TECHNICAL REPORT
RERF TR 14-80
業 績 報 告 書

RERF TR 14-80

PRELEUKEMIC STATE IN ATOMIC BOMB SURVIVORS
被爆者における前白血病状態

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放影研
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RADIATION EFFECTS RESEARCH FOUNDATION
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A cooperative Japan - United States Research Organization
日 米 共 同 研 究 機 関

ACKNOWLEDGMENT
謝　辞

The author is grateful to Professor Atsushi Kuramoto and Assistant Professor Nanao Kamada, Department of Internal Medicine, Research Institute for Nuclear Medicine and Biology, Hiroshima University, and to Professor Haruto Uchino, First Division, Department of Internal Medicine, Faculty of Medicine, Kyoto University, for their guidance.

御指導いただきました広大原医研内科蔵本 淳教授，鎌田七男助教授，京大医学部内科内野治人教授に深謝致します．

A paper based on this report was published in the following journal:
本報告に基づく論文は下記の雑誌に掲載された．

Medical Journal of Hiroshima University 28:435-83, 1980

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放影研業績報告書集

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放影研 RERF RADIATION EFFECTS RESEARCH FOUNDATION
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Research Project 研究課題 29-60

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SUMMARY

Hematology data before onset of leukemia were available for 55 of the 1,462 acute leukemia cases collected by RERF to the end of June 1976; 8 of the 55 showed ill-defined preleukemic state and 2 had polycythemia. The preleukemic state was characterized by anemia, leukopenia, and morphological abnormalities of RBC, platelets, and WBC. Preleukemic state was not excessively frequent among cases of leukemia in atomic bomb survivors exposed to high dose.

In the Adult Health Study, five abnormalities characteristic of the preleukemic state, i.e., anemia, leukopenia, relative neutropenia, relative lymphocytosis, and relative monocytosis were analyzed. The prevalence of these abnormalities was not significantly high in survivors exposed to high dose. Leukemia prevalence was high especially in those who presented leukopenia, relative neutropenia, or relative lymphocytosis.

INTRODUCTION

It is well known that the incidence of leukemia is high in A-bomb survivors.[1] Kamada and Uchino[2,3] reported preleukemic state in A-bomb survivors. Leukemia of the exposed was not different to that of nonexposed, and no findings specific to preleukemic state in the survivors were found, but they raised the question whether there may be many cases of leukemia in the survivors who presented preleukemic state. Also, it is unknown to what extent cases with blood abnormalities considered characteristic of preleukemic state so far have actually become

要 約

1967年6月末までに放影研で収集した急性白血病症例1,462例のうち，発症前の血液データが存在する症例が55例あり，そのうち，前白血病状態を呈した症例は8例で，多血症は2例であった．前白血病状態の特徴は，貧血，白血球減少，及び赤血球，血小板，白血球の形態異常であった．高線量被爆者の白血病において，前白血病状態を示す症例が多いとは言えなかった．

成人健康調査対象者において，前白血病状態の特徴である5項目の血液異常ー貧血，白血球減少，相対的好中球減少，相対的リンパ球増多，相対的単球増多ーについて解析を行った．上記5項目の有病率は，高線量被爆者に有意に高くはなかった．白血病発生率は，特に，白血球減少，相対的好中球減少，相対的リンパ球増多を呈した症例に高かった．

緒 言

原爆被爆者において白血病の発生率が高いことはよく知られている．[1] 鎌田と内野[2,3]は被爆者の前白血病状態について報告し，白血病と同様前白血病状態にも被爆者に特異的な所見を見いださなかったものの，被爆者白血病に前白血病状態を呈する症例が多いのではないかという疑問を提出した．また，現在まで前白血病状態の特徴とされている諸血液異常が，どの程度白血病へ移行するか全く不明で

Approved 承認 7 November 1980

Printed 印刷 March 1981

leukemic. It is considered important to clarify the above two points.

MATERIALS AND METHODS

The RERF Leukemia Registry[4] had registered by June 1976 a total of 1,462 cases of acute leukemia, 732 in Hiroshima and 730 in Nagasaki. Retrospective study showed that among these 1,462 cases, records or data of peripheral blood or bone marrow tests performed at ABCC before onset of acute leukemia were available for only 55 cases, 43 in Hiroshima and 12 in Nagasaki.[5] First, the hematological findings of these cases were reviewed and then the relationship of concomitant factors to the development of preleukemic state was analyzed.

At RERF, biennial examinations (Cycle) have been performed since 1958 on the Adult Health Study (AHS) fixed sample of about 20,000 subjects composed of survivors and their controls.[6] Five abnormalities characteristic of preleukemic state were selected. Cases that could be classified as showing such abnormalities for three consecutive Cycles or for at least 4 continuous years were chosen, and the relationship of the radiation dose associated with their prevalence was examined. Further, using the 8,951 subjects who underwent examination Cycles 1-3, analysis of acute leukemia risk during the 12 years after Cycle 3 was made comparing the subjects having abnormalities with those without such state.

RESULTS

Table 1 lists the 55 selected cases by type of acute leukemia, sex, age at onset, date of onset, exposure dose (T65D),[7] and the main hematological changes during the preleukemic stage. In the 55 cases whose hematological data were available, 53 were A-bomb survivors and 2 were not in the city at the time of the bomb (ATB). Peripheral blood abnormalities were found in 10 cases of which 8 (14.5%) were considered as indistinct preleukemic state and 2 (3.6%) as polycythemic. Table 2 lists only the eight preleukemic cases by sex, age at onset, exposure dose, diagnosis, and brief clinical course.

The main abnormal findings in the eight cases with preleukemic state were leukopenia with less than 4,000/mm^3 WBC counts and anemia with less than 11.0 g/100 ml of hemoglobin. Many of

ある．上記二点の解明は，極めて重要と思われる．

材料及び方法

放影研の白血病登録[4]によれば1976年6月までに，急性白血病として広島732例，長崎730例，合計1,462例が登録されている．遡及調査によって，これら1,462症例のうち，発病以前に当所で行われた末梢血液若しくは骨髄検査の記録や資料が保存されている症例は，わずかに55例（広島43例，長崎12例）であることが判明した．[5] 初めにこれらの症例について，血液学的所見を検討し，次いで前白血病状態の発現と随伴因子との関係を解析した．

当所では，成人健康調査として，被爆者とその対照群で構成される約20,000名の固定集団の定期検診を1958年以来2年周期で行っている．[6] 前白血病状態に特徴的な5項目の血液異常を選定した．3周期にわたって，つまり，少なくとも継続して4年間これらの異常を呈した症例が選び出され，その有病率と放射線量との関係を検討した．更に，第1—第3周期の検診を受けた8,951名を対象に，第3周期検診後12年間に発症した急性白血病のリスクについて，異常を呈した者と正常な者とを比較し，解析を行った．

結　果

表1に55例の病型，性，発病年齢，発病年月日，被曝線量（T 65D），[7] 前白血病期中の主たる血液学的変化を示した．血液学的資料が記録保存されていた55例中，53名は被爆者，2名は原爆時市外居住者であった．末梢血の異常を認めたのは10例で，そのうち8例（14.5%）は不明確な前白血病状態と考えられ，2名（3.6%）は多血症と思われた．表2に前白血病症例8例の性，発病年齢，被曝線量，診断名，簡単な臨床経過を一括して示した．

前白血病状態と考えられる8例の末梢血異常所見は，4,000/mm^{3}未満の白血球減少とヘモグロビン11g/100ml未満の貧血であった．白血球減少の内容は好中球減少

TABLE 1 ACUTE LEUKEMIA CASES WITH HEMATOLOGIC DATA AVAILABLE PRIOR TO ONSET, RERF LEUKEMIA REGISTRY, AS OF 30 JUNE 1976
表1　発症前の血液学的データが存在する急性白血病症例
放影研白血病登録，1976年6月30日現在

MF No.	Sex	Onset			Dose in rad	Hematologic Abnormality
		Yr.	Mo.	Age		
Acute Granulocytic Leukemia						
[redacted]	M	1958	8	56	611	
	F	1953	1	25	936	
	M	1975	4	75	Not in City	
	M	1958	9	16	485	
	M	1966	6	71	325	
	F	1968	8	62	Not in City	
	F	1952	5	22	279	
	M	1957	3	51	730	
	M	1959	12	19	513	
	F	1966	4	64	77	
	M	1974	9	64	91	Polycythemia
	F	1963	3	57	335	Leukopenia, Anemia, Neutropenia, Lymphocytosis
	F	1966	10	57	450	
	M	1956	6	53	228	
	M	1972	9	45	11	
	M	1974	10	44	3	
	M	1959	5	27	0	
	F	1959	4	19	82	
	F	1966	5	71	271	
	F	1967	9	47	292	Leukopenia, Thrombopenia, Monocytosis
	F	1957	7	49	448	
	M	1958	1	76	867	
	F	1965	8	67	0	Polycythemia vera
	F	1952	8	51	342	
Acute Lymphatic Leukemia						
[redacted]	M	1958	3	14	276	
	F	1949	6	13	348	
	M	1971	10	56	180	
	F	1957	8	25	126	
	F	1959	6	23	29	
	M	1960	12	23	19	
	F	1951	5	24	828	
	F	1962	9	73	95	
	M	1951	11	17	595	
	F	1955	7	12	9	
Acute Monocytic Leukemia						
[redacted]	M	1958	7	69	163	
	F	1950	9	15	581	
	M	1958	6	30	154	
	F	1967	8	49	0	Leukopenia, Anemia, Thrombopenia, Neutropenia, Lymphocytosis
	F	1970	12	48	364	Anemia
	F	1959	4	27	118	
	F	1953	6	31	573	
	M	1963	9	70	38	
	M	1960	3	32	182	
Erythroleukemia						
[redacted]	F	1968	4	55	350	Leukopenia, Anemia, Neutropenia, Lymphocytosis, Monocytosis
	F	1975	7	76	18	
	F	1971	12	63	594	

→

TABLE 1 Continued 表 1 続き

MF No.	Sex	Onset Yr.	Onset Mo.	Onset Age	Dose in rad	Hematologic Abnormality
[redacted]	F	1970	3	61	483	Leukopenia, Anemia, Monocytosis
Acute Leukemia, Type Unknown						
[redacted]	F	1965	4	39	163	Leukopenia, Anemia
	F	1964	9	36	256	
	F	1954	3	12	539	
	M	1950	3	16	653	
	F	1953	12	30	Unknown	
	M	1960	6	28	Not in City	
	M	1954	5	54	160	
	M	1958	12	51	344	Leukopenia, Anemia

TABLE 2 CLINICAL SUMMARY OF 8 CASES
表 2 8 症例の臨床総括

Case		Clinical Summary
1 ([redacted]) AMOL	Dec. 1953	Hb 9.9 anemia persisted
48 F 364 rad	Feb. 1962	Left breast cancer Op. with ^{60}Co radiation
	Dec. 1970	PB Juvenile cell (+) HUH admission Diagnosis: AMOL
	Jun. 1971	Deceased. Autopsy (+)
2 ([redacted]) ERYTH	Jul. 1954	Hb 9.05 Mar. 1959-WBC 2,500 Mo 20%, leukopenia persisted
56 F 350 rad	Feb. 1965	Mo 14%, monocytosis persisted
	Apr. 1968	HUH admission Diagnosis: ERYTH
	Jul. 1969	Deceased. Autopsy (+)
3 ([redacted]) ERYTH	Jul. 1958	Hb 10.1 WBC 3,100 anemia, leukopenia persisted
61 F 483 rad	Jan. 1959	BM erythroid hyperplasia
	Jul. 1970	HUH admission Diagnosis: ERYTH
	Feb. 1971	Deceased. Autopsy (+)
4 ([redacted]) AMOL	Jul. 1954	Hb 9.0 WBC 2,900 anemia, leukopenia persisted
49 F 0 rad	May 1965	Subcutaneous bleeding Jan. 1966 BM erythroid hyperplasia
	Aug. 1967	WBC 54,000 Juvenile cell (+) Sep. 1967 HUH admission Diagnosis: AMOL
	Oct. 1967	Deceased. Autopsy (+)
5 ([redacted]) AGL	Jul. 1956	Hb 10.8 anemia persisted
58 F 335 rad	May 1960	WBC 2,350 leukopenia persisted
	Mar. 1963	WBC 22,200 Aug. 1963 Memorial hospital admission Diagnosis: AGL
	Sep. 1963	Deceased. Autopsy (+)
6 ([redacted]) AGL	Nov. 1948	Hb 10.8 1951-58 PB normal
47 F 292 rad	Aug. 1960	Hb 11.0 WBC 3,200 Jul. 1962 WBC 2,200 Mo 20% Juvenile cell (+)
	Aug. 1962	BM erythroid hyperplasia
	Sep. 1967	Deceased at Citizens Hospital Diagnosis: AGL Autopsy (−)
7 ([redacted]) AL	Oct. 1954	Hb 9.9 WBC 2,400 Apr. 1956 Hb 10.4 WBC 2,900
51 M 344 rad	Oct. 57-Feb.58	RCH admission (Leukopenia)
	Apr. 1958	RCH admission Dec. 1958 PB Blast (+) BM Blast 80%
	Feb. 1959	Deceased. Autopsy (+)
8 ([redacted]) AL	Jun. 1954	Hb 9.5 Oct. 1960 Hb 11.4 WBC 3,200 Jul. 1962 Hb 11.0 WBC 2,200
40 F 163 rad	Apr. 1965	Low back pain, tiredness May 1965 bleeding tendency
	Jun. 1965	Sasebo North Hospital admission Jul. 1965 PB Blastoid cell (+)
	Oct. 1965	Deceased. Autopsy diagnosis: AL

Hb: Hemoglobin (g/100 ml) Op: Operation PB: Peripheral blood HUH: Hiroshima University Hospital WBC: White blood cell count (/mm^3) Mo: Monocyte BM: Bone marrow RCH: Red Cross Hospital

TABLE 3 DURATION OF PERIPHERAL BLOOD ABNORMALITY
表3　末梢血液異常の持続期間

Case	Abnormality	Duration	Case	Abnormality	Duration
1	Anemia	17 years	5	Anemia	3 years
				Leukopenia	7
2	Anemia	1	6	Leukopenia	9 (probable)
	Leukopenia	9		Thrombopenia	5 (probable)
3	Anemia	15	7	Anemia	4
	Leukopenia	17		Leukopenia	4
4	Anemia	13	8	Anemia	11
	Leukopenia	13		Leukopenia	11
	Thrombopenia	1			

the leukopenia cases showed granulopenia but not always so, because the same cases sometimes had a normal differential blood count. Two cases had monocytosis in excess of 20% in the differential and the absolute number also was in excess of 500/mm^3. In one case, juvenile granulocytes appeared in the peripheral blood 5 years before leukemia was diagnosed. Anemia was mild in almost every case with the hemoglobin level being 9.0-11.0 g/100 ml and no blood transfusions being required. Serum iron levels were normal or slightly high in most cases. Bone marrow puncture was performed on three of the eight cases and all cases showed hyperplasia of erythroblasts. All five cases on which morphological abnormalities of the peripheral blood smear could be studied had earlier presented anisocytosis, polychromasia, and poikilocytosis, with a remarkable presence of ovalocytes in some and especially marked poikilocytosis in other cases. In many cases, morphological abnormalities of platelets appeared later than the morphological abnormality of RBC. The presence of large-sized platelets was remarkable and some had few platelet granules. In many cases, morphological abnormalities of WBC appeared much later than the morphological abnormalities of platelets, and the main abnormalities were binucleated cells, hypersegmentation, Pelger-Hüet-like anomaly, and decrease of neutrophil granules. As morphological abnormalities in the bone marrow, the erythroblast showed slight megaloblastic changes and the WBC series showed the same changes as in the peripheral blood. There was no specific abnormality in the megakaryocytes. Such preleukemic abnormalities persisted for 4 to 17 years (Table 3).

Table 4 compares the prevalence of preleukemic state by exposure dose, but there was no

を示す症例が多いが，常にそうとは限らず，同一症例が正常な白血球分類を示すこともあった．また2例においては20%の単球増多が認められ，その絶対数も500/mm^{3}を越えていた．1例においては白血病と診断される5年前に末梢血に顆粒球系の幼若細胞の出現が見られた．貧血はいずれの症例においても程度が軽く，ヘモグロビンがほとんど9.0−11.0g/100ml台で輸血を必要とするものはなかった．血清鉄は正常ないしやや高目の症例がほとんどであった．骨髄穿刺は8例中3例に行われていたが，全症例赤芽球系の過形成を示していた．末梢血における形態異常は，標本を検索できた5例すべてに早期から赤血球の大小不同，多染性，異型性が認められ，卵円形赤血球症が顕著な症例や異型性が殊に高度な症例があった．血小板形態異常は赤血球形態異常よりも遅れて出現する例が多く，大型のものが顕著で血小板顆粒がほとんどないものもみられた．白血球形態異常は血小板形態異常より更に遅れて出現する例が多く，その異常としては，二核細胞，過分葉，Pelger-Hüet様異常，好中球顆粒の減少が主なものであった．骨髄における形態異常については，赤芽球系に軽度の巨赤芽球のような変化を示し，また，白血球系は末梢血と同様の変化を示した．巨核球系には特別な異常は認められなかった．以上のような前白血病異常は4年から17年間持続していた（表3）．

表4では被曝線量別にみた前白血病状態の発現頻度を比較したが，統計学的に有意差は認められなかっ

TABLE 4 PREVALENCE OF PRELEUKEMIC STATE AMONG ACUTE LEUKEMIA CASES BY DOSE
表4　急性白血病症例の線量別前白血病状態の有病率

Dose in rad	Cases	Preleukemic State
Unknown	1	0 (0.0 %)
250 +	28	6 (21.4 %)
100-249	9	1 (11.1 %)
1-99	11	0 (0.0 %)
0 & NIC	6	1 (16.7 %)
Total	55	8 (14.5 %)

$\chi^2[3] = 3.217$ $P > .10$ *(Excluding unknown dose)*

TABLE 5 CRITERIA OF PERIPHERAL BLOOD ABNORMALITIES CHARACTERISTIC OF PRELEUKEMIC STATE
表5　前白血病状態に特異な末梢血液異常の基準

Item		Criteria		Duration in years
A Anemia	Male	Hemoglobin	<12.0 g/100 ml	4
	Female	Hemoglobin	<11.0 g/100 ml	4
B Leukopenia		Leukocytes	<4,000/mm³	4
C Relative neutropenia		Neutrophils	<40 %	4
D Relative lymphocytosis		Lymphocytes	50 % +	4
E Relative monocytosis		Monocytes	10 % +	4

statistically significant difference indicating increased prevalence of preleukemic state in acute leukemia cases among A-bomb survivors exposed to high dose.

Five hematological abnormalities characteristic of preleukemic state based on the above-described peripheral blood data of the AHS sample were selected; namely, anemia (male hemoglobin <12.0 g/100 ml, female <11.0 g/100 ml), leukopenia (<4,000/mm^3), relative neutropenia (<40%), relative lymphocytosis (≥50%), and relative monocytosis (≥10%) (Table 5). Thrombocytopenia could not be studied because platelets were not accurately counted, although the numbers were estimated.

The prevalence of the five selected abnormalities was studied for relationship to radiation dose in the AHS subjects undergoing biennial examinations since July 1958 for whom data of peripheral blood tests of three consecutive Cycles are completely available.

た．すなわち，高線量被爆者の急性白血病に前白血病状態の発現率が高いとはいえなかった．

上述の成人健康調査対象者の末梢血検査データに基づいて，前白血病に特徴的な5項目の血液異常を選定した．つまり，貧血（ヘモグロビン　男＜12.0g/100ml，女＜11.0g/100ml），白血球減少（＜4,000/mm³），相対的好中球減少（＜40%），相対的リンパ球増多（≧50%），相対的単球増多（≧10%）の5項目である（表5）．血小板については数の推定のみで正確な算定は行われていないので血小板減少症に関しては検討ができなかった．

1958年7月以来定期検診を受け，連続した3回の周期の末梢血検査データが完全に揃っている成人健康調査対象者について，上述の5項目の血液異常の有病率と被曝線量との関係を検討した．

TABLE 6 PREVALENCE OF PERSISTENT PRELEUKEMIC STATE (ANEMIA, MALE) IN AHS SUBJECTS, BY DOSE & CYCLE, JULY 1958-JUNE 1976
表6　成人健康調査対象者における継続的前白血病状態（貧血，男性）の有病率，線量別，検診周期別，1958年7月－1976年6月

Examination Cycle	Item	T65 Dose in Rad				Total	Test of Significance** (df = 2)
		Control 0 & NIC	Low 1-99	High 100+	Unknown		
1–3	Subjects	1654	873	649	129	3305	
	Cases	20	9	6	1	36	
	Rate (10^{-3})	12.1	10.3	9.2	7.8	10.9	.536
	Relative Risk*	1.0	.8	.9	–	–	P >.10
2–4	Subjects	1911	915	814	171	3811	
	Cases	17	7	9	4	37	
	Rate (10^{-3})	8.9	7.7	11.1	23.4	9.7	1.569
	Relative Risk	1.0	.8	1.4	–	–	P >.10
3–5	Subjects	1911	919	789	180	3799	
	Cases	23	2	10	3	38	
	Rate (10^{-3})	12.0	2.2	12.7	16.7	10.0	9.031
	Relative Risk	1.0	.1	1.2	–	–	.01<P<.05
4–6	Subjects	1775	864	730	160	3529	
	Cases	30	9	6	1	46	
	Rate (10^{-3})	16.9	10.4	8.2	6.3	13.0	3.442
	Relative Risk	1.0	.6	.6	–	–	P >.10
5–7	Subjects	1642	804	678	159	3283	
	Cases	19	9	6	–	34	
	Rate (10^{-3})	11.6	11.2	8.8	–	10.4	.068
	Relative Risk	1.0	.9	.8	–	–	P >.10
6–8	Subjects	1548	745	632	155	3080	
	Cases	21	9	8	2	40	
	Rate (10^{-3})	13.6	12.1	12.7	12.9	13.0	.121
	Relative Risk	1.0	.9	1.0	–	–	P >.10
7–9	Subjects	1442	693	590	156	2881	
	Cases	22	6	5	–	33	
	Rate (10^{-3})	15.3	8.7	8.5	–	11.5	2.243
	Relative Risk	1.0	.6	.6	–	–	P >.10

**Standardized relative risk adjusted for age ATB (<15, 15-29, 30-44, 45+).*
***Mantel and Haenszel's procedure after adjustment for age ATB.*

Table 6 shows the prevalence of anemia in males by dose as observed for seven periods of three Cycles each. No consistent difference was noted by dose in the prevalence of anemia among males except during Cycles 3-5.

Table 7 shows the prevalence of anemia in females analyzed as for males. In females, as in males, no significant difference was noted in the prevalence of anemia between the dose groups, except during Cycles 5-7.

Table 8 shows the prevalence of leukopenia by dose. No significant differences by dose were

男性の貧血について線量別にみた有病率を3周期ごとの7期間について観察した結果を表6に示した．第3－5周期間を除き，男性の貧血の線量別有病率には一貫した差異は認められなかった．

表7には男性の場合と同様に女性の貧血の有病率の解析結果を示した．男性と同様，被曝線量別にみたその有病率は，第5－7周期間を除き有意差は認められなかった．

表8には白血球減少の有病率を線量別に示した．第

TABLE 7 PREVALENCE OF PERSISTENT PRELEUKEMIC STATE (ANEMIA, FEMALE) IN AHS SUBJECTS, BY DOSE & CYCLE, JULY 1958-JUNE 1976
表7　成人健康調査対象者における継続的前白血病状態（貧血，女性）の有病率，線量別，検診周期別，1958年7月－1976年6月

Examination Cycle	Item	T65 Dose in Rad				Total	Test of Significance** (df = 2)
		Control 0 & NIC	Low 1-99	High 100+	Unknown		
1–3	Subjects	2709	1749	1010	178	5646	
	Cases	89	40	26	9	164	
	Rate (10^{-3})	32.9	22.9	25.7	50.6	29.0	4.240
	Relative Risk*	1.0	.7	.8	–	–	P >.10
2–4	Subjects	3176	1851	1215	231	6473	
	Cases	103	42	32	9	186	
	Rate (10^{-3})	32.4	22.7	26.3	39.0	28.7	3.958
	Relative Risk	1.0	.7	.8	–	–	P > .10
3–5	Subjects	3241	1896	1188	228	6553	
	Cases	98	37	35	10	180	
	Rate (10^{-3})	30.2	19.5	29.5	43.9	27.5	4.406
	Relative Risk	1.0	.7	.9	–	–	P >.10
4–6	Subjects	3095	1822	1109	215	6241	
	Cases	104	47	39	10	200	
	Rate (10^{-3})	33.6	25.8	35.2	46.5	32.0	2.100
	Relative Risk	1.0	.8	1.0	–	–	P >.10
5–7	Subjects	2900	1672	1054	206	5832	
	Cases	96	35	45	10	186	
	Rate (10^{-3})	33.1	20.9	42.7	48.5	31.9	3.427
	Relative Risk	1.0	.6	1.2	–	–	.01<P<.05
6–8	Subjects	2766	1561	1001	202	5530	
	Cases	74	37	30	6	147	
	Rate (10^{-3})	26.8	23.7	30.0	29.7	26.6	.616
	Relative Risk	1.0	.9	1.0	–	–	P >.10
7–9	Subjects	2585	1477	971	201	5234	
	Cases	66	27	23	5	121	
	Rate (10^{-3})	25.5	18.3	23.7	24.9	23.1	2.066
	Relative Risk	1.0	.7	.8	–	–	P >.10

*, ** *See Table 6.*

noted up to Cycles 4-6. However, in the three periods subsequent to Cycles 5-7, statistically significant differences by dose were noted and the risk in the low and high dose groups was significantly higher than in the control group. However, because no significant difference in prevalence was noted between the low and high dose groups in Cycles 6-8 and 7-9, this phenomenon is believed to have been due to some factor other than dose effect. Other abnormalities did not show any significant difference by dose.

The risk of acute leukemia was compared between subjects having blood abnormalities characteristic of preleukemic state during Cycles

4－6周期までは線量別に有意差はなかったが，第5－7周期以後の3期間では線量別に統計学的有意差を認め，対照群と比較して低線量と高線量群のリスクが有意に高かった．しかし，第6－8周期及び第7－9周期では低線量群と高線量群間の有病率には有意な差は認められなかったので，この現象は線量効果以外の要因によるものと推察される．その他の項目についても線量別に有意差は認められなかった．

急性白血病のリスクについて，第1－3周期において前白血病状態に特異な血液異常を示した者と示さな

TABLE 8 PREVALENCE OF PERSISTENT PRELEUKEMIC STATE (LEUKOPENIA) IN AHS SUBJECTS, BY DOSE & CYCLE, JULY 1958-JUNE 1976

表8 成人健康調査対象者における継続的前白血病状態(白血球減少)の有病率，線量別，検診周期別，1958年7月－1976年6月

Examination Cycle	Item	T65 Dose in Rad				Total	Test of Significance** (df = 2)
		Control 0 & NIC	Low 1-99	High 100+	Unknown		
1–3	Subjects	4363	2622	1659	307	8951	
	Cases	23	23	10	1	57	
	Rate (10^{-3})	5.3	8.8	6.0	3.3	6.4	2.609
	Relative Risk*	1.0	1.6	1.2	–	–	P >.10
2–4	Subjects	5087	2766	2029	402	10284	
	Cases	38	26	11	–	75	
	Rate (10^{-3})	7.5	9.4	5.4	–	7.3	1.833
	Relative Risk	1.0	1.2	.8	–	–	P >.10
3–5	Subjects	5152	2815	1977	408	10352	
	Cases	43	28	17	1	89	
	Rate (10^{-3})	8.3	9.9	8.6	2.5	8.6	.292
	Relative Risk	1.0	1.1	1.1	–	–	P >.10
4–6	Subjects	4870	2686	1839	375	9770	
	Cases	52	34	22	3	111	
	Rate (10^{-3})	10.7	12.7	12.0	8.0	11.4	.594
	Relative Risk	1.0	1.1	1.1	–	–	P >.10
5–7	Subjects	4542	2476	1732	365	9115	
	Cases	53	33	35	3	124	
	Rate (10^{-3})	11.7	13.3	20.2	8.2	13.6	8.788
	Relative Risk	1.0	1.1	1.9	–	–	.01<P<.05
6–8	Subjects	4314	2306	1633	357	8610	
	Cases	46	45	28	4	123	
	Rate (10^{-3})	10.7	19.5	17.1	11.2	14.3	9.428
	Relative Risk	1.0	1.8	1.8	–	–	.001<P<.01
7–9	Subjects	4027	2170	1561	357	8115	
	Cases	36	35	20	2	93	
	Rate (10^{-3})	8.9	16.1	12.8	5.6	11.5	6.157
	Relative Risk	1.0	1.8	1.6	–	–	.01<P<.05

*, ** *See Table 6.*

1-3 and those without such abnormalities. Among the 8,951 subjects examined in Cycles 1-3, 8 developed acute leukemia by June 1976, of whom 4 had had hematological abnormalities including 3 erythroleukemia and 1 acute monocytic leukemia (Table 9). It was found that cases showing anemia (female), leukopenia, relative neutropenia, and relative lymphocytosis had a statistically significant higher risk of developing acute leukemia later than those without such abnormalities (Table 10). The risk of acute leukemia seemed high especially among the cases in which leukopenia persisted, relative neutropenia and relative lymphocytosis were present, and the granulocyte productivity of hematopoietic organs had nonspecifically decreased.

かった者とを比較した．第1－3周期の検査を受けた8,951名から，その後1976年6月までに急性白血病を発病した者は8名であり，うち4名には血液異常が認められ，その病型は赤白血病3例，急性単球性白血病1例であった(表9)．貧血(女性)，白血球減少，相対的好中球減少，相対的リンパ球増多を呈した者は，正常者に比較し，急性白血病のリスクが統計学的に有意に高いことが認められた(表10)．特に白血球減少が継続し，相対的好中球減少と相対的リンパ球増多があり，造血器における顆粒球生産能が非特異的に低下している症例における急性白血病のリスクが高く思われた．

TABLE 9 ACUTE LEUKEMIA CASES WHO DEVELOPED LEUKEMIA AFTER EXAMINATION CYCLE 3 BY HEMATOLOGIC DATA OF PRELEUKEMIC STATE DURING CYCLES 1-3

表9　第1－3周期中に認められた前白血病状態の血液学的所見の有無別の第3周期以後に発症した急性白血病症例

MF #	Sex	Age	Type	Onset		Persistent Preleukemic State*				
				Yr.	Mo.	A	B	C	D	E
[redacted]	M	44	AGL	1975	Apr.	–	–	–	–	–
	F	46	ERYTH	1968	Apr.	–	+	+	+	–
	M	44	ALL	1971	Jan.	–	–	–	–	–
	F	51	ERYTH	1971	Dec.	–	–	–	+	–
	F	49	AGL	1966	Oct.	–	–	–	–	–
	F	41	AMOL	1967	Aug.	+	+	+	+	–
	F	50	ERYTH	1970	Mar.	+	+	–	–	–
	F	36	AMOL	1970	Dec.	–	–	–	–	–

**See Table 5*

TABLE 10 RISK OF ACUTE LEUKEMIA IN AHS SUBJECTS WHO RECEIVED HEMATOLOGIC EXAMINATION DURING CYCLES 1-3 WITH RESPECT TO 12-YEAR FOLLOW-UP PERIOD, BY PRELEUKEMIC STATE DURING CYCLES 1-3

表10　第1－3周期中血液検査を受けた成人健康調査対象者を対象に行った12年間の追跡調査で認めた急性白血病の前白血病状態別リスク

Persistent Preleukemic State Cycles 1-3		Subjects	Leukemia	Rate (10^{-3})	90% Confidence Limits		Relative Risk*	Test of Significance** (df=1)
					Upper	Lower		
A Anemia, Female	Yes	164	2	12.20	38.41	2.17	17.2	χ^2= 10.32
	No	5482	4	0.73	1.67	.25	1.0	P < .01
B Leukopenia	Yes	57	3	52.63	135.96	14.39	102.8	χ^2=111.82
	No	8894	5	0.56	1.18	.22	1.0	P < .001
C Relative Neutropenia	Yes	29	2	68.97	217.24	12.26	86.3	χ^2= 60.48
	No	8922	6	0.67	1.33	.29	1.0	P < .001
D Relative Lymphocytosis	Yes	18	2	111.11	350.00	19.75	184.5	χ^2=116.89
	No	8933	6	0.67	1.33	.29	1.0	P < .001

**Standardized relative risk adjusted for age ATB (<40, 40-59, 60+).*
***Mantel and Haenszel's procedure after adjustment for age ATB.*

DISCUSSION

Blood abnormalities preceding leukemogenesis were reported as early as 1900.[8,9] The word "preleukemia" was first used in 1949 by Hamilton-Paterson[10] and Mallarmé[11] when each of them reported three cases. However, the term "preleukemia" apparently came into general use after Block et al[12] made a detailed report

考　察

白血病発症に先行する血液異常は，既に今世紀の初めから報告がある．[8,9]〝前白血病〟(Preleukemic) という言葉が用いられたのは，1949年 Hamilton-Paterson[10] 及び Mallarmé[11] が各々3例を報告したのが最初である．しかしこの言葉が一般に使用されるようになったのは，Block ら[12] が急性骨髄性ある

entitled "Preleukemic acute human leukemia" on 12 cases which showed blood abnormalities prior to development of acute myelogenous or stem cell leukemias. Subsequently, many reports began to appear, including those of Linman,[13] Saarni and Linman,[14] and Uchino and Kamada[2,3] in Japan. In September 1975, an international symposium entitled "Hemopoietic dysplasias (Preleukemic states)" was held in Paris.[15] To date, however, no clear definition or diagnostic criterion has been established. That is, opinions vary widely, from that which makes a broad interpretation including as preleukemia even the group hematologically normal at present but with a high probability of developing leukemia in the future (a sibling whose identical twin has developed leukemia, a person exposed to radiation, etc.), to that which includes hematological diseases with high probability of developing acute leukemia in the terminal stage (myeloproliferative disorders, sideroblastic anemia, etc.), and to that which strictly confines it to cases that have developed leukemia which presented some hematological disorder before onset. It seems that it is now the consensus of investigators[16-18] to consider it as the blood abnormality observed before leukemia finally developed.

Among changes in the peripheral blood, hematocytopenia is present in almost all cases. Anemia, among them, invariably develops in almost all cases, but the degree is various, ranging from mild to severe. Oval macrocytosis, especially like that related to deficiency of vitamin B_{12} or folic acid, has been emphasized.[19,20] Besides, anisocytosis and poikilocytosis are also known. Appearance of erythroblast is frequently noted. In many cases, WBC count decreases to below 4,000/mm^3 and often monocytosis is seen. Pelger-Hüet-like anomaly and giant or hypersegmented neutrophils appear among the neutrophils and there are findings of maturation disorder. Thrombopenia is frequently seen, but there are also cases in which the platelet count is normal or increased. Morphologically, large size and presence of granular abnormality are reported.

Bone marrow findings frequently show hyperplasia, but some show normoplasia or hypoplasia. Hyperplasia of erythroblasts is characteristic, with the immature type being rather numerous and a megaloblast-like abnormality presented. There are also cases that show ringed sideroblasts with increase of iron in

いは幹細胞性白血病に先行して血液異常の見られた12例につき"Preleukemic acute human leukemia"の表題で詳細に報告してからであろう．その後Linman,[13] Saarni 及び Linman[14] そして日本では鎌田，内野[2,3]をはじめ，多くの報告が相次いで行われた．1975年9月には，パリで，"Hemopoietic dysplasias (Preleukemic states)"と題する国際シンポジウムが開かれた.[15] しかし現在に至るまで，前白血病についての明確な定義及び診断上の基準は確立されていない．したがって，諸家の意見は広範囲に分かれている．すなわち広義の解釈では，現在血液学的に正常であるが将来において白血病を発症する可能性の高い者(一卵性双生児の一方が白血病の場合残りの一人，放射線被曝者など)また，末期において急性白血病を発症する可能性の高い血液疾患(骨髄増殖性疾患，鉄芽球性貧血など)を前白血病状態の定義に含めるが，狭義の解釈では，発症前に何んらかの血液異常を呈した白血病に限定している．現在のところ，前白血病状態を，白血病となったものでその発病以前に認められる血液異常ととらえるのが，諸家[16-18]の一致した見解と思われる．

末梢血における変化は血球減少がほとんどの例に見られる．なかでも貧血は必ず発症すると言ってよいが，その程度は軽いものから重いものまで種々である．特にビタミンB_{12}や葉酸欠乏時に認められるような卵形大赤血球増多が強調されている.[19,20] その他大小不同や異型性も知られており，また赤芽球の出現がしばしば見られる．白血球数は4,000/mm^{3}未満の減少を示す例が多く，しばしば単球増多がある．好中球系にはPelger-Hüet様異常及び巨大若しくは過分葉好中球が出現し，成熟障害の所見を呈する．血小板数も多数の例で減少しているが，正常ないしは増加の例もある．形態的には大型で顆粒異常を有することが報告されている．

骨髄所見は過形成の例が多いが，正形成性，低形成性のものもある．赤芽球系の過形成が特徴的で，やや幼若型が多く，巨赤芽球様の異常を示す．また

erythroblasts when iron staining is done. Granulocyte series show no increase of myeloblasts and promyelocytes (i.e., diagnosis of leukemia cannot be made). However, increase of myelocytes or metamyelocytes is sometimes seen. Megakaryocytes usually increase in number and show various morphological abnormalities.

Comparing the peripheral blood abnormalities of eight cases which showed preleukemic state in this report with those cases reported to date, it seems that the hematocytopenia, especially anemia, was mild in degree and preleukemic state was long. This probably is because the analysis was made on data of examinations conducted for many years on a special population of A-bomb survivors and their controls. Morphological abnormalities of the peripheral blood and bone marrow cells were in agreement with past reports.

There was no case of acute lymphocytic leukemia although two were of unclassified type. All were leukemia of the hemocytic system, with origin in the bone marrow. This also was in agreement with past reports.

Kamada and Uchino[2,3] reported on preleukemic state among A-bomb survivors and raised the question that many of the leukemia cases among them may have had preleukemic state. In the present analysis, six of the eight cases concerned survivors exposed to a heavy dose of 250 rad or more. This may be due to the special character of the study which evolved around the proximally exposed survivors.[6,21] Prevalence by exposure dose showed no statistically significant difference. Thus, the findings did not suggest the prevalence of preleukemic state was increased in acute leukemia developing in survivors exposed to heavy dose.

At ABCC, Moloney and Lange[22] published a paper entitled "Observations of early phases of leukemia", but this was primarily a report on chronic granulocytic leukemia which does not belong in the category of preleukemia. Hoshino et al[23] studied leukemia occurring from 1947 to 1962. Of the cases, 44 (32 acute leukemia and 12 chronic leukemia) had received hematology examination at ABCC before onset, but none of the 32 acute leukemia cases had presented preleukemic state. However, increase of atypical and abnormal lymphocytes in the peripheral blood was noted 3 to 4 years before the clinical

鉄染色を行うと赤芽球の鉄は増加し，輪状鉄芽球を呈する症例もある．顆粒球系では骨髄芽球や前骨髄球の増加は見られない（すなわち，白血病とは診断できない）が，骨髄球ないし後骨髄球が増加していることがある．巨核球は通常数が増加し種々の形態異常を示す．

さて本報告における前白血病状態を呈したと考えられる8例の末梢血異常であるが，従来の報告例と比較すると，血球減少，特に貧血は軽度で，前白血病状態の期間が長いように思われる．これは被爆者及びその対照という特殊の集団に対して長年行われてきた．検診を基にした解析のためであろう．末梢血液及び骨髄細胞の形態異常は，今までの報告と一致するものであった．

2例は病型不明であるが，急性リンパ球性白血病は1例もなかった．症例はすべて骨髄に起源をもつ血球系の白血病であった．これも従来の報告と一致する．

鎌田と内野[2,3]は，被爆者の白血病について報告を行い，被爆者白血病では前白血病状態を有する症例が多いのではないかという疑問を提出した．今回の解析でも8例中6例が250rad以上の高線量被爆者で占められていたが，これは近距離被爆者を中心とした研究の特異性によるものであろう．[6,21] 被曝線量別の発現率では統計学的に有意差を認めなかった．すなわち，高線量被爆者の急性白血病に前白血病状態の発現率が高いとは言えなかった．

ABCCではMoloneyとLange[22]が"Observations of early phases of leukemia"と題する論文を発表しているが，これは主に慢性骨髄性白血病について述べたもので，前白血病の範ちゅうに入らない．星野ら[23]は1947－62年の間に発症した白血病について調査を行った．この間，44例（急性白血病32例，慢性白血病12例）が発病前ABCCで血液検査を受けていたが，急性白血病症例32例の中には，前白血病状態を呈した症例はなかった．しかし，急性及び慢性の白血病の臨床的診断が確立される3－4年前から末梢血液

diagnosis of acute or chronic leukemia was established, and this was regarded as the immunological reaction of the host to the basic clone of leukemia cells.

In the present study, 7 of the 8 cases regarded as having preleukemic state developed leukemia in or after 1963, and 1 developed the disease in 1958 and is included in the 32 cases of Hoshino et al. These investigators made no classification of preleukemic state, and this is believed due to the difference in the method of analysis and criteria. That is, without analyzing the cases individually, they classified them into leukemia and control groups, and compared the mean values. They adopted the criterion of less than 3,000/mm^3 WBC for leukopenia but gave no detailed description for anemia.

As stated, there is no established definition for preleukemia and there are no definite standards for the various types of hemocytopenia. However, since fixed values are needed to analyze a large number of cases, hematologically acceptable standards as shown in Table 5 were set up. Further, the peripheral blood data of the study population were only obtained biennially. The findings of peripheral blood abnormalities just once or twice (during 2 years) seemed to be inadequate for considering the relationship to preleukemia. Cases with abnormalities persisting for three examination Cycles (at least 4 years) were selected and the relationship to exposure dose was analyzed. The results did not indicate an increased prevalence of blood abnormalities characteristic of preleukemic state among the heavily exposed survivors who as a group have a high risk of leukemia.

The prevalence of acute leukemia was significantly higher than in persons without hematological abnormality in the group that had presented any of the abnormalities of anemia (female), leukopenia, relative neutropenia, and relative lymphocytosis among the five that were described as preleukemic state. The prevalence of leukemia was high especially in cases that had presented leukopenia, relative neutropenia, or relative lymphocytosis. These three conditions can be detected by simple routine tests, which may serve as screening for the preleukemic state. Although such abnormalities are not specific, we should carefully follow the cases with any such involvement.

中に異型リンパ球及び異常リンパ球の増加が認められ，彼らはこれを白血球細胞の基礎クローンに対する宿主の免疫反応と考えている．

本報告では，前白血病状態を有するとした８例のうち７例は1963年以降に白血病を発症したが，１例は1958年の発症で，星野らの32例の中に含まれている．星野らは前白血病状態とは分類しなかったが，これは解析方法及び診断基準の相違によるものと思われる．すなわち，彼らは，症例を個々に検討せず，白血病を発症した群と対照群とに分類して平均値を比較した．また，白血球減少として3,000/mm^3 以下という基準を採用したが，貧血に関しては詳細に記述していない．

先に述べたように，前白血病状態の定義はまだ確立されておらず，種々の血球減少についても明確な基準はない．しかし，多数例を解析するためには一定の数値が必要であるので，血液学的に容認される基準として表５のように設定した．また，調査集団の末梢血液データは２年に１回得られるのみである．１回ないし２回（２年間）だけの末梢血異常の所見では，前白血病状態との関連性を考慮する場合不十分であると思われたため，３回の検診周期少なくとも４年間で異常の継続した症例を抽出し，被曝線量との関係を解析した．結果は，白血病のリスクの高い集団である高線量被爆者に前白血病状態に特徴的な血液異常の有病率が多いとは言えなかった．

前白血病状態と規定した５項目中，貧血（女性），白血球減少，相対的好中球減少，相対的リンパ球増多のいずれか一つを示した群の急性白血病の発生率は正常者に比べて有意に高かった．特に，白血球減少，相対的好中球減少，相対的リンパ球増多を呈した症例の白血病発生率は極めて高かった．これら３項目は，簡単で日常よく行われている検査によって探知できるが，それらの検査は，前白血病状態の探知検査として役立つかもしれない．上記の異常は特異的な異常ではないが，これらの異常を呈した症例を慎重に経過観察すべきである．

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