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Whole-blood Phagocytic and Bactericidal Activities of Atomic Bomb Survivors, Hiroshima and Nagasaki

Sumiko Sasagawa, Ph.D.; Yasuhiko Yoshimoto, Ph.D.; Emiko Toyota, M.D.; Shotaro Neriishi, M.D.; Michio Yamakido, M.D.; Miyo Matsuo, M.D.; Yutaka Hosoda, M.D.; Stuart C. Finch, M.D.

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Whole-blood Phagocytic and Bactericidal Activities of Atomic Bomb Survivors, Hiroshima and Nagasaki

Sumiko Sasagawa, Ph.D.[1]; Yasuhiko Yoshimoto, Ph.D.[2]; Emiko Toyota, M.D.[1]; Shotaro Neriishi, M.D.[1]; Michio Yamakido, M.D.*; Miyo Matsuo, M.D.[1]; Yutaka Hosoda, M.D.[1]; Stuart C. Finch, M.D.[3]

Departments of [1]Clinical Studies, [2]Epidemiology, and [3]Chief of Research

Summary

This in vitro study evaluated the phagocytic and bactericidal activities of leukocytes in aliquots of whole blood from Hiroshima and Nagasaki atomic bomb survivors for *Staphylococcus aureus*. The data were analyzed by multiple linear regression using the equation $Y = b_0 + \sum_{i=1}^{7} b_i X_i + \sum_{i=1}^{3} c_i (X_i X_4) + e$, where X_1, X_2, and X_3 are dummy variables of age categories, X_4, X_5 , X_6, and X_7 are indicator variables for sex, exposure to A-bomb radiation, city, and neutrophils, respectively, and X_iX_4 is interaction between the dummy variables for age categories and sex. Any significant effects of exposure to A-bomb radiation could not be detected for both phagocytic and bactericidal activities of whole blood from A-bomb survivors. In addition, there were no significant effects of age categories, sex or city, except in neutrophil counts.

Introduction

This study was designed to determine whether there is impairment of the phagocytic and bactericidal properties of the blood of Hiroshima and Nagasaki A-bomb survivors for a common bacterial pathogen. For this purpose, an in vitro whole-blood technique was used to evaluate leukocyte phagocytosis and killing of *S. aureus* during a one-hour incubation period.

Resistance to bacterial infection is known to be impaired for a period of weeks or months following acute whole-body exposure to excessive amounts of ionizing radiation.[1,2] This effect is believed to be almost entirely due to

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a reduction of circulating and tissue phagocytic cells. An early report of radiation-induced impairment of granulocyte function[1] has not been confirmed by others.[3,4] There is no clear clinical evidence that increased susceptibility to bacterial infection persists in heavily exposed persons following return to normal levels of tissue and circulating leukocytes. However, if it is possible that a reduced bacterial resistance mechanism is continued in A-bomb survivors, it is sufficiently important to justify intensive investigation and also to provide a baseline for possible future comparisons. The whole-blood method used in this study is believed to be more of a physiological index of bacterial resistance mechanisms than are those techniques which evaluate only the function of isolated polymorphonuclear leukocytes.

Materials and Methods

Subjects

The A-bomb survivors in this study were selected during the years 1979-81 on the basis of T65DR kerma estimates from the Adult Health Study population of Hiroshima and Nagasaki. The exposed group of 129 persons had T65DR kerma estimates of 1 Gy or higher. The mean DS86 marrow radiation dose was 1.34 Gy for 129 persons in the exposed group, which consisted of 95 persons with a mean kerma dose of 1.40 Gy in Hiroshima and 34 persons with a mean kerma dose of 1.19 Gy in Nagasaki. One hundred fifty-eight persons in the 0 Gy control group were age- and sex-matched to persons in the exposed group. Both groups contained about twice as many females as males and fewer persons in the older age-group (13 persons aged 80-89 years) than in the younger age-group (93 persons aged 50-59) as shown in Table 1.

Experimental Procedure

The procedure used to evaluate blood phagocytic and bactericidal activities was that of Castro et al[5] with slight modifications. Five milliliters of venous blood was drawn into a syringe containing heparin (20 U/ml) and then were transferred into a sterile Erlenmeyer flask in a water bath shaker at 37°C until initiation of the assay procedure. A complete blood count with a differential leukocyte count was obtained on each aliquot of blood while still in the Erlenmeyer flask. The total time lapse between venipuncture and commencement of assay was usually about 30 minutes, but was in no case longer than two hours. Aseptic techniques were maintained for all procedures throughout the study.

Bacteria

Beta-hemolytic, coagulase-positive, phage type 80 or 81 *S. aureus* were grown overnight in tryptic soy broth and then were serially diluted in normal saline to obtain approximately 5×10^4 colony-forming units per milliliter in the final saline suspension. When examined microscopically, approximately 90% of the colony-forming units consisted of five individual cocci or less, but aggregations with up to 16 organisms occasionally were observed. Sonication of the bacterial suspension for 15 sec resulted in dispersion of the gross bacterial aggregates, but significant numbers of bacteria occasionally persisted in pairs, even when

Table 1. Composition of the subjects

City	Sex	Dose (Gy)	Age at Examination						Total (persons)
			30-39	40-49	50-59	60-69	70-79	80-89	
Hiroshima	Male	0	1	5	4	6	10	2	28
		1+	2	4	7	4	7	3	27
	Total		3	9	11	10	17	5	55
	Female	0	2	11	21	15	7	0	56
		1+	4	11	19	15	14	5	68
	Total		6	22	40	30	21	5	124
Nagasaki	Male	0	2	5	6	4	7	1	25
		1+	3	3	4	0	0	0	10
	Total		5	8	10	4	7	1	35
	Female	0	6	13	19	9	2	0	49
		1+	1	5	13	2	1	2	24
	Total		7	18	32	11	3	2	73
	Sum total		21	57	93	55	48	13	287
Male		0	3	10	10	10	17	3	53
		1+	5	7	11	4	7	3	37
	Total		8	17	21	14	24	6	90
Female		0	8	24	40	24	9	0	105
		1+	5	16	32	17	15	7	92
	Total		13	40	72	41	24	7	197
0 Gy Control			11	34	50	34	26	3	158
1+ Gy Exposed			10	23	43	21	22	10	129
	Total		21	57	93	55	48	13	287

sonication was continued for five minutes. When disruption of bacterial clumps was necessary because of excessive clumping, sonication was continued only for a maximum of 15 sec to avoid excessive heat generation.

Assay Procedure

One-half milliliter of the *S. aureus* saline suspension was added to 4.5 ml of heparinized blood in an Erlenmeyer flask. The final concentration of staphylococcal colony-forming units in the whole-blood test solution ranged from 5,000 to 10,000/ml. The ratio of mature polymorphonuclear leukocytes to bacterial units varied from 400/1 to 800/1. Immediately after the blood was inoculated, the flask was shaken in a vortex mixer to obtain optimal dispersion of bacteria. An aliquot of 0.1 ml was then added to a petri dish of agar to determine the baseline bacterial counts (I_0). Another 0.1 ml aliquot from the whole-blood test solution was lysed by adding it to a tube containing 1.9 ml of distilled water for 1-3 minutes before it was added to agar (L_0). This treatment ruptured

leukocytes, but had no effect on the viability of the bacteria. The inoculated whole blood was incubated in a water bath shaker at 37°C for 60 minutes. At 15, 30, and 60 minutes, each test solution was thoroughly mixed in a vortex mixer, after which intact 0.1ml aliquots were plated directly in agar (I_t). In addition, a duplicate 0.1ml aliquot from the whole-blood test solution was lysed by means of osmotic shock before plating as noted above (L_t). All agar plates were incubated for 24 hours at 37°C after which the colonies were counted. The number of neutrophils remained constant throughout the 60 minutes of incubation and their viability, as measured by the trypan blue dye exclusion test, was unimpaired.

Calculation of phagocytosis and killing of bacteria

Each I_t value represented a count of the total number of viable bacteria in a blood sample which had not been phagocytized at the time the sample was plated. The difference between the total bacterial count at time "0" and that of a later sample (i.e., 60 minutes) indicated the number of bacteria phagocytized during the elapsed time interval (i.e., 60 minutes).

Each L_t value indicated the number of viable bacteria in the blood at the time the sample was plated, including the bacteria which may have been phagocytized but were not killed. The difference between the total bacterial count at time "0" and that of a later sample indicated the number of bacteria killed during the elapsed time interval.

The colony counts of I_t at sampling times of 15, 30, and 60 minutes were designated I_{15}, I_{30}, and I_{60}, respectively. In a similar manner, the colony counts of L_t were designated L_{15}, L_{30}, and L_{60}. Phagocytosis and killing of bacteria designated as P and K, respectively, were calculated as follows (with subscript t referring to sampling times of 15, 30 or 60 minutes):

$$P_t = L_0 - I_t \ (\geq 0)$$
$$K_t = L_0 - L_t \ (\geq 0)$$

Statistical analysis

Multiple linear regression analyses of P_{60} and K_{60} with independent variables for age, sex, neutrophil count, and exposure to A-bomb radiation were applied to evaluate the effects of A-bomb radiation on blood phagocytosis and killing. Logarithmically transformed values of both P_{60} and K_{60} were used as dependent variables to provide error variation which was closer to that of the normal distribution. The logarithmically transformed peripheral neutrophil counts at the time of the examination were used in the regression analysis. As described below, dummy variables (code the two possible values by 1 and 0) were used for sex, city, age, and exposure. The results for individuals in the study were divided into age categories <49, 50-59, 60-69, and 70+ years. The P_{60} and K_{60} values did not show a linear trend by age. The P_{60} and K_{60} means in the female age-group 50-59 were the lowest. The parameters of age were estimated in contrast to the age-group of 50-59 years. The P_{60} and K_{60} means in the male age-group

60-69 were significantly higher than were those of the female age-group 50-59. Therefore, the data also were analyzed using a model with age and sex interaction as noted below. The model using dummy variables was as follows:

$$Y = b_0 + \sum_{i=1}^{7} b_i X_i + \sum_{i=1}^{3} c_i (X_i X_4) + e \quad , \qquad (1)$$

where X_i,i=1,2,3 are dummy variables for the four age categories; X_4 is the indicator variable for sex (1 for male and 0 for female); X_5 is the indicator variable for exposure; X_6 is the indicator variable for city; X_7 is ln(neutrophil); and $X_i X_4$ is interaction between the dummy variables for age categories and sex.

Results

Time course of phagocytosis and killing of *S. aureus* by whole blood

Figure 1 demonstrates the time course of the mean colony counts for the intact (I) and lysed (L) samples with standard deviations (SD) for the A-bomb exposed and control groups. The mean values of the colony counts for the lysed samples showed a gradual reduction over a period of 60 minutes to approximately 30% of the initial value in both exposed and control groups. The mean values of the intact samples were always lower than those of their lysed counterparts. The time course of the mean values of phagocytosis (P) and killing (K) of bacteria with SD for the A-bomb-exposed group and the control group is shown in Figure 2. Both P and K increased in a time-dependent manner, as I and L decreased with time (Figure 1). No city differences in the indices of P_{60} and K_{60} between Hiroshima and Nagasaki were observed (Tables 2 and 3).

Effects of A-bomb exposure on phagocytosis and killing of bacteria by whole blood

Simple comparisons between exposed and control groups for the values representing phagocytosis and killing at 15, 30, and 60 minutes of incubation were not significantly different (Figure 2).

Results of regression analysis were summarized in Tables 2 and 3. In the regression analysis, logarithmically transformed values of both P_{60} and K_{60} were used as dependent variables to lead to an error variation which is closer to that of the normal distribution, since both P_{60} and K_{60} were distributed with a right tail.

There were statistically suggestive interactions in the preliminary analysis between sex and age for both P_{60} and K_{60}, indicating that some age- and sex-related effects exist in neutrophil phagocytic activity, in addition to the neutrophil count. Therefore, age divided into four categories, sex, and neutrophil counts was used as the independent variable in addition to exposure in the multiple linear regression analyses. The city variable was also tested for its influence on P_{60} and K_{60}. Females aged 50-59 years were chosen as a baseline group and were used as a dummy variable since the number of persons in this group was the largest. After adjusting for variables such as city, age, sex, and neutrophil counts, the effect of

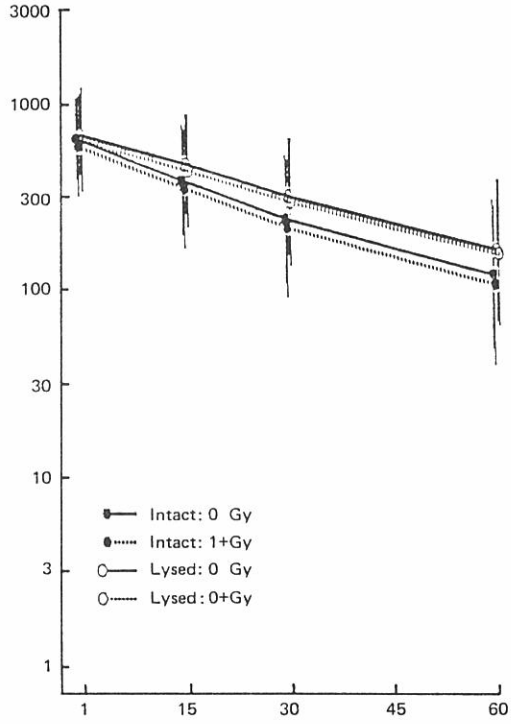

Figure 1. Time Course of Colony Counts for Blood Aliquots of Intact and Lysed Plates by Dose

The mean value ± standard deviation (SD) for the number of viable *S. aureus* at specific time intervals for lysed blood samples (L) are shown by open circles and for the intact samples (I) by solid circles. A solid line represents the time course of colony counts for the 158 controls and a broken line represents the 129 persons exposed to 1+ Gy. The ordinate indicates logarithmic colony counts per 0.1 ml of blood. The abscissa indicates sampling time (minutes).

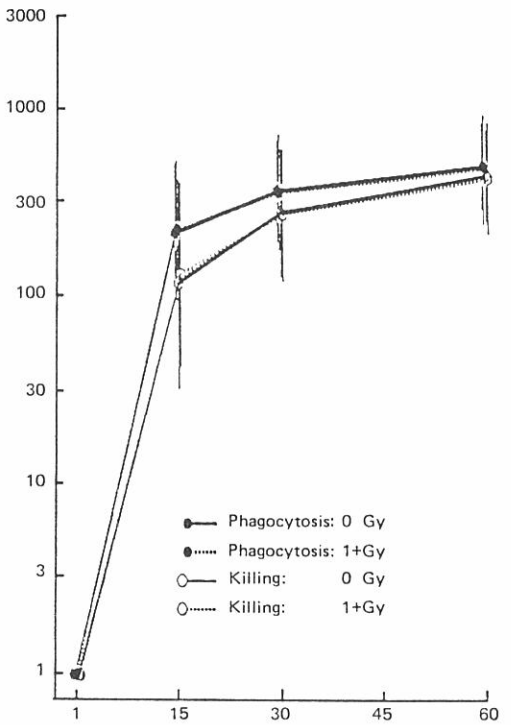

Figure 2. Comparison of Whole-Blood Phagocytosis and Killing of *S. aureus* by Dose

The mean value ± standard deviation (SD) for the number of bacteria phagocytized at specific time intervals is represented by closed circles and for the number of bacteria killed by open circles. Solid lines represent the time courses of the phagocytosis and killing of *S. aureus* for the 158 controls and broken lines represent 129 persons exposed to 1+ Gy. The ordinate indicates logarithmic number of bacteria per 0.1 ml of blood. The abscissa indicates sampling time (minute).

Table 2. Results of multiple linear regression analysis for examining phagocytosis at 60 minutes (logarithm of P_{60})

Variable		Coefficient (SE)*	t-value (p-value)
Constant	(b_0)	3.368 (0.911)	3.70 (p=0.000)
City	(b_6)	−0.041 (0.076)	−0.55 (p=0.586)
Sex	(b_4)	0.017 (0.147)	0.11 (P=0.909)
Dose	(b_5)	−0.020 (0.073)	−0.28 (p=0.781)
ln(neutrophil)	(b_7)	0.340 (0.113)	3.00 (p=0.003)
Age(-49)	(b_1)	0.094 (0.107)	0.88 (p=0.381)
Age(50-59)		-	-
Age(60-69)	(b_2)	0.018 (0.116)	0.16 (p=0.875)
Age(70+)	(b_3)	0.125 (0.129)	0.97 (p=0.332)
Age(-49)× Sex**	(c_1)	−0.021 (0.204)	−0.10 (p=0.917)
Age(50-59)× Sex**		-	-
Age(60-69)× Sex**	(c_2)	0.246 (0.234)	1.05 (p=0.295)
Age(70+)× Sex**	(c_3)	0.023 (0.213)	0.11 (p=0.914)

	Sum of Squares	df	Mean Square	F-ratio	P-value
Regression	5.2094	10	0.5209	1.505	0.137
Residual	95.5635	276	0.3463		

Multiple correlation coefficient: r=0.2274 (r^2=0.0517)

*Standard error.
**Interaction age and sex.

Table 3. Results of multiple linear regression analysis for examining the killing at 60 minutes (logarithm of K_{60})

Variable		Coefficient (SE)*	t-value (p-value)
Constant	(b_0)	2.835 (0.934)	3.04 (p=0.003)
City	(b_6)	0.032 (0.077)	0.42 (p=0.678)
Sex	(b_4)	0.006 (0.151)	0.04 (P=0.967)
Dose	(b_5)	−0.037 (0.075)	−0.50 (p=0.620)
ln(neutrophil)	(b_7)	0.390 (0.116)	3.36 (p=0.001)
Age(-49)	(b_1)	0.057 (0.110)	0.52 (p=0.606)
Age(50-59)		-	-
Age(60-69)	(b_2)	−0.010 (0.119)	−0.08 (p=0.993)
Age(70+)	(b_3	0.126 (0.132)	0.95 (p=0.343)
Age(-49)× Sex**	(c_1)	−0.003 (0.209)	−0.01 (p=0.989)
Age(50-59)× Sex**		-	-
Age(60-69)× Sex**	(c_2)	0.311 (0.240)	1.29 (p=0.197)
Age(70+)× Sex**	(c_3)	−0.000 (0.218)	−0.00 (p=0.999)

	Sum of Squares	df	Mean Square	F-ratio	P-value
Regression	6.3664	10	0.6366	1.750	0.070
Residual	100.4207	276	0.3639		

Multiple correlation coefficient: r=0.2442 (r^2=0.0596)

*Standard error.
**Interaction age and sex.

dose on P_{60} and K_{60} was not statistically significant (Tables 2 and 3). No effect for city or sex was observed. In addition, there were no significant variations in the coefficients for either P_{60} and K_{60} for any of the age categories. Only ln(neutrophil) significantly influenced either P_{60} or K_{60}. Age and sex interactions were not shown to be significant for either P_{60} or K_{60} (Tables 2 and 3).

Discussion

This study was designed to determine whether there is impairment of the phagocytic and bactericidal properties of the blood of Hiroshima and Nagasaki A-bomb survivors for a common bacterial pathogen. For this purpose, an in vitro whole-blood technique was used to evaluate leukocyte phagocytosis and killing of *S. aureus* during a one-hour incubation period. The test system employed in this in vitro investigation was proposed as a rapid method for evaluating both the phagocytosis and intracellular killing of a particular organism by the phagocytic leukocytes of the blood. Thus, any reduction in colony count was a reflection of phagocytosis, even if killing was not immediate but occurred in agar after plating. Lysis of the leukocytes in one of the blood samples incubated with bacteria prior to plating in agar permitted the release and subsequent growth of organisms which were phagocytized but not killed. The difference between the total number of organisms recovered from the lysed sample and the total number recovered from the intact sample provided an index of intracellular bactericidal activity. Clumping artifacts have been eliminated from the system.

The major type of cell in the peripheral blood responsible for the phagocytosis and killing of invading pathogens is the neutrophil. If the bone marrow is injured by radiation, microbicidal functions of neutrophils released from the bone marrow may be impaired. Such an effect should be transient, but if it is not or if there is impairment of opsonins or other factors in the blood which contribute to the removal and destruction of bacteria in the blood, the test which was employed should indicate the presence of such abnormalities. It also is quite possible that impairment of cell function and important immunologic mechanisms as late radiation effects in A-bomb survivors could influence blood phagocytic and bactericidal activities.

In this study, no impairment of in vitro blood phagocytosis or killing of a common gram-positive pathogen was demonstrated for persons exposed to high levels of A-bomb radiation 33-35 years previously. These observations are consistent with other in vitro studies of leukocyte function in A-bomb survivors which have demonstrated normal phagocytosis and aerobic glycolysis,[4] as well as random migration and chemotaxis.[6] They also are consistent with clinical studies which have failed to demonstrate any radiation-related increased susceptibility of A-bomb survivors for bacterial infections as a late effect.[3] They are, however, not consistent with some other *in vitro* studies of polymorphonuclear function in A-bomb survivors which suggest possible late effects of A-bomb exposure on chemotaxis,[7] lysosomal enzyme release, and superoxide anion production.[8]

It is not easy to resolve the differences in results which have been observed for in vitro granulocyte function in A-bomb survivors, but functional impairment in these cells at this late date seems improbable. It is known that massive acute radiation doses are required to induce alterations in human neutrophil function. Holley et al[9] reported that in vitro irradiation of more than 500 rad* was required to impair chemotaxis and more than 20,000 rad for impairment of phagocytosis. Another *in vitro* study with human polymorphonuclear leukocytes irradiated with ^{60}Co gamma-rays showed that chemotaxis, lysosomal enzyme release, and superoxide anion production, both induced by fMet-Leu-Phe in conjunction with cytochalasin B, tend to decrease with increasing doses up to 30 Gy.[10] Rat polymorphonuclear leukocytes irradiated in vitro with 2,000 rad also showed decreased respiratory capacity.[11] These in vitro studies have required lethal or supralethal doses of ionizing radiation in order to produce abnormal effects in polymorphonuclear leukocytes. If such effects were induced in vivo they would not be sustained because of the rapid turnover of these cells. Only the massive induction of somatic mutation causing functional impairment of granulocyte stem cells could account for the continued production of functionally abnormal neutrophils for many years. Persistent somatic mutations have been observed for erythrocyte glycophorin A and lymphocyte chromosomes in A-bomb survivors, but these changes involve only a small number of cells and do not result in functional impairment.[12,13]

Differences in white cell-testing techniques may be responsible for differences in results among the various studies. These differences should be resolved, but even confirmation of some impairment in neutrophil function is unlikely to have any clinical significance. There is no evidence of A-bomb survivors having increased susceptibility to bacterial infections on the basis of either clinical[14–16] or mortality[17] studies.

Our study did not demonstrate any significant difference for P_{60} and K_{60} between males and females. This observation is consistent with one other study of phagocytic function.[18] There are other reports, however, of sex variations in neutrophil function. One study of polymorphonuclear leukocytes from males over the age of 60 demonstrated enhanced luminol-dependent chemiluminescent response and protease activity in comparison to females of the same age.[19] Some studies[7,8] have demonstrated sex differences for neutrophil adhesion, chemotaxis, and lysosomal enzyme release. Currently, there are no adequate explanations for sex differences in leukocyte functions.

There are a number of reports in the medical literature relating to age alterations in neutrophil function. Some biochemical and physiological processes in polymorphonuclear leukocytes have been reported to change with age. Fulop et al[19] demonstrated a diminished change in both glutathione and oxidized glutathione levels during phagocytosis in the polymorphonuclear leukocytes of

**Traditional radiation units are retained if they appear originally in the material being cited. In all current RERF reports, the International System of Units is employed.*

a group of aged subjects. It has been shown that the granulocytes from elderly persons exhibit reduced chemotaxis,[20] producing lower levels of cyclic AMP and releasing less myeloperoxidase in response to stimulation with fMet-Leu-Phe than do granulocytes from younger people.[20] An age-related decline in lysosomal enzyme release from polymorphonuclear leukocytes after fMet-Leu-Phe stimulation has also been demonstrated.[21] The phagocytic activity of isolated neutrophils using opsonized zymosan has been shown to be age-related, without significant differences between males and females.[18] There also are reports showing no significant age changes in neutrophil functions. Neutrophil metabolism and phagocytosis/killing activities in a group of aged volunteers has been shown not to differ significantly from those for a much younger age-group.[22] Another study failed to demonstrate differences in neutrophil chemotaxis between groups of elderly and young persons.[23] In our study, age-related alterations in bacterial phagocytosis and killing were not clearly demonstrated. Thus, aging effects on neutrophil function are inconclusive and additional studies are needed.

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RERF TR 1-89
研究課題 8-77

業 績 報 告 書

原爆被爆者における全血法による貪食能及び殺菌能，広島・長崎

Whole-blood Phagocytic and Bactericidal Activities of Atomic Bomb Survivors, Hiroshima and Nagasaki

笹川澄子[1]，吉本泰彦[2]，豊田恵美子[1]，錬石昇太郎[1]，山木戸道郎*，
松尾美代[1]，細田　裕[1]，Stuart C. Finch[3]

[1]臨床研究部，[2]疫学部及び[3]研究担当理事

要　約

本研究では，広島及び長崎の原爆被爆者から得た血液を用い，黄色ブドウ球菌に対する白血球の貪食能及び殺菌能の評価を行った．データは，方程式 $Y=b_0+\sum_{i=1}^{7} b_i X_i+\sum_{i=1}^{3} c_i(X_i X_4)+e$ を用いた多変量解析法によって解析した．ここで X_1，X_2，及び X_3 は年齢区分のダミー変数，X_4，X_5，X_6 及び X_7 はそれぞれ性，原爆被爆の有無，市，及び好中球数の指示変数，$X_i X_4$ は年齢区分のダミー変数と性のそれとの間の相互作用を示す．原爆放射線被爆の変数は被爆者の血液の貪食能及び殺菌能に何ら有意な影響を示さなかった．また，好中球数以外の年齢区分，性，市の変数にも有意な影響は認められなかった．

* 放影研専門委員，広島大学医学部第二内科学教室
要約以外の訳文はない．

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