes occurred between Periods I and II, following the high exposure of Period I.

While external radiation exposure is probably the most likely cause of the observed changes in the hemogram of the exposed individuals, the possibility of internal body deposition of active materials exists. So little is known at the present time of the uptake of materials of the type considered in this study, the biological half-life of these substances, and their organ deposition, that the possibility of "internal" deposition must remain somewhat in doubt. Since, however, elaborate precautions to guard the personnel against ingestion of the material were taken, and since actual proven instances of oral, nasal or wound contamination are very few, "internal" radiation from bodily deposition of the radioactive materials is a remote possibility. The presence of other hematological toxic agents has been strictly discounted in occupational environment of the individuals. No details of their private environments or their histories before coming to the Project would indicate possible hematological abnormalities.

In so far as the authors have been able to determine, no other groups with comparable numbers of exposed personnel, with comparable consistent dosage of a similar level, and with comparable accurate hematological and exposure data, exist at the Los Alamos Project or at other AEC installations. The possibility of confirming the findings given in this report through the study of other groups seems, at the present time, slight indeed.

Disregarding of the positive findings that are felt to be present in the data does not seem entirely justified on the basis that the most rigid criteria are not met. Where it is possible to demonstrate a highly significant difference in lymphocyte values between exposed and control groups, and where demonstration of the progressive development of this deviation, based on an unsatisfactory starting point and few subsequent points, carries an uncertainty of only 2 percent, careful consideration must be given to the possibility that a definite and possible serious change has occurred in the individuals in question. The fact that the exposure level to which these men were subjected is below the currently accepted level is further disquieting.

An absolute lymphocyte value of 1500 in an apparently healthy individual would not necessarily be a cause for alarm. Where, however, this value represents a relatively large decrease from a well-established previous norm, it should be given careful consideration.

F. Summary

1. Changes in the hemograms of 10 individuals chronically exposed to low-level gamma radiation over a three-year period are reported.
2. The possible correlation between the decrease in circulating lymphocytes noted and the whole-body ionizing radiation received by the individuals in question is discussed.

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3. R. A. Fisher, "Statistical Method for Research Workers" (New York, Hafner Publishing Company Inc., 1948).

TABLE I

GAMMA EXPOSURE OF "EXPOSED" GROUP IN ROENTGENS

Individual	1	2	3	4	5	6	7	8	9	10	Total	Weekly Avg. Per Man
Period												
I	11.62	13.84	9.72	10.11	13.67	12.77	9.19	8.73	8.43	9.56	107.64	0.276
II	2.33	8.31	3.98	3.51	5.98	5.73	6.13	3.87	4.33	7.99	52.16	0.134
III	2.97	4.24	3.92	3.21	8.65	4.66	3.55	5.74	5.78	7.19	49.91	0.128
IV	4.25	2.69	6.90	3.35	7.25	6.28	5.42	7.25	8.11	8.15	59.65	0.153
Total	21.17	29.08	24.52	20.18	35.55	29.44	24.29	25.59	26.65	32.89	269.36	0.691
Weekly Avg. Per Man	0.136	0.186	0.157	0.129	0.228	0.189	0.156	0.164	0.171	0.211	1.727	0.173

TABLE II

SUMMARY OF HEMATOLOGICAL DATA
OF EXPOSED GROUP

Individual		1	2	3	4	5
Period	No. of Counts	35	37	39	24	38
I	W.B.C.	8509 ± 223*	7918 ± 206	6491 ± 190	6461 ± 250	6322 ± 230
	Neutrophils	5365 ± 188	5175 ± 154	4014 ± 138	4212 ± 216	3776 ± 176
	Lymphocytes	1743 ± 71	1869 ± 69	1665 ± 68	1387 ± 87	1727 ± 59
II	No. of Counts	27	36	25	13	35
	W.B.C.	7688 ± 247	6635 ± 179	5775 ± 135	5621 ± 418	5433 ± 167
	Neutrophils	4644 ± 235	4500 ± 162	3784 ± 86	3662 ± 275	3270 ± 130
	Lymphocytes	1727 ± 102	1401 ± 67	1290 ± 66	1121 ± 134	1454 ± 59
III	No. of Counts	25	32	20	13	25
	W.B.C.	7655 ± 363	7919 ± 310	6227 ± 398	5500 ± 290	5289 ± 137
	Neutrophils	4677 ± 257	5391 ± 258	3887 ± 233	3445 ± 220	3217 ± 119
	Lymphocytes	1612 ± 101	1568 ± 88	1487 ± 63	1189 ± 101	1426 ± 79
IV	No. of Counts	20	28	34	13	26
	W.B.C.	7590 ± 391	7075 ± 205	5700 ± 169	6269 ± 420	5430 ± 241
	Neutrophils	5036 ± 308	4966 ± 188	3536 ± 110	3991 ± 352	3438 ± 243
	Lymphocytes	1418 ± 95	1388 ± 75	1446 ± 86	1223 ± 87	1287 ± 72

*Denotes Standard Error of the Mean

TABLE II (Cont'd)

Individual		6	7	8	9	10	Average (1 - 10)
Period	No. of Counts	34	30	39	39	34	
I	W. B. C.	7985 ± 249*	7133 ± 202	9452 ± 268	10474 ± 268	7243 ± 180	7797 ± 440
	Neutrophils	4312 ± 205	3918 ± 172	4812 ± 205	7859 ± 228	4688 ± 120	4814 ± 477
	Lymphocytes	2325 ± 142	2021 ± 66	2764 ± 135	1719 ± 76	1601 ± 75	1882 ± 128
II	No. of Counts	28	36	31	34	30	
	W. B. C.	6914 ± 172	6563 ± 150	7798 ± 237	9355 ± 356	6742 ± 144	6853 ± 381
	Neutrophils	3785 ± 168	3455 ± 132	4290 ± 214	7020 ± 313	4765 ± 121	4318 ± 336
	Lymphocytes	1865 ± 110	1955 ± 85	2087 ± 97	1589 ± 79	1165 ± 68	1566 ± 109
III	No. of Counts	24	33	27	27	22	
	W. B. C.	7258 ± 208	6639 ± 150	7631 ± 214	9948 ± 447	6948 ± 209	7101 ± 423
	Neutrophils	4083 ± 166	3460 ± 109	4240 ± 164	7651 ± 428	4804 ± 126	4485 ± 412
	Lymphocytes	1790 ± 94	2012 ± 91	2004 ± 99	1527 ± 102	1253 ± 72	1587 ± 86
IV	No. of Counts	28	32	32	30	28	
	W. B. C.	6886 ± 216	7347 ± 180	8159 ± 204	9263 ± 353	7461 ± 399	7118 ± 366
	Neutrophils	4016 ± 177	4007 ± 150	4892 ± 204	7300 ± 282	5302 ± 301	4648 ± 361
	Lymphocytes	1642 ± 71	2124 ± 89	1918 ± 112	1811 ± 97	1348 ± 98	1560 ± 96

*Denotes Standard Error of Mean

TABLE III

SUMMARY OF HEMATOLOGICAL DATA
FOR CONTROL GROUPS

Periods I - IV

Period	W.B.C.	Neutrophils	Lymphocytes
I	7009 ± 248**	4164 ± 206	1983 ± 66
I*	7654 ± 391	4648 ± 293	2133 ± 108
II	6790 ± 250	4079 ± 204	1927 ± 72
III	6865 ± 263	4001 ± 212	2026 ± 77
IV	6844 ± 327	3994 ± 230	2042 ± 87
IV*	7053 ± 267	4223 ± 245	2049 ± 96

*Denotes Random Control Group
**Denotes Standard Error of the Mean

TABLE IV

SIGNIFICANCE OF THE DIFFERENCES OF MEAN VALUES FOR CONTROL GROUPS AND THE DIFFERENCES OF MEAN VALUES FOR EXPOSED GROUPS

Periods Compared	Control Groups			Exposed Group		
	W. B. C.	Neutrophils	Lymphocytes	W. B. C.	Neutrophils	Lymphocytes
I & II	-0.6	-0.3	-0.6	-1.6	-0.8	-1.9
I* & II	-1.9	-1.6	-1.6			
I & III	-0.4	-0.6	+0.4	-1.1	-0.5	-2.3
I* & III	-1.7	-1.3	-0.8			
I & IV	-0.8	-0.5	+0.5	-1.2	-0.3	-2.0
I* & IV	-1.6	-1.7	-0.7			
I & IV*	+0.1	+0.2	+0.6			
I* & IV*	-1.3	-1.1	-0.6			
II & III	+0.2	-0.3	+0.9	+0.4	+0.3	+0.3
II & IV	+0.1	-0.3	+1.0	+0.5	+0.7	0.0
II & IV*	+0.7	+0.5	+1.0			
III & IV	-0.1	0.0	+0.1	0.0	+0.3	-0.2
III & IV	+0.5	+0.7	+0.2			

*Denotes "random" control group
A positive index of abmodality denotes increase in mean value from first to second period compared; a negative index of abmodality denotes a decrease

TABLE V

SIGNIFICANCE OF THE DIFFERENCES OF EXPOSED-GROUP MEAN VALUES FROM COMPARABLE CONTROL-GROUP MEAN VALUES

Period	W.B.C.	Neutrophils	Lymphocytes
I	+1.6	+1.2	-0.7
I*	+0.2	+0.3	-1.5
II	+0.1	+0.6	-2.8
III	+0.5	+1.0	-3.8
IV	+0.6	+1.5	-3.7
IV*	+0.1	+1.0	-3.6

*Denotes "random" control group used for comparison
A positive index of abmodality denotes increase of exposed group above controls; a negative index of abmodality denotes a decrease

TABLE VI

SIGNIFICANCE OF LYMPHOCYTE DEPRESSION IN EXPOSED GROUP
(On the Basis of Regression Coefficients)

Individual	Regression Coefficient* (b_i)
1	- 109.0
2	- 127.6
3	- 46.0
4	- 42.4
5	- 134.8
6	- 212.4
7	+ 36.6
8	- 262.1
9	+ 21.4
10	- 67.1
Average Regression Coefficient (b_o)	- 94.3

*In terms of decrease in lymphocytes per nine-month period.

Since the individual regression coefficients differ among themselves somewhat more than would be expected on the variation of the points around each line, the hypothesis that the average slope differs significantly from zero is tested against the variation among the regression coefficients.

The square of the standard deviates, $s^2, = \frac{\sum(b_i - b_o)}{9} = 9,040$

$$t = \frac{b_o}{\frac{s}{\sqrt{10}}} = -3.14$$

t with 9 degrees of freedom is significant at between the 2% and 1% level.

