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BONE MARROW CYTOLOGY IN HIROSHIMA ATOMIC BOMB SURVIVORS 5 YEARS FOLLOWING EXPOSURE

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SUMMARY

Bone marrow aspiration smears obtained from 35 individuals, 5 years following exposure to the Hiroshima atomic bomb, were intensively evaluated for radiation related cytologic abnormalities. No definite radiation related changes were observed, but some findings were very suggestive. The most interesting of these was the occurrence of internuclear bridges joining erythroid precursors in the marrow smears of seven (20%) of the heavily exposed survivors. Although not specific it is likely that this lesion is indicative of residual stem cell damage and some degree of ineffectual erythropoiesis. The bone marrow morphologic lesions may be good markers of residual radiation damage but they are too infrequent in their occurrence to be of value as a biologic dosimeter. The findings in this study also suggest that a gradual disappearance of radiation induced late bone marrow changes continues for periods of 3 to 5 years or more following high dose acute radiation exposure.

要約

広島の原爆被爆者35名の被爆5年後に入手した骨髄穿刺塗抹標本を，放射線に関連のある細胞学的異常の有無について，徹底的に検討した．放射線と明確な関係を有する変化は認められなかったが，非常に示唆的な所見があった．このうち最も興味深いのは，高線量被曝者のうち7例(20%)の骨髄塗抹標本にみられた赤芽球に連結する核間橋の発現であった．この病変は特異的ではないが幹細胞障害の残存およびある程度の赤血球形成能の低下を示すものと思われる．骨髄の形態学的病変は放射線残存障害のよい指標であるかもしれないが，その頻度が余りに低いので，生物学的線量計としては価値がない．この研究では，放射線によって誘発された骨髄像の変化が，高線量被曝後3ないし5年以上の間継続して漸減したことも示唆している．

INTRODUCTION

The acute radiation hematologic effects in man are well known.[1-7] The occurrence of leukemia as a late sequelae of excessive exposure to ionizing radiation also is well recognized,[5,8-10] but very few observations have been made in man during the years immediately following recovery from the acute radiation injury.

Many bone marrow examinations have been performed on the A-bomb survivors in Hiroshima and Nagasaki over the years, but most exami-

緒言

ヒトにおける血液学的な急性放射線障害はよく知られている．[1-7] 大量の電離放射線被曝の後遺症として白血病が発生することもよく知られているが，[5,8-10] 急性放射線障害からの回復直後の数年間のヒトについての観察はほとんど行われていない．

広島および長崎の原爆被爆者について多くの骨髄検査が行われてきたが，その大部分は血液障害の診断

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nations have been for the purpose of diagnosis of a possible blood dyscrasia. The bone marrow aspiration smears evaluated in this report are unique in that they were obtained from exposed survivors who were not suspected of having an underlying hematologic problem.

を目的としたものであった．本調査で評価を行った骨髄穿刺塗抹標本は血液学的疾患の疑いのない被爆者から入手したものであるという点で他に類例のないものである．

MATERIALS AND METHODS

At RERF 54 bone marrow aspiration smears which had been obtained from a group of heavily exposed Hiroshima survivors recently were identified. The aspirates were obtained in 1950, 5 years following exposure to mixed gamma-neutron radiation from the A-bomb in Hiroshima. These marrow aspirates were part of an extensive clinical and laboratory investigation that was carried out on 78 survivors in an ophthalmology program at ABCC who had experienced moderate to severe acute radiation signs and symptoms following A-bomb exposure. The purpose of the study was to determine if other late manifestations of radiation injury existed in this population with known radiation induced ophthalmological disease. The initial findings from this study were reported by Fillmore[11] whose comments were: "At the time of the study the hematological findings did not disclose any blood dyscrasias.... The aspiration sternal marrow specimens obtained on 27 patients were compatible with the peripheral hematological findings."

Radiation dose estimates (T65 dose*) were available for 45 of the 54 patients for whom bone marrow slides were available. The distri-

材料および方法

広島の高線量被曝者のうち54名から入手していた骨髄穿刺塗抹標本をこの度，放影研で確認した．これらの標本はガンマー線および中性子から構成された広島の原爆放射線に被曝して5年後の，1950年に入手されたものである．これらの骨髄穿刺標本は，ABCC眼科調査対象者中，被爆後中等度ないし重度の急性放射線症状を経験した78名について実施された広範な臨床調査の一環として入手されたものである．当時の調査目的は放射線誘発性の眼科学的疾患を有する対象集団に，その他の放射線後障害が認められるかどうかを調べるために行われた．この調査の初期所見は Fillmore[11] によって報告された．すなわち，「診察時の血液学的所見では血液疾患はみられなかった....27名から得た胸骨骨髄液の検査所見は，末梢血液検査所見と一致していた.」

骨髄標本を入手した54名のうち45名について推定線量値（T65線量*）が得られていた．その54名の線量

*In the late 1960s and early 1970s radiation dose assignments were completed for most A-bomb survivors in the Life Span Study.[12,13] This Sample contains virtually all persons in both cities who are known to have been exposed to substantial amounts of ionizing radiation from the bombs. Thus, most persons who had severe acute radiation symptoms and developed radiation induced posterior lenticular lesion are in the Life Span Study and have T65 dose estimates. It was not possible to calculate T65 doses for some individuals for whom there were shielding problems which were too complex to permit the calculation of accurate dose estimates. T65D is not a whole-body dose but represents the first collision absorbed dose to a small mass of tissue in the radiation field, where the survivor was located at the time of exposure. The total dose is computed from the sum of gamma and first collision neutron doses in rad (1 rad = 100 ergs/g = 10^{-2} J/kg). In the near future dosimetry calculations will permit specific tissue dose estimates (e.g., bone marrow dose).

1960年代末期から1970年代初期にかけて寿命調査の対象被爆者[12,13]に対する線量の推定は完了した．この対象者には両市において相当量の原爆による電離放射線に被曝したことが判明しているすべての人々が実質的に含まれている．したがって重度の急性放射線徴候を示し放射線誘発性の水晶体後部病変の生じた大部分の人々は寿命調査の対象者であり，暫定推定線量（T65線量）が得られている．正確な線量推定ができないほど複雑な遮蔽状況下にあった一部の人々についてはT65線量は計算できなかった．T65線量は全身線量ではなく，被爆時にいた放射線野における小さな組織塊への第一次衝突の吸収線量を表わす．総線量は rad 単位でガンマー線線量と第一次衝突中性子線量とを合計して計算されたものである．（1 rad = 100 ergs ／ g = 10^{-2} J ／ kg）．近い将来，骨髄線量のような特定の組織線量の推定もできるようになるであろう．

TABLE 1 DISTRIBUTION OF INDIVIDUALS WITH BONE MARROW STUDIES IN HIROSHIMA IN 1950 BY RADIATION DOSE ESTIMATE

表1　広島の1950年骨髄調査標本のある被爆者の推定線量別分布

Number of persons	T65 dose in rad
3	more than 1000
4	751-1000
10	501-750
9	401-500
9	301-400
8	201-300
1	101-200
1	less than 100
9	not calculated

TABLE 2 AGE, SEX, AND DIAGNOSIS FOR CONTROLS FOR 1950 HIROSHIMA BONE MARROW STUDY

表2　広島の1950年骨髄標本調査の対照者；年齢，性および診断別

Age	Sex	Diagnosis
48	F	Menorrhagia
2	M	Hepatomegaly
62	M	Laennec's cirrhosis
62	F	Hemosiderosis
75	M	Pernicious anemia in remission

bution of all 54 individuals by dose is shown in Table 1. There were 30 males and 24 females with ages ranging between 12-69 years. Control specimens were not drawn at the time of the ophthalmology study in 1950, but bone marrow aspiration smears from five nonexposed persons who were examined at about that time were studied for purposes of comparison. None of the persons was anemic at the time of examination, and none was believed to have had any bone marrow abnormality (Table 2).

Specimens from persons without a T65 dose were deleted from the study. Also deleted were nine marrow smears which were felt to be of too poor quality to be adequately reviewed. The marrow aspirated from the 5 nonexposed persons were added to the 36 satisfactory smears from the ophthalmology study following which each was reviewed without knowledge of exposure dosage. A differential count on 4000 erythroid precursors was performed on each bone marrow smear, whenever possible. All cytologic abnormalities in the progenitor cells of the erythroid

別分布は表1に示す．男性30名，女性24名で年齢は12－69歳であった．1950年の眼科学的調査の際には，対照血液標本は採取されなかったが，同じ時期に検査を受けた5名の非被爆者から入手した骨髄穿刺塗抹標本を比較のために調べた．検査時には，いずれの例にも貧血はなく，骨髄異常があると思われるものもいなかった（表2）．

T65線量値の得られていない対象者から採取した標本は調査から除外した．また，質的に不良で適切な評価ができないと考えられた9枚の骨髄塗抹標本も除外した．眼科調査対象者から得た36の良好な塗抹標本に5名の非被爆者から得た標本を加え被曝線量を知らせないで調べた．各骨髄塗抹標本について，可能な限り，赤芽球4,000個の分類像を調べた．赤芽球におけるすべての細胞学的異常を注意深く記録

series were carefully recorded. All myeloid precursors were not separately recorded, but all aberrations in the myeloid series were noted in relation to the 4000 erythroid precursors which were counted. Particular attention was paid to abnormalities which have been associated with radiation injury in previously reported studies.[14] These included bi- and tri-nucleated cells, chromosomal bridging in ana- and tele-phase, nuclear fragments (karyomeres), abnormal mitoses, hypersegmentation, and giant nuclei.

した．顆粒球系の幼若細胞については個別に記録しなかったが，顆粒球系の全ての異常は，4,000個の赤芽球と比較検討した．これまで報告された調査[14]で放射線障害と関係のあった異常については特に注意を払った．この異常には二核および三核細胞，分裂後期および終期の染色体橋，核断片(核節)，異常有糸核分裂，過分断，および巨核などがある．

The clinical charts for the exposed individuals were reviewed upon completion of the bone marrow studies. The subsequent clinical course over the following years was also noted. Pertinent information which was recorded in 1950 was as follows:

a. Medical history and physical examination
b. Hemoglobin, hematocrit, erythrocyte count, reticulocyte count, and total and differential leukocyte count
c. Urinalysis
d. Stool for ova and parasites
e. Sputum for acid fast bacilli
f. Serologic test for syphilis
g. Chest radiograph

骨髄検査が完了した時点で被爆者の臨床記録を再検討した．また，その後の臨床経過にも注意した．1950年に記録された資料は次のようなものであった．

a．病歴および診察
b．ヘモグロビン，ヘマトクリット，赤血球数，網状赤血球数，白血球数および白血球分類像
c．検尿
d．寄生虫および虫卵のための検便
e．抗酸性菌のための喀痰検査
f．血清梅毒検査
g．胸部X線検査

RESULTS

A summary of findings for each bone marrow aspirate reviewed is shown in Table 3. The most frequent abnormality noted was binucleation of cells in the erythrocytic series. Binucleated erythroid precursors were divided into "early" and "late" according to the maturation characteristics of their nuclei and cytoplasm. The "early" binucleated cells included pronormoblasts and basophilic normoblasts (Figure 1A). The transition between basophilic normoblast and polychromatophilic normoblasts provided a vague dividing line between "early" and "late" forms. Any cell that was clearly identified as a polychromatophilic normoblast or orthochromatic normoblast was included in the "late" binucleated series (Figure 1B).

結　果

各骨髄穿刺塗抹標本の検査所見の概要を表3に示す．最も多く見られた異常は赤血球系の二核細胞であった．二核の赤芽球はその核および細胞形質の成熟度によって「初期」と「後期」に分けた．「初期」の二核細胞には前正赤芽球と好塩基性正赤芽球が含まれていた(図1A)．好塩基性正赤芽球から多染性正赤芽球への移行は不明確ながらも一応「初期」と「後期」の形態上の境界線とした．多染性正赤芽球または正染性正赤芽球として明らかに確認された細胞はすべて「後期」の二核細胞系に入れた(図1B)．

Some uncertainty arose when attempting to differentiate a true binucleated cell from a mitotic cell, late in anaphase, prior to initiation of cytokinesis. In this study, a cell was considered to be a late mitotic cell if the cytoplasm was overtly elliptoid with extreme eccentricity of the nucleus (Figure 1C), or if the nuclear

真性の二核細胞と，分裂後期の終わり，細胞質分裂開始前の細胞との区別に不明確なところがあった．この調査では，細胞形質が明らかに楕円形で核が極度に偏っているか(図1C)，核染色質が均一に凝縮

TABLE 3 SUMMARY FINDINGS OF BONE MARROW ASPIRATION SMEARS FOR PERSONS IN 1950 HIROSHIMA BONE MARROW STUDY

Special Bone Marrow Differential Studies, 5 Years Following Exposure, Hiroshima

表 3　広島の1950年骨髄穿刺標本調査所見の総括

特別骨髄分類調査，被爆 5 年後，広島

MF No.	Dose in Rad	Erythroblasts Counted	Binucleated Cells			Late Mitosis		Nucleated	Karyomeres		Internuclear Bridges	Mitotic Bridges	Mitosis			
			Early Erythrocytes	Late Erythrocytes	Myelocytes	Erythrocytes	Myelocytes	Tri Quad	Erythrocytes	Myelocytes			Erythrocytes	Myelocytes	Undetermined	Total
[redacted]	440	4000	9	13	2	14		1 myelo	3	4		4	7	8	19	34
	212	650	-	2						1			3	2		5
	755	4000	1	5	1	4						1	7	8	34	49
	443	4000	2	12	2	14			3	2		4	2	3	45	50
	707	4000	5	11	3	14			4	1		2	2	14	42	58
	348	4000	10	14	1	10	2	1 tri 1 quad		1		8				46
	313	4000	4	4	2	20			19	2	5	3	2	2	21	25
	540	4000	3	4		10			2			2	1	1	35	37
	567	3000	-	3	1	1			3	2			1	3	4	8
	380	4000	4	13	1	7			2	3		3	4	9		37
	997	4000	2	5	1	1			2			3	13	7	32	52
	432	3000	1	15	1	3			2		1	1	2	2	24	28
	1041	4000	2	3		5			2			1				27
	269	4000	-	6	1	6			3			1		1	23	21
	511	4000	1	7	-	7			3			2	4	4	18	26
	382	1750	1	6	3	3			3			1	0	2	14	16
	NIC	4000	2	10	1	5			3	1			1	4	39	44
	228	4000	4	14	2	2		1 quad	8	2		4	1	5	49	55
	322	4000	2	7	1	3			2	1		1		5	19	21
	382	4000	2	13	1	3			7	2	1	1				39
	NIC	3000	2	4	9	1			3	1			1	3	12	16
	711	4000	1	13	1	10		1 tri 1 quad	3			5	1	8	35	44
	478	4000	2	10	-	1	1		1					8	29	37
	293	4000	-	5	-	4		1 tri					1			20
	96	4000	2	15	1	3			4			1	4	5	14	23
	552	4000	-	7	2	5			1			2	1	3	17	21
	652	4000	2	11	-	4	2	1 tri myelo	-		2		4	3	16	23
	206	2000	-	5	1	4			-			1				17
	280	3500	-	15	3	1			3					2	28	30
	401	4000	-	10	2	8					3		4	8	6	18
	NIC	4000	-	10	-	7			13							18
	1568	3000	-	10	1	-			2							18
	625	1000	1	4	-	5			10					2	11	13
	434	4000	-	2	3	1		1 quad (?)								15
	140	4000	4	13	-	2			5		2	1		4	37	41
	NIC	1700	1	2	-	4										13
	336	4000	1	10	3	3			7				7	11	20	38
	NIC	4000	-	4	-	9			1							8
	474	4000	2	6	-	3			1							34
	317	4000	2	10	2	6			2		1					31
	203	4000	-	11	2	5			7							18

TABLE 4 MITOTICALLY CONNECTED ABNORMALITIES: BINUCLEATED AND LATE MITOTIC CELLS
表4 分裂に関係ある異常；二核および分裂後期細胞

T65 Dose in rad	n	Number of cells per 1000 erythroblasts				
		Binucleated		Total binucleated	Late mitotic	Total binucleated + late mitotic
		"Early"	"Late"			
0+NIC	5	0.35 (0.15)	1.70 (0.33)	2.05 (0.34)	1.59 (0.37)	3.64 (0.38)
1-199	2	0.75 (0.13)	3.50 (0.25)	4.25 (-)	0.62 (0.13)	4.88 (0.13)
200-399	15	0.53 (0.18)	2.62 (0.24)	3.16 (0.31)	1.46 (0.32)	4.61 (0.43)
400-599	11	0.44 (0.17)	2.10 (0.37)	2.54 (0.44)	1.54 (0.36)	4.08 (0.68)
600+	8	0.49 (0.12)	2.42 (0.42)	2.90 (0.46)	1.61 (0.56)	4.51 (0.94)
Difference in means		NS P>.05	NS	NS	NS	NS

n – number of marrow smears examined
Figures in parentheses are the standard error

chromatin was not uniformly condensed (Figure 1D).

In comparing the frequency of binucleated cells (either "early" or "late" erythroblasts) per 1000 erythroblasts, no statistically significant difference between the results obtained in the different dose groups in comparison to those of the nonexposed persons was demonstrated (Table 4). Late mitoses, as defined above, also were enumerated. Statistical analysis failed to reveal a gradient with dose.

The frequency of karyomeres (Table 5) was found to be independent of dose although the 600+ rad group had a striking incidence of 8 per 1000 erythroblasts. An example of a karyomere is shown in Figure 2A.

Mitotic bridging (Intranuclear connections between segregating chromosomal fragments, Figure 2B) was noted in the smears of only exposed persons. A gradient with dose and statistical significance were not demonstrated (Table 5).

Internuclear bridges between interphase erythroid cells (Figures 2C &,3A,B,C,D) were noted in seven

されていない場合（図1D）は，分裂後期の細胞とみなした．

赤芽球1,000個中の二核細胞（「初期」または「後期」）の頻度の比較では，非被爆者群と比較して，各線量群について得た結果には統計学的に有意な差はなかった（表4）．上記定義に基づく分裂後期細胞についても同様の比較を行った．統計学的解析では線量に伴う傾向は認められなかった．

核節の頻度（表5）は，線量とは無関係であったが，600 rad以上の被曝者群では赤芽球1,000個中に8という著しい発生率を示した．核節の例を図2Aに示す．

分裂橋一分断している染色体断片間の核内連結（図2B）一は被爆者の標本にのみ認められた．線量による傾向および統計学的有意性は示さなかった（表5）．

中間期の赤芽球間の核間橋（図2C－図3A，B，C，

TABLE 5 MITOTICALLY CONNECTED ABNORMALITIES: KARYOMERES AND MITOTIC BRIDGES

表5 分裂に関係ある異常；核節および分裂橋

	T65 Dose in rad					Difference in means
	0+NIC	1-199	200-399	400-599	600+	
Number examined	5	2	15	11	8	
Karyomeres	1.05 (0.58)	1.13 (0.13)	1.13 (0.32)	0.46 (0.10)	8.00* (1.20)	NS
Mitotic bridges	0 (-)	0.25 (-)	0.38 (0.11)	0.33 (0.11)	0.36 (0.16)	NS

* One case had 10 karyomeres
Figures in parentheses are the standard error

TABLE 6 ROUGH MITOTIC INDEX: ERYTHROID AND MYELOID CELLS COMBINED

表6 分裂指標の概要；赤血球および骨髄球合計

	T65 Dose in rad					Difference in means
	0+NIC	1-199	200-399	400-599	600+	
Number examined	5	2	15	11	8	
Total mitoses per 1000 erythroblasts	6.10 (1.52)	8.00 (2.25)	7.92 (0.62)	7.38 (0.92)	10.00 (1.15)	suggestive $.05<P<.10$

Figures in parentheses are the standard error

marrows. Radiation dose estimates of greater than 300 rad had been made for six of the seven persons. Strict criteria were used for identifying internuclear bridges. Many examples of intercytoplasmic bridging were noted but only those cells which were clearly linked from nucleus to nucleus with a fine strand of chromatin-like material were counted. Though internuclear bridging was not observed in the smears from the nonexposed persons, their paucity precluded establishment of any statistical significance.

Mitotic figures were enumerated in the course of counting the 4000 erythroid precursors. When possible, they were differentiated as myelocytic or erythrocytic. A very rough mitotic index (total number of mitoses, erythroid, myeloid, and undetermined combined, per 1000 erythroblasts) is shown in Table 6. There does appear to be a gradient with dose. This finding is suggestive but not significant ($.05<P<.10$).

Other rare findings in selected marrows included tri- and quadra-nucleated erythroid and myeloid cells, one case of neutrophil hypersegmentation,

D）は7例に認められた．このうち推定放射線被曝線量300 rad以上のものは6例であった．核間橋には厳格な基準を設けた．細胞形質間橋の例は多く認められたが，染色体様の細い線維状物質で核と核が明瞭に連結された血球のみを数えた．非被爆者の骨髄塗抹標本には核間橋は認められなかったが，標本数が少ないために統計学的有意性の確定はできなかった．

赤芽球4,000個を数える過程で分裂細胞数を数えた．可能な場合には，顆粒球系と赤血球系に分類した．非常におおまかな分裂指数（赤芽球1,000あたりの，赤血球系，顆粒球系および不明のものを合わせた分裂総数）を表6に示す．線量による傾向があるようである．この所見は示唆的ではあるが有意ではない（$.05<P<.10$）．

特定の骨髄塗抹標本から得たその他の珍しい所見には三核および四核の赤芽球および顆粒球，1例の好

and several instances of apparent multipolar mitoses (Figure 4). Though none of these abnormalities was noted in the controls, statistical significance cannot be attached.

There was excellent agreement between observers concerning the bone marrow findings in the marrow smears. There also was essential agreement between the examiners regarding the interpretation of several hundred photomicrographs of various cytologic aberrations which were observed.

Medical records for 32 of the 36 exposed patients were available for review. Analysis of hematologic parameters at the time of bone marrow aspiration did not reveal anemia (all hemoglobin values greater than 10 g/100 ml) or reticulocytosis (all reticulocyte counts less than 1.3 %) in any of the cases. In 17 persons the stool was positive for parasites. Not infrequently intestinal parasitism was accompanied by moderate eosinophilia. Common parasites included Ascaris lumbricoides, Necator americanus, and Trichuris trichiura. Active pulmonary tuberculosis was detected in two individuals in the study.

Of the 45 exposed persons, 11 died during the 26 years following the 1950 visit to ABCC. The average age at death was 75. There were three deaths due to gastric carcinoma. All other deaths were from causes which are not believed to be radiation related. None of the controls or exposed persons has developed leukemia or other primary blood dyscrasia.

DISCUSSION

Several striking cytologic abnormalities were observed in the bone marrow aspiration smears of a number of the adults in this study who had been heavily exposed 5 years previously to the Hiroshima A-bomb. The majority of these abnormalities involved the erythroid series. Many of the morphologic lesions noted were nonspecific in type and were similar to those which previously had been reported by Fliedner et al[14,15] in a group of eight men who had been exposed to mixed gamma-neutron radiation as a result of a critical excursion during the processing of waste ^{235}uranium, 3½ years previously. The most likely explanation for the occurrence of these lesions is that of persistent radiation induced stem cell damage which persists for periods of at least 3 to 5 years. In view of the

中球過分葉および数例の明白な多極分裂(図4)があった．これらの異常はいずれも対照者には認められなかったが，統計的有意性はない．

骨髄塗抹標本の所見については観察者の間で非常によい意見の一致があった．また，観察された種々の細胞学的異常を写した数百枚の顕微鏡写真の判定に関しても検査者間で本質的に意見が一致した．

被爆対象者36名のうち32名について医学記録を入手した．骨髄穿刺の際の血液学的パラメーターの分析ではいずれの対象者にも貧血(ヘモグロビン値は全員10g／100ml以上)や網状赤血球増多症(網状赤血球数は全員1.3%以下)はみられなかった．17名の検便で寄生虫が認められた．腸の寄生虫感染のあった者に中等度の好酸球増多症がしばしば認められた．一般に認められた寄生虫としては，回虫，アメリカ鉤虫および鞭虫であった．活動性の肺結核は2名に認められた．

被爆者45名のうち11名は1950年にABCCへ来所以後の26年間に死亡していた．平均死亡年齢は75歳であった．胃癌による死亡が3例あった．その他の死因は全て放射線に関連があるとは思われないものであった．対照者および被爆対象者ともに白血病あるいはその他の主要な血液疾患の発生したものはなかった．

考　察

本調査の実施5年前に原爆よりの高放射線量に被曝した成人対象者の骨髄穿刺塗抹標本に，数種の著明な細胞学的異常が認められた．これらの異常の大多数は赤血球系に認められた．形態学的異常の多くは特殊なものではなく，^{235}ウラニウム廃棄物の処理中に生じた臨界エクスカーションの結果ガンマー線および中性子の混合放射線に被曝した8人の男性について Fliedner ら[14,15]の3年半経過した時点で報告したものと類似していた．これらの障害の発生の原因は，少なくとも3ないし5年間持続する放射線誘発の幹細胞障害であると考えるのが最も妥当であろう．これらの障害の多くが赤血球系のものであり，

erythroid nature of most of these lesions and their occurrence in certain incipient and subclinical hemolytic states it seems very likely that they are associated with some degree of ineffectual erythropoiesis.

Although there is good reason to believe that there is an association between the occurrence of certain cytologic aberrations and excessive radiation exposure,[14,15] this is not established in our study either by means of radiation dose relationships or in comparison to the changes in the bone marrows of the nonexposed individuals. In order to establish the radiation relationship with certainty it would have been helpful if more marrow smears had been available for study from persons without exposure or in the "low dose" exposure range. Nonetheless, the availability of some bone marrow smears from individuals exposed to a wide range of relatively high doses has made it possible to look for dose related effects. For this sample, however, there were so few marrow smears from nonexposed persons for comparison purposes that statistical significance for any modality evaluated probably is not important. Furthermore, consideration also must be given to the possibility that subclinical illness in the nonexposed persons may have influenced bone marrow function so that the bone marrow smears in these individuals do not constitute good controls. Rather than dwell on the importance of any single change or proof of its relationship to radiation it seems much more important to interpret the overall meaning of the bone marrow changes of the exposed persons in terms of possible alterations in marrow function and the nature of the underlying biological change.

Bone marrow characteristics were expressed in relative numbers so that variations in cellularity had little influence on the final results. It also should be emphasized that most of the observed abnormalities represented distinct changes in cell morphologic configuration. Changes were not dependent on such factors as the quality of the stains so that the information presented is believed to be quite reliable. Observer bias was not a factor since all cytologic studies were done without knowledge of exposure.

The previous results reported by Fliedner et al[14,15] constitute the most definitive studies of late radiation induced bone marrow changes that have been published. Of the eight men who

また溶血状態の初期あるいは亜臨床的状態下で発生することに鑑みて，おそらくある程度の赤血球形成異常と関係があると思われる．

ある種の細胞学的異常の発生と強度の放射線被曝との間に関係があると信ずる理由はあるが，[14,15] 本調査では被曝放射線量との関係あるいは非被爆者の骨髄における変化との比較のどちらによってもこのことを立証できない．放射線との関係を立証するには非被爆者あるいは「低線量」被曝者からもっと骨髄塗抹標本を入手できていたら役に立ったであろう．いずれにしても，広範囲にわたる比較的高線量に被曝した人からある程度の骨髄塗抹標本を入手できたことは線量関係の影響を探索することを可能にした．しかし，比較に利用できる非被爆者からの標本数が非常に少なかったため，どのような形で統計学的有意性を評価しても重大な意味をもたないと思われる．さらに，非被爆者に亜臨床的疾患があれば，それが骨髄機能に影響し，そのためにその人の骨髄塗抹標本は良い対照標本にならない可能性があることも考慮しなければならない．ただ一つの変化の重要性や，その変化の放射線との関係の証明に固執するよりも，被爆者の骨髄像変化の総体的な意味を，骨髄機能に起こり得る変化および根本的な生物学的変化の性状の見地から解釈を加えることのほうがより重要であると思われる．

骨髄像の特質は相対的数値で示されたので，細胞充実性における差異は最終的結果にはほとんど影響を及ぼさなかった．観察された異常の大部分は細胞の形態学的形状における明確な変化であったことも強調すべきである．これらの変化は染色剤の質などの要因に左右されなかったので，得られた情報はかなり信頼性があると考えられる．細胞学的検査は全て被爆の有無に関する知識なしに行われたので，観察者による偏りはない．

先の Fliedner ら[14,15] の報告はこれまでに発表された放射線誘発の骨髄像後発変化の研究の中で最も明確なものである．被曝者8名のうち5名は推定線量

had been exposed five received "high" dose exposure with estimated whole-body radiation between 236-365 rad. Three in the "low" dose group had estimated exposures of 68.5, 68.5, and 22.5 rad, respectively. Serial bone marrow aspirations were performed on persons in this group during the immediate postexposure period.[15] Two types of cytologic abnormalities were described in these early marrows: 1) Cells injured directly, and 2) "mitotically connected abnormalities" (noted in both mitotically active cells and interphase cells). For mitotic cells in ana- or tele-phase, they described "bridges" of chromosomal material between separating fragments. Also described were cells late in anaphase in which a chromosome or chromosomal fragment had strayed from the mitotic spindle, thus removed from further karyokinesis. Mitotically connected abnormalities in interphase cells included nuclear fragments (karyomeres), binucleated cells and "giant" cells of the myelocytic series.

Followup bone marrow aspirations on the individuals involved in the Oak Ridge accidental radiation excursion and four healthy controls were evaluated 3½ years later.[14] The most significant finding in the bone marrow aspiration smears was an increased number of binucleated and, occasionally, trinucleated erythroblasts. An increased number of erythroblasts with karyomeres was reported, although its significance was not established. They also observed the frequent occurrence of chromosomes or chromosomal fragments discarded from karyokinesis in cells in mitosis. Two examples of tripolar mitoses were noted in the course of counting 15,000 erythroblasts from the high dose group.

Fliedner et al[14] in their study focused on the occurrence of binucleated erythroblasts. They determined the frequency of binucleated red cell precursors per 1000 erythroblasts and reported a mean of 5.8 for the five men in the high dose group and 2.25 for the two men in the low dose group and 1.2 for the control cohort. While the difference between the high dose group and the controls was statistically significant, that between the low dose and the controls was not. Our study did not demonstrate a statistical difference for erythroid binucleation between exposed and controls. The mean value for the frequency of binucleated erythroblasts per 1000 erythroblasts in our exposed people was considerably lower than the mean value for

236ないし365 radの全身照射という「高線量」を受けた．「低線量」を受けた3名はそれぞれ推定68.5, 68.5, 22.5 radの線量に被曝した．被曝直後この人々について連続して骨髄検査が行われた.[15] これらの初期の骨髄に次の2種類の細胞学的異常が認められた．すなわち，1)細胞の直接損傷，ならびに2)「細胞分裂に伴う異常」(分裂活動中の細胞および中間期の細胞の両方に認められた)．分裂後期あるいは終期の細胞については，分離している断片間に染色体「橋」を認めた．また，染色体あるいは染色体断片が紡錘体から離れて，その後の核分裂から除外された分裂後期の終わりの細胞も認められた．中間期の細胞における細胞分裂に伴う異常には顆粒球系の核断片(核節)，二核細胞，および巨細胞があった．

Oak Ridgeでの放射線事故にあった被曝者と4人の健常な対照者について骨髄標本の追跡検査が3年半後に実施された.[14] この検査で最も重要な所見は二核，ときに三核の赤芽球の数が増加していたことであった．核節をもつ赤芽球の数が増加していることが報告されたが，その有意性は確立されなかった．彼らはまた，分裂中の細胞の中にしばしば分裂から放出された染色体あるいは染色体断片があることを認めた．高線量群の赤芽球15,000個を数える過程で2件の三極分裂が認められた．

Fliedner ら[14]は二核赤芽球の発生に注目し，赤芽球1,000個当たりの二核赤芽球の頻度を調べ，高線量群の5名については平均5.8，低線量群の2名については2.25，対照群については1.2であると報告した．高線量群と対照群との間の差は統計学に有意であったが，低線量群と対照群との間の差は有意ではなかった．本調査では被爆者と対照者との間に二核赤芽球に関する統計学的な差は認められなかった．本調査の被爆対象者における赤芽球1,000個当たりの二核

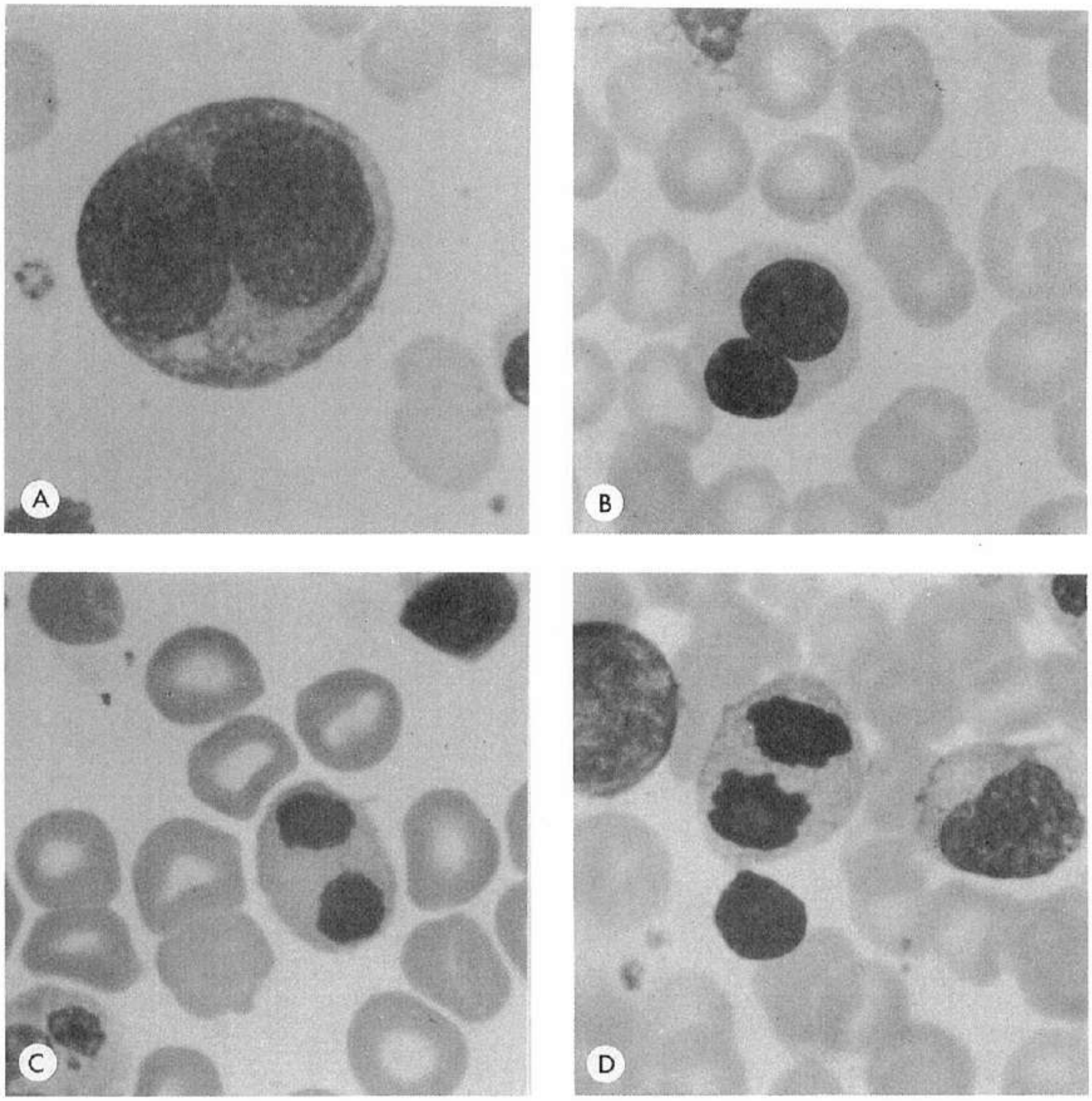

Figure 1

図1

A: "Early" binucleated erythroblast. B: "Late" binucleated normoblast. C: Late mitosis (erythroblast); note elliptoid cytoplasm with eccentricity of the nuclei. D: Late mitosis (erythroblast); nuclear chromatin not uniformly condensed.

A：初期二核赤芽球．B：後期二核赤芽球．C：後期分裂（赤芽球），楕円形の細胞形質と核の偏位に注目のこと．D：後期分裂（赤芽球），核染色質は均一に凝縮されていない．

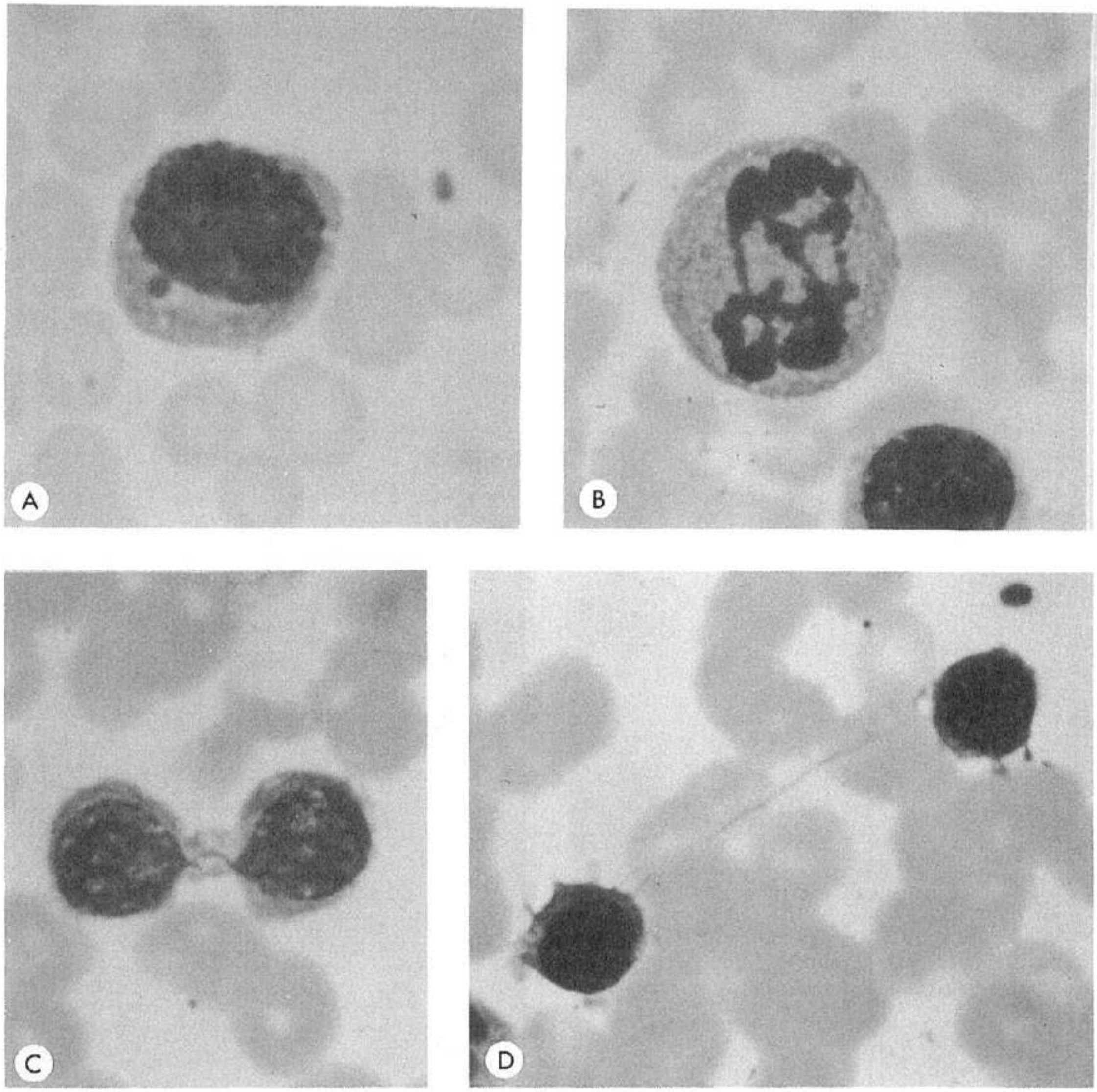

Figure 2

図 2

A: Karyomere. B: Mitotic "bridging." C: Internuclear bridge; two erythroblasts with a bridge of chromatin sheathed in cytoplasm. D: Internuclear bridge.

A：核節．B：分裂橋．C：核間橋，細胞形質で被包された染色質橋を有する二個の赤芽球．D：核間橋．

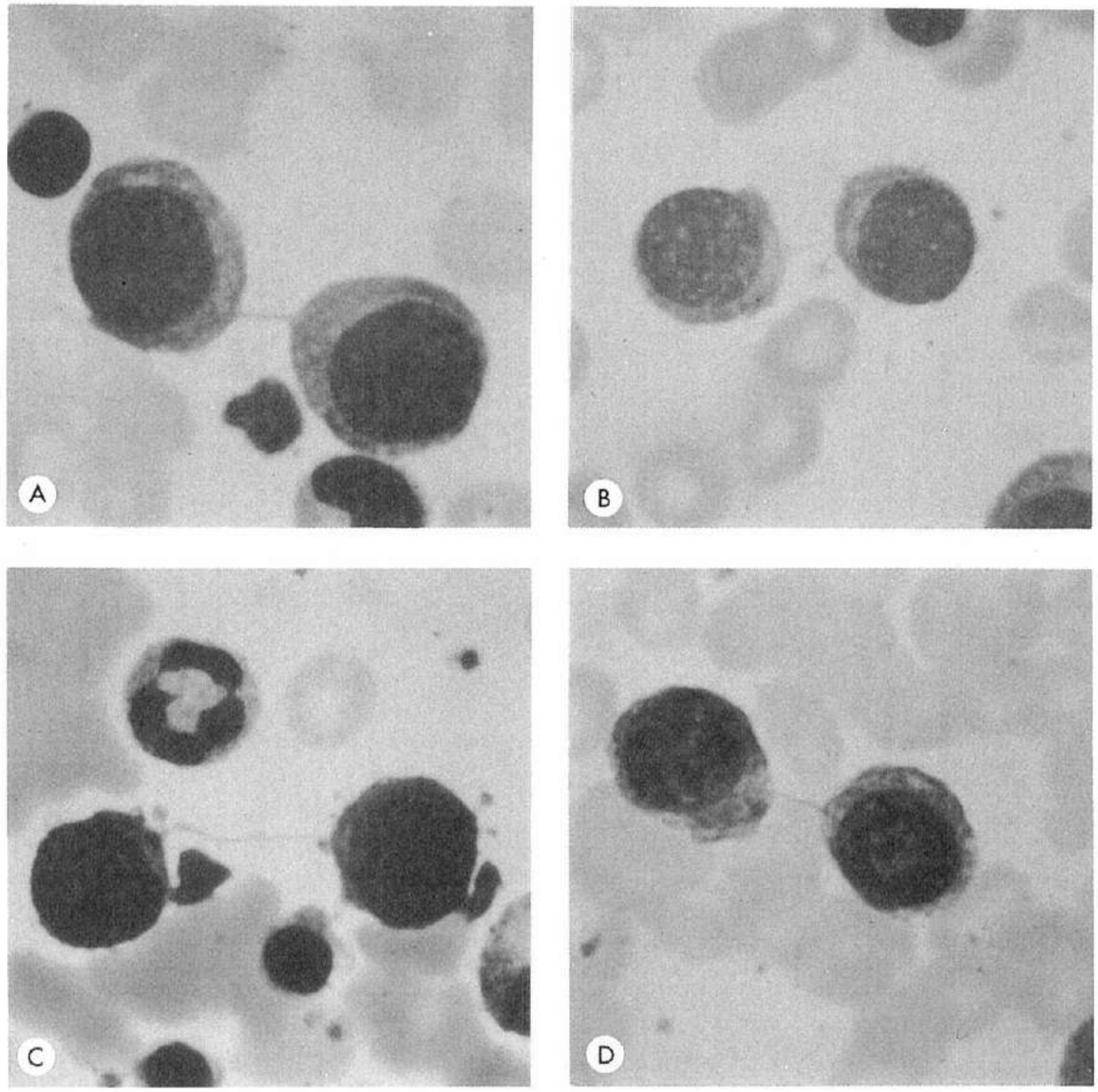

Figure 3
図 3
A,B,C,D: Internuclear bridge.
A, B, C, D：核間橋.

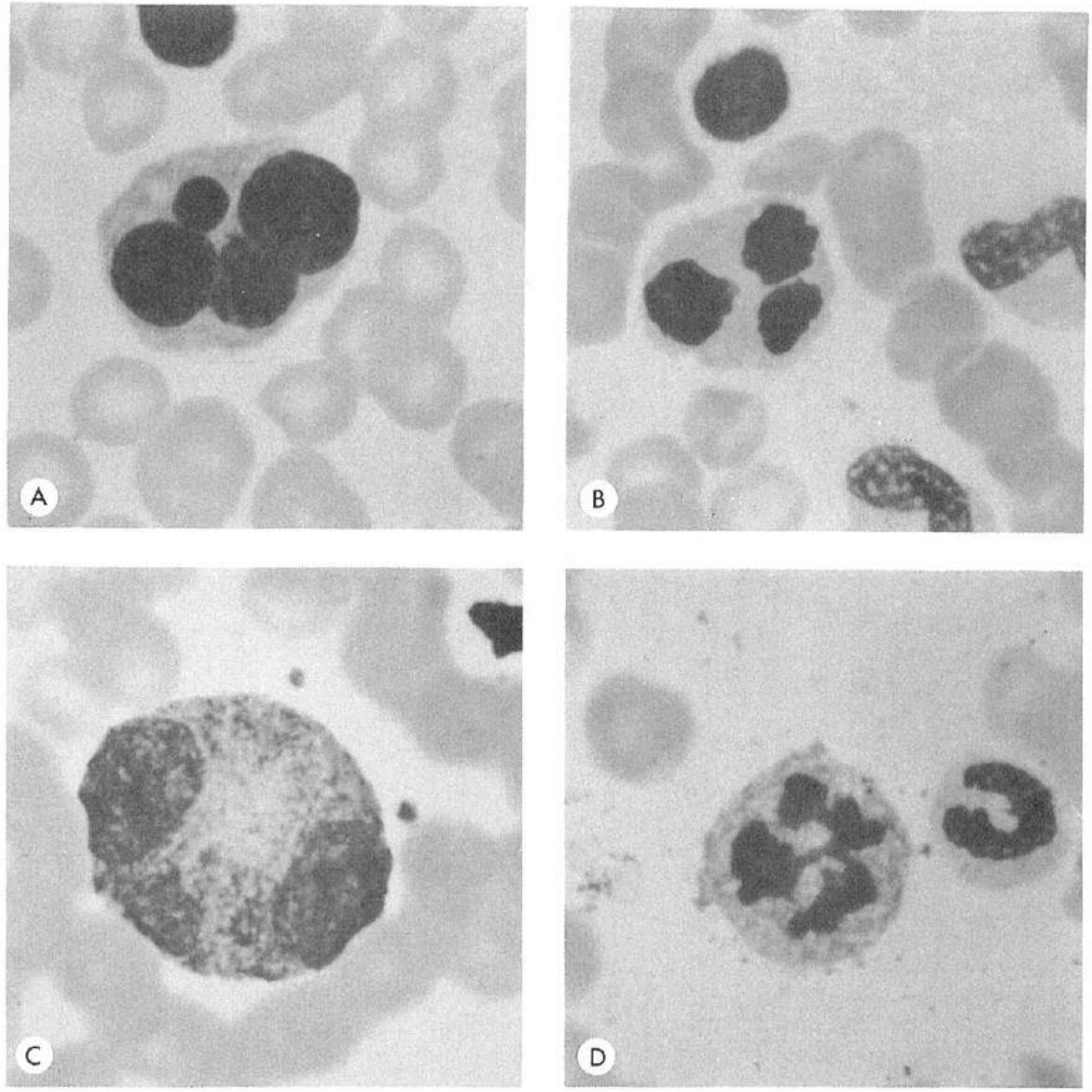

Figure 4
図 4

A: Multinucleated erythroblast. B: Trinucleated erythroblast. C: Trinucleated myelocyte. D: Multipolar mitosis.

A：多核赤芽球．B：三核赤芽球．C：三核顆粒球．D：多極分裂．

the Fliedner et al[14] high dose group. The possibility that the difference between our data and theirs might be due to different criteria for distinguishing late mitoses from binucleated cells has been considered. Cronkite[16] has stated that he considers a cell to be binucleated and not in mitosis if the two nuclei are not connected and if there is no significant constriction of the cytoplasm. Fliedner et al[14] relied on nuclear chromatin structure, stating that a cell late in anaphase has not completed its nuclear membrane and that the chromatin pattern is not yet distinct.[19] In order to test the possibility that differences in morphologic criteria might be responsible for our failure to demonstrate an increase in binucleated erythroid precursors, the data were analyzed using the sum of total binucleated cells plus "late" mitotic cells. The addition of "late" mitotic cells to the unequivocally binucleated cells still did not clarify the issue.

赤芽球頻度の平均値は Fliedner ら[14] の高線量群の平均値よりかなり低かった．本調査の資料と Fliedner らの資料との間の差は分裂後期の細胞と二核細胞とを区別する基準の差によるのかもしれないことが考えられる．Cronkite[16] は，二つの核が連結されておらず，形質が著しく圧縮されていなければ分裂中の細胞ではなく二核細胞であると考えると述べている．Fliedner ら[14] は，核染色体の構造[19] を基準にし，分裂後期の終わりの細胞ではその核膜が完成しておらず染色質パターンも明瞭でないと述べている．本調査で二核赤芽球の増加を認めなかったのは形態学的な基準の差異に因る可能性があることから，二核細胞数と「後期」の分裂細胞数を加えた合計数を用いて資料を解析した．明確な二核細胞に「後期」の分裂細胞を加えても，問題点は解消できなかった．

Fliedner et al[14] derived their information from bone marrow aspirations obtained 3½ years after exposure, while the data in our study was obtained from marrow smears which had been prepared 5 years post exposure. It is conceivable that 5 years was enough time for additional marrow recovery to have occurred. Fliedner et al[14] had reported mitotically connected abnormalities in 50% of cells from each of the acute, post exposure marrows in their study. Mitotic abnormalities had dropped to approximately 4% of cells in each marrow at the time of reexamination, 3½ years later. Though there is little basis for extrapolating these data, one might conjecture that, had bone marrow examinations been performed on the members of the Oak Ridge group 1 or 2 years later, differences between controls and exposed might have become insignificant.

Fliedner ら[14] の資料は被曝3年半後に入手した骨髄塗抹標本から得たものであるが，本調査の資料は被爆5年後に作成された骨髄標本から得たものである．5年の経過によって，さらに多くの骨髄回復が起こるに十分な時間があったと考えられる．Fliedner ら[14] は被曝直後に各例の骨髄細胞の50%に分裂に伴う異常を認めたと報告した．この異常は3年半後の再検査の際には各例の骨髄細胞のほぼ4%に減少していた．この資料について補外法を適用する基礎的資料はほとんどないが，もし Oak Ridge での被曝者の骨髄検査が1年か2年後に行われていたら，対照群と被曝群との間の差は有意でなくなっていたと推量することもできる．

Increased binucleation of erythroid precursors is not a unique marker for radiation exposure. It invariably is present in excessive amounts in a rare form of refractory anemia which is known as congenital dyserythropoietic anemia (CDA).[18,19] Erythroid multinuclearity is observed in 10%-50% of all erythroblasts in the bone marrow aspiration smears from patients with all three types of CDA.[19,20] Essentially, the characteristics of CDA are those of ineffective erythropoiesis; inappropriately low reticulocyte counts coupled with marked erythroid hyperplasia in the marrow, accelerated plasma iron turnover,

二核赤芽球の増加は放射線被曝特有の指標ではない．二核赤芽球は，先天性赤血球形成異常性貧血として知られる珍しい型の不応性貧血には必ず多数認められる．[18,19] 赤血球系の多核は3種類の先天性赤血球形成異常貧血患者の骨髄標本の全赤芽球の10%－50%に認められる．[19,20] 本質的に，本症の特徴は赤血球形成異常である．すなわち，骨髄における著しい赤血球過形成，血漿鉄転換の促進，および血漿鉄

and poor plasma iron utilization.[21] The etiology of these congenital dyserythropoiesis remains unknown.

Binuclearity of bone marrow erythroid precursors (at a lower rate than in CDA) is also a common finding in several other disease processes. Megaloblastic anemias are frequently associated with a striking erythroblastic multinuclearity.[21-23] Schwarz[24] states that the frequency of binucleated cells in a given marrow roughly parallels the regenerative activity of the erythroid precursors and is a frequent finding in hemolytic anemias. This has been noted by others as well.[23,25,26] Binuclearity is often reported in erythroleukemia.[25,26] There have been spurious reports of binucleated erythroblasts in iron deficiency, as well as with vitamin E deficiency.[26,27]

Binucleated erythroblasts are present in variable numbers in normal bone marrows. Berman[23] examined the marrows of eight healthy individuals and noted the incidence of plurinuclear erythroblasts to vary from 1.0-5.1 per 1000 uninuclear erythroblasts. In the four controls of Fliedner et al[14] a mean incidence of binucleated erythroblasts was 1.2, while the mean for the high dose group was 5.8 per 1000. Both values are within the range of Berman's normals. Fliedner et al[14] noted this and states that a statistical comparison was made only with their own controls since they were studied in the same manner as their irradiated subjects.

Schwarz[24] has observed that in the normal bone marrow most binucleated erythroblasts are generally mature and are close to denucleation, with the cytoplasm being orthochromatic or slightly polychromatic. He has found it exceptional for a binucleated nucleus to have proerythroblastic features. In the "late" bone marrows from Oak Ridge, Fliedner et al[14] emphasized the abnormal occurrence of "early" binucleated erythroblasts (corresponding to proerythroblasts and basophilic normoblasts). The incidence of "early" binucleated erythroblasts in their high dose group was 1.4 per 1000 as compared to essentially zero in the low dose and control groups. In our study, a modest increase was noted for the exposed subjects in all dose groups as well as in the controls (Table 4). A slight increase in the occurrence of karyomeres also was a frequent finding in most of the bone marrow smears in our study.

利用の低下を伴う異常に低い網赤血球数である.[21] これらの先天性赤血球形成異常の病因はまだ不明である.

骨髄の二核赤芽球は他の数種の疾患においても認められる所見である(ただし，本症よりも低率). 巨大赤芽球性貧血ではしばしば多核赤芽球の著しい増加が認められる.[21-23] Schwarz[24] は，骨髄における二核細胞の頻度は赤芽球の再生能におおむね匹敵し，溶血性貧血にしばしば見られる所見であると述べている. これについては他にも報告がある.[23,25,26] 二核赤芽球は赤白血病にもしばしば認められている.[25,26] 鉄欠乏症,[26] およびビタミンE欠乏症[27] にも二核赤芽球に関し類似の報告があった.

正常な骨髄に二核赤芽球は認められるが，その数は一定でない. Berman[23] は8人の健常な人の骨髄を調べて多核赤芽球の頻度が単核赤芽球1,000個当たり1.0－5.1と一様でないことを認めた. Fliedner ら[14] の4人の対照者については二核赤芽球の平均頻度は1.2であったが，高線量群の平均値は1,000個当たり5.8であった. この二つの値は Berman の示した正常値の範囲内にあった. Fliedner ら[14] はこれを承知していたが，彼らの調査の対照者は対象被曝者と同じ方法で調査したのでその者だけについて統計学的比較を行ったと述べている.

Schwarz[24] は，正常骨髄においては，ほとんどの二核赤芽球は成熟し，脱核状態に近く，細胞形質は正染性またはやや多染性であると報告している. 二核赤芽球の核が前赤芽球の特性を示すことは例外的であると述べている. Oak Ridge の「後期」の骨髄標本において，Fliedner ら[14] は二核赤芽球の異常発生が「初期」(前赤芽球および好塩基性正赤芽球に相当するもの)に起こることを強調した. 彼らの調査では「初期」の二核赤芽球の発生率は低線量群および対照群では実質的に零であるのに対して高線量群では赤芽球1,000個当たり1.4であった. 本調査では各線量群の被爆対象者および対照者にわずかな増加が認められた(表4). 核節発生のわずかな増加も本調査の骨髄塗抹標本の大部分にしばしば認められた.

Fliedner et al[14] reported an increased number of erythroblasts with karyomeres, but absolute numbers were not reported. The term karyomere usually is used to describe an aberrant nuclear fragment.[24] There probably is little difference between a karyomere and a Howell-Jolly body except that Howell-Jolly bodies are identified only in erythroid cells and only after the nucleus is extruded. Discombe[28] demonstrated that Howell-Jolly bodies evolve from chromosomes that fall away from the mitotic spindle during abnormal mitosis. Presumably, at the completion of mitosis these fragments coalesce into smaller nuclear bodies. Bessis[29] believes that Howell-Jolly bodies are surrounded by normal nuclear membrane on the basis of his electron microscopic studies.

Fliedner ら[14]は核節を伴う赤芽球の数に増加が認められると報告したが，絶対数の記載はなかった．核節は普通異常な核断片を表現する用語である.[24] Howell-Jolly 体が赤血球のみに認められ，核が押し出された後にだけ確認される点を除いては，核節と Howell-Jolly 体の間にはおそらくほとんど差はないと考えられる．Discombe[28]は Howell-Jolly 体が異常な核分裂の際に紡錘体から脱落した染色体から発生することを確かめた．多分，核分裂が終了した時点ではこれらの断片はさらに小さな核断片に融合するのであろう．Bessis[29]は電子顕微鏡による研究の結果に基づいて Howell-Jolly 体が正常な核膜に包まれているとしている．

Fliedner et al[4] found that karyomeres in rats labeled with tritiated thymidine under certain circumstances, indicating that they still retained the capacity to synthesize DNA. They made the point that, in a functional sense, karyomeres must be considered to be ectopic nuclear material and not mere remnants of karyorrhexis.

Fliedner ら[4]はラッテの核節はある特定の状況の下でトリチウム標識チミジンでラベルできることを発見し，このことによって依然DNA合成能を有していることを示した．彼らは，機能的な意味では核節は脱落した核物質と考えるべきで単なる核崩壊残遺物ではないことを主張した．

The present study does not indicate that bridging of chromosomal material in mitotic cells can be used as a reliable marker of persistent radiation injury. It remains a relatively rare finding. Fliedner et al[14] have reported inter-chromosomal bridging only in the myelocytic cells of their patients who had been irradiated 3½ years previously.

本調査では，分裂中の細胞における染色体物質橋を放射線障害持続の信頼できる指標として用い得ることを示すわけではない．この所見は比較的珍しいものである．Fliedner ら[14]は3年半前に被曝した患者の顆粒球にのみ染色体間橋を認めると報告している．

Pluripolar mitoses were uncommon in our study and had no significance as a radiation marker. Fliedner et al[14] attached some importance to their finding of three independent tripolar mitoses in the high dose group, noting that Berman[23] failed to observe a single pluripolar mitosis in 53,167 erythroblasts of eight healthy controls. The fact that it is seen so infrequently and so inconsistently does not lend itself to a study of statistical significance, and leaves the observation of dubious importance.

多極分裂は本調査では珍しく，放射線指標としての意味はなかった．Fliedner ら[14]は，Berman[23]が8人の健常な対照者の赤芽球53,167個中に多極分裂球を一つも観察できなかったことに対して，高線量群で3個の三極分裂球が認められたことはかなり重要であると考えた．多極分裂球は非常に珍しく，出現が不定であることから統計学的有意性を調べるのには有用ではなく，発見されてもそのもつ重要性は不明である．

The most interesting finding in our review of "late" marrows was the occurrence of internuclear erythroid bridges in the bone marrow smears of seven survivors. Though found mainly in the heavily irradiated subjects, its incidence was once again too infrequent to be used as a reliable radiation marker and even less so as a dosimeter.

この「後期」の骨髄標本についての調査で最も興味ある所見は7名の被爆者の骨髄塗抹標本における赤血球系の核間橋の発生であった．これは主に高線量被曝者に認められたが，その発生率は信頼できる放射線指標として用いるには，その頻度はあまりにまれであり，生物学的線量として用いるにはなおさらである．

Internuclear bridging is a rare finding, but it has been reported as a distinguishing feature of type I CDA.[20,21] Lewis et al[26] have done electron microscopic studies on type I CDA and have demonstrated a narrow sheath of cytoplasm surrounding the chromatin-like strand of material that bridges the nuclei of the two, otherwise distinct, erythroblasts. This phenomenon is dramatically demonstrated in Figure 2C in our study.

It is possible that these internuclear bridges found in interphase cells are the end result of a process which began as chromosomal bridging in a mitotic cell. In autoradiographs of marrow obtained from subjects exposed to large doses of ionizing radiation and then incubated in vitro with tritiated thymidine, Fliedner et al[30] reported one instance in which an internuclear bridge was labeled along with the two nuclei which were connected. The inference drawn was that the internuclear bridge was still functional chromatin-like material, able to synthesize DNA in conjunction with both nuclei.

As was mentioned, criteria for the identification of internuclear bridges were very strict. Pure cytoplasmic bridges were not included. Fliedner et al[14] do not appear to differentiate between internuclear bridging and cytoplasmic bridging between two interphase erythroblasts. In their study of late marrows they state that they did not quantitate the apparent increase in red cell precursors with cytoplasmic bridges between cells in the high dose group. Lewis et al[26] have investigated cytoplasmic bridging with the aid of an electron microscope and have demonstrated what appears to be a spindle bridge consisting of microtubules, sheathed by cytoplasm, running between two erythroblasts. Schwarz[24] also noted intercellular cytoplasmic bridging and attributed it to "residual interzonal fibers".

In our study, intercellular bridging, purely by cytoplasmic extension, was not enumerated because it was felt that this could be an artifact of preparation. Without the aid of an electron microscope to clearly demonstrate micro-tubular structures streaming down a tube of cytoplasm from one tube to the next, one could not be sure that he was not simply viewing "sticky" membranes from two cells that had been juxtaposed during preparation. On the other hand, the observation of chromatin material connecting two separate interphase erythroblasts

核間橋は珍しい所見であるが，先天性赤血球造血異常性貧血I型の特徴として報告されている.[20,21] Lewisら[26]は本症I型について電子顕微鏡検査を行い，二つの赤芽球の核を連結する染色質様物質の橋を取り囲む細長い鞘状の細胞形質の存在を認めた．すなわち，この二つの別個の赤芽球は一本の糸状の染色質様物質の橋によって連結されていた．この現象は本調査の図2Cに明確に示されている．

中間期の細胞に見られるこれらの核間橋は，分裂中の細胞で初め染色質橋として認められた過程の結末であるかもしれない．高線量の電離放射線に被曝した人々から入手して試験管内でトリチウム標識チミジンと共に培養した骨髄のオートラジオグラフ法で，Fliedner ら[30]は連結した二つの核と共に核間橋がラベルされた一例を報告した．これから得た結論は，核間橋は依然として，機能的には染色質様物質であり，二つの核と共にDNA合成能があるということである．

前述のように核間橋の確認基準は非常に厳格であった．純然たる細胞形質橋は含めなかった．Fliednerら[14]は中間期の二つの赤芽球間の核間橋と細胞形質橋とを区別していないようである．彼らの後期骨髄調査では，高線量群における細胞間に細胞形質橋をもつ赤芽球に認められた増加を量的に調べなかったと述べている．Lewis ら[26]は電子顕微鏡を用いて細胞形質橋を観察し，それが微細管から成り，細胞形質に包まれ，二つの赤芽球間を連結する紡錘体橋と思われるものであると報告している．Schwarz[24]も細胞間の細胞形質橋を認めており，これを「残留帯間線維」と考えた．

本調査では，純然たる細胞形質の伸展による細胞間橋は標本作成段階における人工的産物であり得ると考えたため数えなかった．一つの細胞形質管から次のものへ流れる微細管構造物を明確に確認できる電子顕微鏡によらなければ，標本作成中に近接した粘着力を有する二つの細胞膜を観察しているのではないという確証はないであろう．他方，二つの別個の中間期の赤芽球を連結する染色質物質は人工的なも

is unlikely to be artifactual. Though internuclear bridging was not observed frequently enough in the exposed cases to be a statistically valid dosimeter of radiation injury, it remains a curious finding in these "late" marrows.

のではなさそうである．核間橋は統計学的に確かな放射線障害の線量計とするには被爆者間に認められる頻度が少なかったが，「後期」骨髄に認められたこの所見は不可解である．

The "mitotic index" is an indication of the proliferative capacity of the marrow.[31] In an earlier paper, Fliedner et al[14] point out that determining the mitotic indexes from ordinarily prepared bone marrow smears is inaccurate. Mitosis should be properly enumerated in Feulgen-squash preparations. With their caution in mind, in our study mitoses were recorded in the course of counting 4000 erythroblasts. Without regard to specific cell type, our rough mitotic index has a statistically suggestive gradient with increasing dose (Table 6). The rough mitotic index was 6/1000 for the control cohort and 10/1000 for the 600+ rad group. Both animal and plant experiments have demonstrated that exposure to ionizing radiation can cause a lengthening of the mitotic interval. If a cell, damaged by radiation, were to spend a longer time in mitosis, the probability in time would be increased. Thus, as Fliedner points out, radiation injury might give a misleading high mitotic index.

「分裂指数」は骨髄の増殖能を示す.[31] 初期の報告で，Fliedner ら[14] は通常の方法で準備した骨髄塗抹標本から分裂指数を求めるのは正しくないと指摘している．分裂数はフォイルゲン染色標本で正確に数えるべきである．彼らの注意を考慮して，本調査では赤芽球4,000個を数え，その間に認められた分裂球数を記録した．特定血球型にとらわれることなく実施した本調査の大まかな分裂指数は線量の増加に伴って統計学的に示唆的な傾向が認められた(表6)．大まかな分裂指数は対照群については 6／1,000 で 600 rad 以上の群については10／1,000 であった．動物および植物実験によって，電離放射線被曝が分裂間隔を延長させ得ることが証明されている．放射線によって損傷を受けた細胞が分裂に長い時間を要すれば，時間当たりの確率は増加するであろう．したがって，Fliedner が指摘するように，放射線障害のため誤って高い分裂指数を示す可能性がある．

Because the mitotic index in our study was determined without Feulgen-squash preparations and the different cell lines in mitosis were not differentiated, little significance in terms of radiation injury can be appropriately attributed to the suggestive gradient with dose. In their study of the Oak Ridge survivors, Fliedner et al[14] did prepare Feulgen-squash preparations on the late marrows and the mitotic indexes were not found to be statistically different from the controls.

本調査では分裂指数の測定にフォイルゲン染色標本を用いず，また分裂中の異なる細胞系の区別をしなかったので，線量に伴う放射線障害の増加が示唆されたが，ほとんど有意性はない．Oak Ridge の被曝者調査で Fliedner ら[14] は後期骨髄のフォイルゲン染色標本を作成したが，分裂指数では対照群と統計学的に差はなかった．

The only other significant report on persisting bone marrow cytologic abnormalities stems from an accidental exposure to fallout radiation in the Marshall Islands in 1954. The incident occurred during a nuclear test in the Marshall Islands (Bikini lagoon). Full details of the incident and the subsequent medical findings from the people exposed are contained in a 20-year review.[32] The most heavily exposed population was a group of 64 people inhabiting Rongelap Island. Their entire exposure was in the form of fallout radiation with a maximum estimated whole-body dose of 175 rad. Bone marrow aspirations from four exposed and two control persons were obtained 9 years after the accident. Conard[32]

骨髄の細胞学的異常の持続に関する残る一つの重要な報告は，1954年に Marshall 群島で起こった放射性降下物への偶発的な被曝から得られたものである．事故は Marshall 群島(Bikini 環礁)で行われた核実験中に起こった．事故の詳細と被曝者のその後の医学的所見は20年間の総括に報告されている.[32] 最も高線量に被曝したのは Rongelap 島に居住する64名の人々であった．彼らはすべて放射性降下物に被曝し，その最大推定全身被曝線量は 175 rad であった．事故の9年後に4人の被曝者と2人の対照者から骨髄標本を採取した．Conard[32] は，赤血球過形成のほ

notes that, in addition to erythroid hyperplasia, there were "abnormalities of the chromatin material with binucleation and an increased frequency of mitotic figures in the normoblastic series." Neither absolute numbers nor statistical significance were reported.

During the course of this accidental fallout in the Marshall Islands, 23 Japanese fishermen aboard the fishing vessel "Fukuryu-maru" (the "Lucky Dragon") were also subjected to fallout from the atomic detonation approximately 90 miles away. Kumatori et al[33] have reported on the bone marrow findings in this group of men, exposed to whole-body radiation in the range of 170-700 rad. Of note, "late" marrows were aspirated on 14 exposed and 4 controls in 1964, 10 years after the initial exposure. Kumatori et al reviewed the marrows in a manner similar to that of our study. They also failed to demonstrate a significant difference between exposed and control marrows for binucleated erythroblasts (mean of 2.0 for exposed versus 1.6 for controls). Three individuals in the exposed group had a relative increase in karyomeres in comparison to both controls and others in the exposed group. No other cytologic abnormalities were reported.

Ineffectual hemopoiesis is likely to occur following bone marrow injury or during the early stages of recovery.[34,35] Impairment of bone marrow function following radiation exposure even though the bone marrow has returned to a morphologically normal appearance and the blood to physiological values has been demonstrated.[36] It seems most likely that these effects are related to impairment of stem cell function or reduction in the number of stem cells capable of multiplication. In a similar fashion, incomplete recovery of damaged stem cells due to ionizing radiation from the A-bomb is most likely for the occurrence of the bone marrow morphologic findings which were observed.

The question frequently is raised as to why a radiation gradient effect involving all individuals in the study cannot be shown. Bond et al[37] have proposed an "injured cell hypothesis" to describe "abortive regeneration" following radiation exposure. According to this hypothesis residual damage in the stem cells having a limited replicative capacity would be the largest in the low to medium dose range rather than in the high dose range. Thus, this hypothesis would be a

かに，「二核を伴う染色体物質の異常および正赤芽球系の分裂頻度増加」があったと述べている．絶対数も統計学的有意性も報告されていない．

Marshall 群島におけるこの降灰の災難で日本の漁船「福竜丸」の23人の乗組員もおよそ90マイル離れた所で放射性降下物をあびた．熊取ら[33]は全身線量170－700 rad に被曝したこの乗組員らの骨髄所見について報告している．特に，「後期」骨髄は初めの被曝から10年後の1964年に14人の被曝者および4人の対照者から採取している．熊取らは本調査と類似した方法で骨髄を検査したが，被曝者と対照者の骨髄の二核赤芽球について有意な差を認めなかった（被曝者平均2.0に対して対照者平均1.6）．被曝者のうち3名は対照者およびその他の被曝者と比較して核節に相対的な増加があった．その他の細胞学的異常は報告されなかった．

造血異常は骨髄損傷後あるいはその回復の初期段階に起こると思われる．[34,35] 放射線被曝後の骨髄機能の損傷は，骨髄が形態学的に正常に戻り血液が生理学的値に回復した後も認められる．[36] これらの影響は幹細胞機能損傷あるいは増殖能力のある幹細胞数の減少に関係がある可能性が最も大きいと考えられる．同様に，原爆の電離放射線に因る幹細胞損傷の不完全な回復が，観察された骨髄の形態学的所見発現の原因である可能性が強いと考えられる．

被曝線量に相当する影響が調査の対象者全員に何故に現われないのかという疑問がしばしば発せられる．Bond ら[37]は放射線被曝後の「不完全再生」を説明するために「損傷細胞説」を提唱している．この仮説によれば，限られた再生能を有する幹細胞では残留障害は高線量域よりもむしろ低線量ないし中線量域で最も大きい．したがって，これによれば，最も高い

reasonable explanation for failure to observe the maximum number of abnormalities in the bone marrows of the individuals with the highest radiation exposure. It is quite possible that these surviving stem cells in individuals in the low dose range had incomplete recovery and were responsible for the morphologic picture of ineffectual erythropoiesis. Acceptance of this explanation, however, does not explain why a number of individuals in the lower dose range failed to clearly demonstrate an increase in the number of the abnormalities which have been defined. This is not easy to explain except that the biological response is not always predictable and may be modulated by the number of endogenous and exogenous influences.[38-41] Some of these factors may impart some degree of bone marrow protection from excessive ionizing radiation exposure.

線量に被曝した人々の骨髄に最も多くの異常が観察されなかったことが合理的に説明できる．低線量域での被曝者におけるこれらの生存幹細胞は回復が不完全で，形態学的な赤血球形成異常像の原因となった可能性がかなり強いと考えられる．しかし，この仮説をいれるとしても，低線量域被曝者の相当数に先に述べた異常の増加が明確に示されなかった理由の説明はできない．このことは，生物学的反応が常に予想できるものではなく，多くの内因性[38,39]および外因性[40,41]の影響を受けて変わる可能性があるという以外に説明し難い．これらの要因の一部が骨髄を過度の電離放射線被曝からある程度まもっている可能性がある．

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