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T AND B CELLS AND PHA RESPONSE OF PERIPHERAL LYMPHOCYTES AMONG ATOMIC BOMB SURVIVORS

原爆被爆者における末梢血リンパ球を用いたT細胞，B細胞及び PHA反応性について

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In the continued interest of accurately defining the late effects of the atomic bombs, the qualitative and quantitative characteristics of the A-bomb radiation exposure doses are periodically refined. If warranted by future dose assessments, the data reported here will be reanalyzed and subsequently reported.

原爆の後影響を引き続いて正確に究明する目的をもって，原爆放射線被曝線量の質的・量的特質について定期的に改良を加えている．今後線量評価によって，その必要性が起これば，本報の資料を再解析の上，改めて報告する．

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原爆被爆者における末梢血リンパ球を用いたT細胞，B細胞及びPHA反応性について

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SUMMARY

Little is known about immune competence in atomic bomb survivors. The following results were observed from this study. T and B cells showed no change in proportion by age or exposure dose. The percentage of T cells was slightly lower in malignant tumor patients than in the control group. However, it was significantly higher in the group with chromosomal aberrations than in the control group. Phytohemagglutinin (PHA) response of peripheral lymphocytes decreased significantly with age in the 0 rad control group and the 200+ rad exposure group, particularly so in the latter. The malignant tumor group also showed lower PHA response than the control group. The PHA response of the chromosomal aberration group was significantly depressed compared with that of the control group.

要 約

原爆被爆者における免疫能についてはあまり知られていない．本研究によって著者らは次のような結論を得た．T及びB細胞の割合は年齢及び被曝線量によって変動はみられなかった．また悪性腫瘍患者におけるT細胞の割合は対照群に比べてわずかに低かった．しかし，対照群に比べて染色体異常を有する群においてT細胞の割合は有意に高かった．末梢血リンパ球の Phytohemagglutinin (PHA) 反応性は，0 rad 対照群と 200 rad 以上の被爆群において加齢と共に有意の低下がみられ，特に後者において顕著であった．悪性腫瘍患者群でも対照群の PHA 反応性より低値を示した．染色体異常群の PHA 反応性は対照群のそれと比べて，有意な低下を示した．

INTRODUCTION

Radiation exposure as well as aging are important factors causing a decrease in immune competence in man. Recently, numerous reports indicate that immune competence in man decreases after

緒 言

ヒトの免疫能を低下させる要因として，放射線被曝は加齢と同様に重要である．近年，各種臓器の悪性腫瘍に対する放射線治療後のヒトの免疫能低下が多数

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TABLE 1 T & B CELLS, AND PHA RESPONSE OF PERIPHERAL LYMPHOCYTES, NUMBER OF AHS SUBJECTS EXAMINED, 1974-77
表1 T細胞，B細胞及び末梢血リンパ球の PHA 反応性について検査した成人健康調査対象者の数，1974－77年

Group	Examination					
	T and B Cell			PHA Response		
	Male	Female	Total	Male	Female	Total
1 Malignant tumor, Definite	6	5	11	5	5	10
2 Malignant tumor, Postoperative	8	30	38	6	23	29
3 Malignant tumor, Probable	6	10	16	3	9	12
4 Chromosomal Aberration	29	48	77	23	38	61
5 Normal, 200+ rad	60	120	180	42	88	130
6 Normal, 100-199 rad	80	124	204	63	99	162
7 Normal, 1-99 rad	42	77	119	36	57	93
8 Normal, 0 rad	135	262	397	102	196	298
9 Normal, not-in-city	1	4	5	1	4	5
Total	367	680	1047	281	519	800

radiotherapy for malignant tumors of various organs.[1-20] However, most of these reports are concerned with effects of local rather than a single whole-body irradiation. It is the consensus of many scientists at present that immune competence in man decreases with age.[21-23]

Among somatic cells the lymphocytes are considered the most sensitive to radiation. Bloom et al[24] and Awa et al[25] have reported chromosomal aberrations as a long-term late effect of radiation exposure. The present study on a sample of A-bomb survivors attempts to clarify the alteration of immune competence in man as a long-term late effect of radiation exposure.

MATERIALS AND METHODS

The RERF Adult Health Study (AHS) sample consists of exposed survivors and their controls. An exposure dose has been estimated for each exposed individual. The subjects of the present study were 1,047 AHS individuals examined during the 4-year period from 1974-77 in Hiroshima (Table 1), including all who received 100 or more rad and, as controls, an equal number of individuals matched by age randomly selected from those exposed to 0 rad, and includes 77 individuals previously identified as having chromosomal aberrations (primary

報告されている.[1-20] しかし，これらの報告のほとんどは全身照射による影響ではなく，局所照射による影響に関するものである．加齢と共にヒトの免疫能が低下することは，現在多くの学者の一致した意見である.[21-23]

ところで，リンパ球は生体の中で最も放射線に対して敏感な細胞であるとされており，放射線被曝の長期にわたる後影響として Bloom ら,[24] 及び阿波ら[25]は染色体異常を報告している．原爆被爆者に対する現在の研究では，放射線被曝の長期にわたる後影響としてのヒトの免疫能の変化を明らかにしようとしている．

対象及び方法

放影研成人健康調査対象者は被爆者とその対照群から成っている．被曝線量は各被爆者について算定されている．本研究の対象は，1974－77年までの4年間に広島で受診した1,047名であり（表1），100 rad 以上の被爆者の全数と，その対照としての被曝線量が0 rad のものから年齢を一致させた同数を任意に選んだものを含み，また，以前に染色体異常ありとされた77名（10%以上の異常細胞がある交換型異常）

exchange-type abnormalities with 10% or more abnormal cells), and 65 individuals with a history of some type of malignant tumor (16 stomach cancer, 14 cervix cancer, 12 breast cancer, 7 thyroid cancer, 3 malignant tumor of large intestine, 2 lung cancer, 2 malignant tumor of head and neck, and 9 other cancers — leukemia, prostate cancer, polycythemia vera, malignant tumor of salivary gland, etc.)

The proportions of T and B cells in peripheral lymphocytes were calculated for all subjects, of which PHA response could be studied for only 800 (Table 1). The average age was 57.5 years for males and 54.3 for females.

Isolation of Peripheral Lymphocytes. A 5-10 ml venous blood sample was drawn into a heparinized syringe and mixed with an equal amount of phosphate buffer saline (PBS). The mixture was then added to 3 ml of Conray-Ficoll 400 solution (33.4% Conray, 9% Ficoll-400, Pharmacia, with a specific gravity of 1.077± 0.001) and centrifuged at 4°C for 30 minutes at 1,550 rpm (about 400× G). The layered lymphocytes were harvested and washed three times with Hanks balanced salt solution (HBSS). The lymphocytes were resuspended in HBSS to provide a final concentration of 3-5× 10^6 cells/ml.

Detection of Peripheral Lymphocyte Subpopulations. For T cell estimation, 0.1 ml of the above lymphocyte suspension (5× 10^6 cells/ml) was mixed with 0.1 ml of 2% sheep red blood cells (SRBC) suspension prepared freshly. The 2% SRBC suspension was prepared by washing commercial SRBC three times with balanced salt solution (BSS) and suspending this in fetal calf serum (FCS, Grand Island Biological Co.). The lymphocyte-SRBC mixture was incubated for 15 minutes at 37°C and then centrifuged for 5 minutes at 500-800 rpm. After standing for one hour at 0°C, the contents were gently stirred and examined microscopically on the hemocytometer. Five hundred lymphocytes and the number of rosette-forming cells (lymphocytes to which four or more SRBC are attached) among them were counted to obtain the percentage of T cells.

B Cell Estimation. A 0.1 ml lymphocyte suspension containing 5× 10^6 cells/ml was mixed with 0.1 ml of 2% suspension of SRBC-hemolysis-complement complex prepared with commercial hemolysin (Toshiba Co.) and fresh human serum

と各種の悪性腫瘍の病歴のあるもの65名(胃癌16, 子宮頸癌14, 乳癌12, 甲状腺癌7, 大腸悪性腫瘍3, 肺癌2, 頭頸部の悪性腫瘍2, 及びその他の癌ー白血病, 前立腺癌, 真性多血球血症, 唾液腺悪性腫瘍等)についても調査を行った.

なお, 末梢血中リンパ球のT及びB細胞の割合は全例について算定したが, PHA反応性は800例しか検査し得なかった(表1). 平均年齢は, 男性57.5歳, 女性54.3歳であった.

末梢血リンパ球の分離. 対象者静脈血5～10mlをヘパリン添加注射器で採取し, 等量のリン酸塩緩衝液(PBS)を加えて混和した. Conray-Ficoll 400 (33.4% Conray, 9% Ficoll-400, Pharmacia, で比重1.077± 0.001) 3 mlに重層し, 4℃, 30分間1,550 rpm(約400×G)で遠沈した. リンパ球層を集め, Hanks balanced salt solution (HBSS)で3回洗浄した. 最終濃度を3～5×10^6個／mlになるようHBSSに再浮遊した.

末梢血リンパ球 subpopulation の検出. T細胞の算定には, 上記リンパ球浮遊液0.1ml(5×10^6細胞／ml)と新鮮な2%ヒツジ赤血球(SRBC)浮遊液0.1mlを混合した. 2% SRBC浮遊液は市販SRBCをbalanced salt solution (BSS)で3回洗浄し, ウシ胎児血清(FCS, Grand Island Biological社製)で2% SRBC浮遊液とした. リンパ球とSRBCの混合液を37℃で15分間反応させ, 500～800 rpmで5分間遠沈した. 0℃で1時間静置した後, 内容をゆっくり攪拌し, 血球計算盤上で鏡検した. リンパ球を500個数え, そのうちロゼット形成細胞(SRBCが4個以上付着したリンパ球)の割合はT細胞の数として%で表した.

B細胞の算定. 5×10^6細胞／mlのリンパ球浮遊液0.1mlと市販のhemolysin (東芝社製)及びヒト新鮮血清をComplement sourceとして調整したSRBC-hemolysis-complement complexの2%浮遊液0.1ml

as complement source. The mixture was incubated for one hour at 37°C, then kept at room temperature for one hour and the rosette-forming cells among the 500 lymphocytes were counted to obtain the percentage of B cells.

を混ぜた．この混合液は37℃で1時間培養し，室温で更に1時間静置し，リンパ球500個中のロゼット形成細胞の数を数えてB細胞の%とした．

Preparation of SRBC-hemolysin-complement Complex Suspension. SRBC thoroughly washed with BSS were mixed with commercial hemolysin diluted to the extent that it would not cause hemolysis and the mixture was incubated at 37°C for 30 minutes. The mixture, washed three times with BSS, was prepared finally into a 2% SRBC suspension. To this, an equal volume of 100-fold dilution of fresh human serum was added and the mixture was incubated at 37°C for 30 minutes for complement fixation. This suspension was washed with BSS three times and a 2% SRBC-antibody-complement complex was prepared using BSS.

SRBC-hemolysin-complement complex 浮遊液の作製．BSS でよく洗浄した SRBC と，溶血を起こさない程度に稀釈した市販の hemolysin を混ぜて37℃で30分間培養した．BSS で3回洗浄後，最終的に2%の SRBC 浮遊液にした．これに等量の新鮮ヒト血清100倍稀釈液を加え，37℃で30分間培養し補体結合を行った．BSS で3回洗浄後，BSS で2% SRBC-antibody-complement-complex を作製した．

Response of Peripheral Lymphocytes to PHA. A 1-2 ml lymphocyte suspension was centrifuged at 1,200 rpm and, using a test medium (RPMI1640 containing 20% FCS), the number of lymphocytes was adjusted to 1×10^6 cells/0.1 ml. To 0.9 ml of a test medium containing PHA (Wellcome Co., 10 μl/ml), 0.1 ml of the lymphocyte suspension was added and the mixture was incubated for three days at 37°C in a 5% CO_2 incubator. For each sample, a control sample with no PHA added was prepared. After incubation, the lymphocytes in each test tube were washed three times with BSS and 10% trichloroacetic acid; smear specimens of the sediment were prepared, stained by Giemsa, and the cells, having transformed into blasts, were identified microscopically. The percentage of such cells in 1,000 lymphocytes was calculated to show PHA response.

PHA に対する末梢血リンパ球の反応性．リンパ球浮遊液1～2 ml を1,200 rpm で遠心分離し，test media (20% FCS 添加 RPMI 1640) で 1×10^6 細胞／0.1ml に調製した．PHA (Wellcome 社製，10μl／ml) を含む test media 0.9 ml を 0.1 ml のリンパ球浮遊液に加え，5% CO_2 恒温器で37℃で3日間培養した．各検体ごとに PHA を加えないものを対照として用意した．培養完了後，各試験管のリンパ球を BSS 及び10%トリクロール酢酸で3回洗浄し，沈渣の塗抹標本を作製し，Giemsa 染色を行って芽球化細胞を顕微鏡下で判定した．1,000個の細胞中の芽球化細胞の割合を算定し，%で PHA 反応性を表した．

RESULTS

Observation of Subjects with neither Chromosomal Aberration nor History of Malignant Tumor. The proportions of T and B cells and PHA response of peripheral lymphocytes by radiation dose are shown in Table 2. In the 397 cases of the control (0 rad) group, the average proportion of T and B cells was 67.1% and 28.5%, respectively. No difference was noted among the dose groups. The average percentage of PHA response cells was 37.5% in the 0 rad group and 34.5% in the 200+ rad group ($.05 < P < .10$).

結　果

染色体異常並びに悪性腫瘍の病歴のないものについての観察．T及びB細胞の割合と末梢血リンパ球の PHA 反応性を被曝線量別に表2に示した．対照群(0 rad) 397例のT及びB細胞の割合の平均値は各々67.1%と28.5%であって，被曝線量群間に差はみられなかった．PHA 反応性の平均値は0 rad 群で37.5%，200 rad 以上群 ($.05 < P < .10$) で34.5%であった．

TABLE 2 PROPORTION OF T AND B CELLS AND PHA RESPONSE BY RADIATION DOSE
表2　線量別にみたT細胞，B細胞の割合及びPHA反応性

		T65 Dose in rad			
		0	1 – 99	100 – 199	200 +
T cells	Subject	397	119	204	180
	%	67.1 ± 7.5	66.2 ± 8.7	66.2 ± 7.3	66.0 ± 7.8
B cells	Subject	397	119	204	180
	%	28.5 ± 8.4	28.7 ± 8.2	28.4 ± 7.4	29.4 ± 8.4
PHA response	Subject	298	93	162	130
	%	37.5 ±15.7	34.7 ±15.6	36.9 ±15.6	34.5 ±14.8

Mean ± standard deviation 平均±標準偏差

TABLE 3 T AND B CELLS AND PHA RESPONSE BY RADIATION DOSE AND AGE
表3　線量及び年齢別にみたT細胞，B細胞及びPHA反応性

		Age at Examination				
		<39	40 – 49	50 – 59	60 – 69	70 +
T cells	Subject	36	103	88	96	74
	0 rad	68.1 ± 6.5	66.5 ± 7.7	67.0 ± 7.9	66.6 ± 7.6	68.1 ± 7.2
	Subject	21	49	54	26	30
	200+ rad	67.5 ± 5.7	65.9 ± 7.4	65.9 ± 8.6	64.3 ± 9.8	66.7 ± 6.3
B cells	Subject	36	103	88	96	74
	0 rad	29.1 ± 8.4	28.2 ± 8.1	27.3 ± 7.9	29.8 ± 8.1	28.4 ± 9.7
	Subject	21	49	54	26	30
	200+ rad	30.4 ± 7.8	29.1 ± 9.3	28.3 ± 8.4	32.6 ± 8.3	28.4 ± 6.8
PHA response	Subject	23	77	68	77	53
	0 rad	38.2 ±15.9	38.4 ±14.4	40.1 ±17.4	36.4 ±14.3	34.5 ±17.1
	Subject	18	39	37	16	20
	200+ rad	39.9 ±14.3	37.7 ±12.5	33.9 ±15.3	29.6 ±16.4	28.1 ±14.5

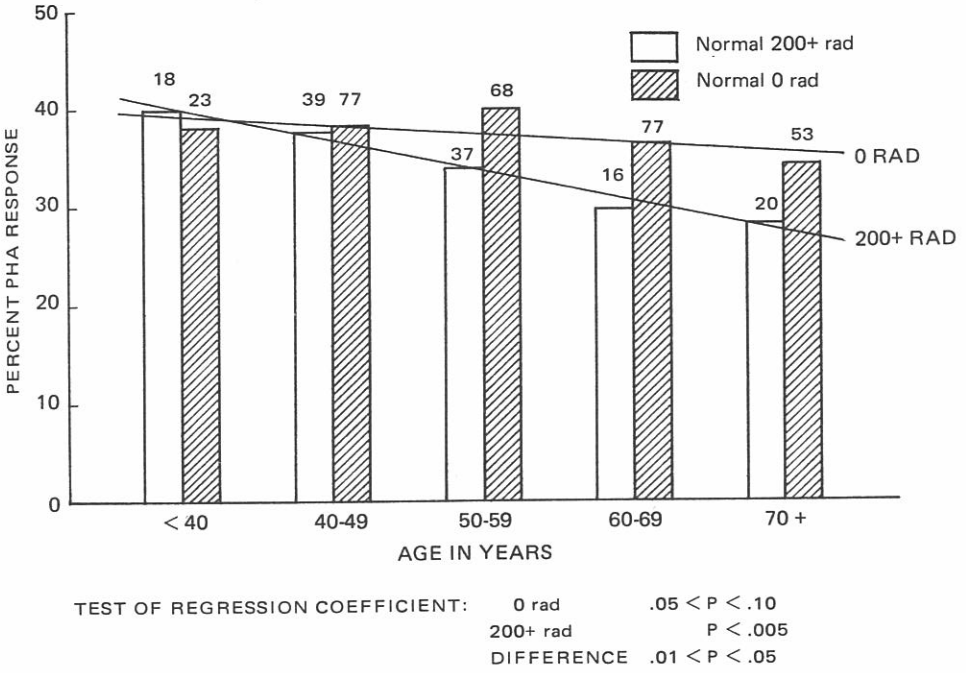
Mean ± standard deviation 平均±標準偏差

Proportions of T and B cells and PHA response were compared between the 0 rad and 200+ rad groups by classifying each group into five age groups (Table 3, Figure 1). The average proportion of T cells tended to be slightly lower and that of B cells slightly higher in the 200+ rad group than in the 0 rad group, but the difference was not statistically significant. There was no evidence of age-associated change in T and B cell proportions. PHA response, on the other hand, was clearly lower in the 200+ rad group than in the 0 rad group in almost all age groups except the youngest (Table 3). PHA response, moreover, decreased with age in the 0 rad group ($.05 < P < .10$) as well as in the 200+ rad group ($P < .005$) the decrease being more remarkable in the latter (Figure 1). The difference in regression co-

T及びB細胞の割合並びにPHA反応性について，五つの年齢群に分け，0 rad群と200 rad以上群の比較を行った（表3，図1）．T及びB細胞の割合の平均値は，200 rad以上群では0 rad群に比べてわずかながらT細胞は低く，B細胞は高い傾向を示したが，統計的には有意でない．年齢によるTあるいはB細胞の割合に変動はみられなかった．しかしPHA反応性は，200 rad以上群では0 rad群に比べて最も若い年齢群を除けば各年代とも明らかに低くなっている（表3）．しかも，PHA反応性は0 rad群においても加齢と共に低下しているが（$.05 < P < .10$），200 rad以上群では加齢に伴うPHA反応性の低下（$P < .005$）は，

FIGURE 1 PHA RESPONSE OF PERIPHERAL LYMPHOCYTES BY RADIATION DOSE & AGE

図1　線量及び年齢別にみた末梢血リンパ球の PHA 反応性



TEST OF REGRESSION COEFFICIENT:

0 rad	.05 < P < .10
200+ rad	P < .005
DIFFERENCE	.01 < P < .05

efficient of PHA response by age between these two groups was statistically significant (.01 < P < .05).

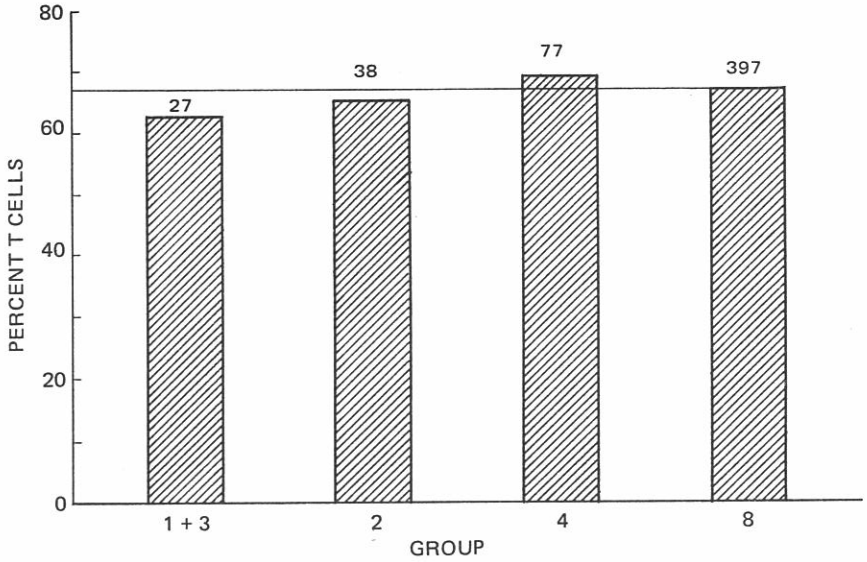
Observation of Groups with History of Malignant Tumor and Chromosomal Aberration. The group with history of malignant tumor showed lower T cell and higher B cell proportions and lower PHA response than the 0 rad group even with adjustment of the difference in age composition (Figures 2-4). The group with chromosomal aberrations showed higher average values for both T (.01 < P < .05) and B cells but significantly lower PHA response (.01 <P<.05) than the 0 rad group. Since it is well known that the frequency of chromosomal aberrations is dose dependent, instead of comparing with the 0 rad group, another comparison was made according to dose level between the groups with and without exchange-type chromosomal abnormalities at the level of 10% or more abnormal cells. As shown in Figure 5, there was no difference in T or B cell proportions nor in PHA response between the two groups.

より顕著にみられる（図1）．この両群における PHA 反応性の年齢による回帰係数の差異は統計的に有意である（.01< P <.05）．

悪性腫瘍の病歴のある群及び染色体異常のある群についての観察． 年齢構成の差異を訂正してみても，悪性腫瘍患者は 0 rad 群よりもT細胞の割合は低く，B細胞の割合は高く，PHA 反応性は低い（図2－4）．染色体異常のある群ではT細胞（.01< P < .05），B細胞の平均値は共に 0 rad 群よりも高いが，PHA 反応性は有意に低くなっている（.01< P <.05）．染色体異常の頻度に線量依存性があることはよく知られているので，0 rad 群と比較せずに，別に10%以上の異常細胞をもつものについて，線量群別に交換型染色体異常のある群とない群について比較してみた．図5に示したように，TあるいはB細胞の割合及び PHA 反応性は両群間に差異は認められない．

FIGURE 2 PERCENT T CELLS IN SUBJECTS WITH MALIGNANT TUMOR & CHROMOSOMAL ABERRATIONS, AGE ADJUSTED

図 2　悪性腫瘍及び染色体異常を有する者におけるT細胞の割合（年齢訂正）



1 Malignant Tumor Definite
2 Malignant Tumor Postoperative
3 Malignant Tumor Probable
4 Chromosomal Aberrations
8 0 rad

1+ 3 vs 8	.10 < P < .25
2 vs 8	.10 < P < .25
4 vs 8	.01 < P < .05

FIGURE 3 PERCENT B CELLS IN SUBJECTS WITH MALIGNANT TUMOR & CHROMOSOMAL ABERRATIONS, AGE ADJUSTED

図 3　悪性腫瘍及び染色体異常を有する者におけるB細胞の割合（年齢訂正）

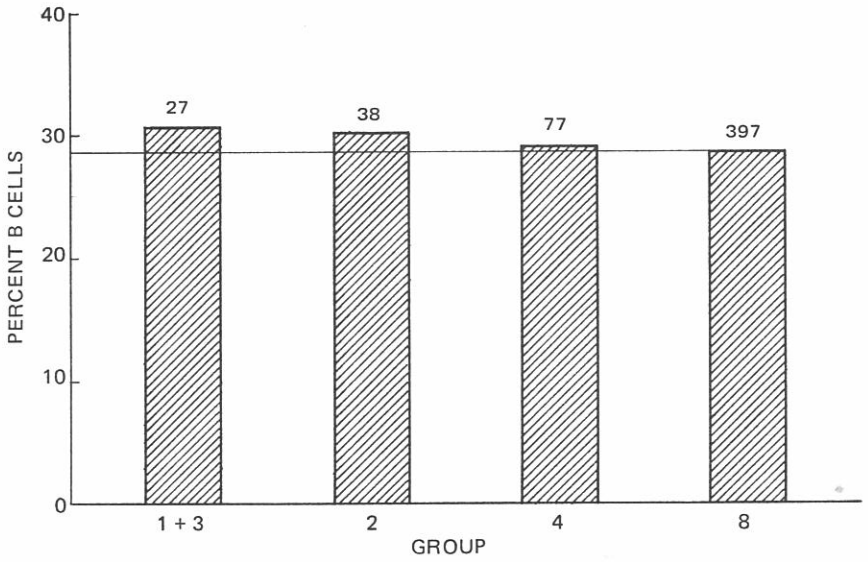
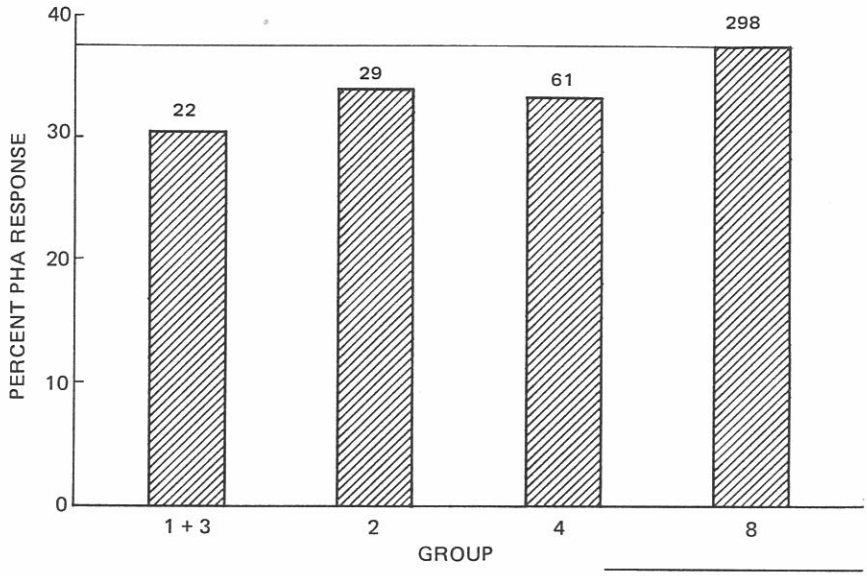


FIGURE 4 PERCENT PHA RESPONSE OF PERIPHERAL LYMPHOCYTES IN SUBJECTS WITH MALIGNANT TUMOR & CHROMOSOMAL ABERRATION, AGE ADJUSTED

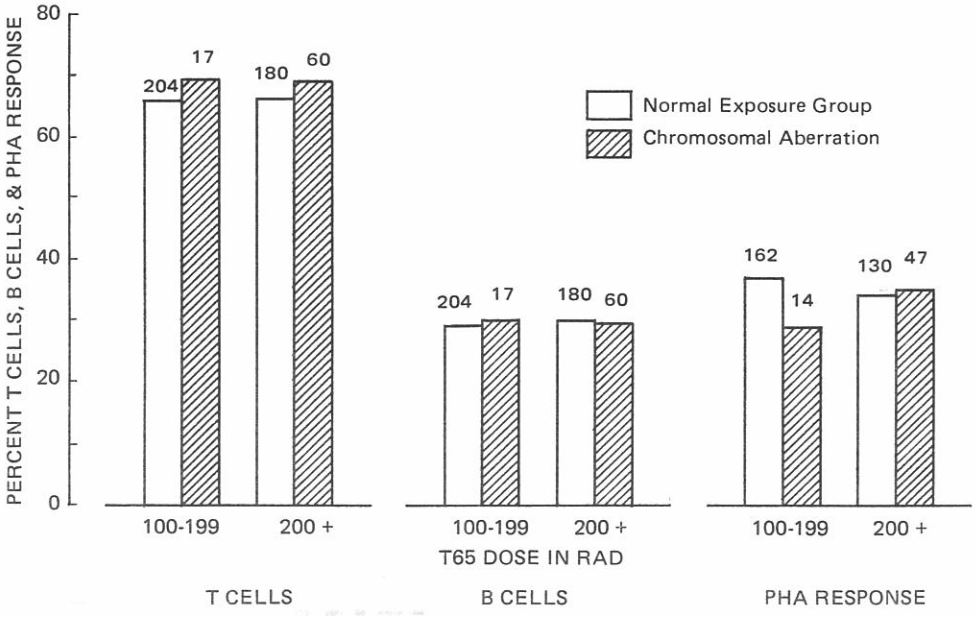
図 4　悪性腫瘍及び染色体異常を有する者における末梢血リンパ球の PHA 反応性（年齢訂正）



1 + 3	vs 8	.05 < P < .10
2	vs 8	.10 < P < .25
4	vs 8	.01 < P < .05

FIGURE 5 COMPARISON BETWEEN CHROMOSOMAL ABERRATION & NORMAL EXPOSURE GROUPS FOR T & B CELLS AND PHA RESPONSE PROPORTIONS BY RADIATION DOSE

図 5　T 細胞，B 細胞の割合及び PHA 反応性について行った染色体異常群及び正常被爆群間の比較，線量別



DISCUSSION

There have been some reports[24-26] that whole-body irradiation causes chromosomal aberrations in man, though few reports have been made regarding its effect on immune competence. We studied the effect of Hiroshima A-bomb exposure (whole-body irradiation with gamma ray and neutrons) on immune competence and found that PHA response of peripheral lymphocytes decreased with age. The decrease was more marked in the 200+ rad group than in the 0 rad group. In other words, the proportion of T and B cells in the peripheral lymphocytes of heavily exposed survivors has not been affected by radiation dose nor by age, however, their response to mitogen (i.e., lymphocyte function) has evidently been disturbed. It is not known at present whether this is the direct effect of exposure of lymphocytes to A-bomb radiation or the intensified effect of aging by A-bomb exposure.

It has been suggested by Fitzgerald[27] that lymphocytes have a long life span. Our findings seem to suggest that the effect of A-bomb exposure on the lymphocyte function still persists. Many investigators consider that there may be a close relation between decreased lymphocyte function and malignant tumors, and high incidence of cancer in A-bomb survivors has been reported.[28-34] Our findings may provide an important clue in studying radiation carcinogenesis.

Liability to infection of A-bomb survivors has not yet been clearly demonstrated. Kato et al[35] studied antibody titer of EB virus in A-bomb survivors, but found no significant correlation with exposure dose. The positive rate of HBs antigen has been reported high in the heavily exposed group.[36] Further, among in utero exposed children of A-bomb survivors, a temporary decrease in influenza antibody-producing competence has been noted in the heavily exposed group. Thus, radiation effects on various aspects of immune competence should be studied using more sensitive indexes in the future.

考　察

全身照射がヒトの染色体異常を起こすことについては幾つかの報告があるが,[24-26] それが免疫能に及ぼす影響について報告したものは少ない．我々は広島の原爆放射線被曝(γ線及び中性子線の全身照射)が免疫能に与えた影響を調査し，加齢と共に末梢血リンパ球の PHA に対する反応性が低下することを明らかにした．かかる低下は 0 rad 群よりも 200 rad 以上群において極めて著しい．換言すれば，高線量被爆者の末梢血リンパ球の中に占めるT及びB細胞の割合は，被曝線量及び加齢の影響は受けないが，細胞分裂促進因に対する反応性(すなわちリンパ球の機能)は明らかに障害を受けている．このことは現在のところ，原爆放射線被曝そのものがリンパ球に直接影響を及ぼした結果なのか，あるいは加齢による影響が被曝により増強されたのか不明である．

リンパ球が長い寿命を有することは Fitzgerald[27] により報告されている．我々の得た結果は，原爆被爆の影響が今日なおリンパ球の機能に残されていることを推定させるものであると言えよう．リンパ球の機能低下と悪性腫瘍の間には密接な関係があるのではないかと多くの人に考えられており，原爆被爆者群に悪性腫瘍の発生が多いという報告がある.[28-34] 我々の得た所見は，放射線による発癌について考察する上で重要な手掛かりを与えるものと考えられる．

原爆被爆者における易感染性はまだはっきり証明されていない．加藤ら[35]は，原爆被爆者における EB ウイルスの抗体価を調査したが，被曝線量との有意の相関を認めていない．HB_S 抗原の陽性率は高線量群に高いことが報告されている.[36] また，胎内被爆児ではインフルエンザ抗体産生能の一時的低下が高線量群に認められている．したがって，将来更に鋭敏な指標を使用して，免疫能のあらゆる面に及ぼす放射線の影響を追求していくべきである．

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