TECHNICAL REPORT
19-75
業 績 報 告 書

# PERIPHERAL BLOOD CHANGES PRECEDING THE DEVELOPMENT OF LEUKEMIA IN ATOMIC BOMB SURVIVORS

## HIROSHIMA AND NAGASAKI, 1947 – 1962

# 原爆被爆者における白血病発病以前の末梢血液変化

## 広島・長崎, 1947 – 62年

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ABCC JNIH

ATOMIC BOMB CASUALTY COMMISSION

国立予防衛生研究所－原爆傷害調査委員会

JAPANESE NATIONAL INSTITUTE OF HEALTH OF THE MINISTRY OF HEALTH AND WELFARE

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HIROSHIMA AND NAGASAKI, JAPAN

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## SUMMARY

The peripheral blood changes in 44 patients who died of either acute leukemia or chronic granulocytic leukemia were evaluated during the preleukemic phase of their clinical illnesses at the time of routine health examination. The most striking finding was the presence of increased numbers of atypical and abnormal lymphocytes in the peripheral blood for periods of 3 to 4 years prior to establishment of the clinical diagnosis of both acute and chronic leukemia. Moderate leukocytosis with left-shifted myeloid cells and basophilia preceded the diagnosis of chronic granulocytic leukemia by 1 or 2 years. Basophilia did not occur in the absence of leukocytosis. The lymphocyte changes suggest the possibility that the host response to underlying clones of leukemic cells may exist for several years prior to the emergence of clinical leukemia. None of the preleukemic hematologic changes which previously have been defined in the preleukemic syndrome for acute leukemia was observed in any of our patients.

## INTRODUCTION

The sequential hematologic changes which occur prior to establishment of the diagnosis of either acute or chronic leukemia are poorly defined.

## 要　約

急性白血病または慢性骨髄性白血病を発病して死亡した44例について，臨床的発病以前の定期検診時における前白血病期の末梢血液変化を検討した．最も顕著な所見は，急性および慢性の白血病の臨床的診断が確立される3年ないし4年前から末梢血液中に異型リンパ球および異常リンパ球の増加が認められたことであった．慢性骨髄性白血病と診断される1年ないし2年前に左方移動を示す骨髄系細胞を伴う中等度の白血球増加および好塩基球増加が認められた．白血球増加がない場合は好塩基球増加は認められなかった．リンパ球の変化が認められたことは，白血病細胞の基礎クローンに対する宿主反応が臨床的な白血病の出現の数年前から存在する可能性を示唆する．急性白血病の前白血病症候群として従来報告されている前白血病性血液変化はどの症例にも認められなかった．

## 緒　言

急性または慢性白血病の診断確立以前に生じる血液変化の経過は十分には明らかにされていない．過去20年間に

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During the past 20 years a number of patients have been described with moderate to severe bone marrow dysfunction for periods of months or years prior to the emergence of acute nonlymphocytic leukemia.[1-16] The peripheral blood and bone marrow changes have been described as part of a preleukemic syndrome. Most patients with this syndrome are older adults and each has been clinically followed either because of significant symptoms or an abnormal blood picture prior to the development of myeloid or monocytic forms of acute leukemia. In contrast, most acute leukemia has an abrupt onset in individuals in all age groups who previously have been in excellent health and have not been followed for any hematologic disorder. Chronic granulocytic leukemia (CGL) tends to be more insidious in its onset and by the time symptoms appear the hematologic picture usually is distinctly abnormal. The character of these early symptoms has made it extremely difficult to observe the preleukemic hematologic features of most patients who develop this type of leukemia. Those changes which have been described in association with the preleukemic syndrome pertain to a relatively small segment of the overall leukemic population and probably are not representative of the total leukemia experience.

Routine health examination at ABCC of a population at high risk for leukemia has provided an unique opportunity to search for preleukemic peripheral blood changes in a limited number of individuals who developed leukemia following exposure to the atomic bombs of Hiroshima and Nagasaki in 1945. In contrast to most previous studies, this retrospective study was directed towards the detection of any peripheral blood changes in healthy individuals which might reflect early evidence of bone marrow dysfunction, one or more years prior to establishment of the diagnosis of either acute or chronic forms of leukemia. A portion of these findings has been noted previously in a preliminary report.[17]

Cytologic and biochemical changes in the blood of four patients at ABCC in the early stages of CGL have been reported by Moloney and Lange.[18] The early hematologic changes in seven patients with acute or subacute leukemia and three additional patients with CGL also were reported by these authors.[19]

## MATERIALS AND METHODS

The clinical records of all patients who developed either acute or chronic leukemia between 1947 and

急性非リンパ球性白血病発現の数か月ないし数年前に，中等度から高度の骨髄機能障害の認められた患者が多数報告されている．[1-16] 末梢血液および骨髄の変化は前白血病症候群の一部とされている．この症候群を有する患者の大部分は高年齢で，各患者は骨髄性または単球性の急性白血病発病以前に，著明な症状や血液像の異常などのために臨床的に経過観察を受けていた．反面，急性白血病の場合は，患者はすべての年齢群にわたり，それまでは健康で血液学的疾患のため経過観察を受けたことのない者が突然発病している．慢性骨髄性白血病は発病時には潜在性であり，症状が現われる時点では血液像は通常すでに明らかに異常である．初期の症状にこのような特徴があるために，この型の白血病患者のほとんどの者の血液の前白血病的特徴を観察することは極めて困難である．前白血病症候群と関係があると記述されているこれらの変化は白血病患者のごく一部に認められるもので，白血病患者全体を代表するものではないと思われる．

ABCCで白血病のリスクの高い人口集団を対象に実施してきた健康診断は，1945年の広島あるいは長崎での原爆被爆後に，白血病の発病をみたという限られた数の者の，前白血病性末梢血液変化を調べるユニークな機会を提供するものである．従来の研究とは対照的に，この遡及的調査は急性または慢性型の白血病の診断が確定される1年またはそれ以前の健康な時期に，骨髄機能障害の早期徴候を示すかも知れない末梢血液変化の検出を目標とした．これらの所見の一部は先の予備的報告の中にある．[17]

Moloney と Lange はABCCで受診した4人の初期慢性骨髄性白血病患者における血液の細胞学的，生化学的変化について報告した．[18] また彼らは7人の急性または亜急性白血病患者および3人の慢性骨髄性白血病患者における初期の血液学的変化についても報告した．[19]

## 材料および方法

広島または長崎において1947年から1962年までの間に，

1962 in either Hiroshima or Nagasaki were reviewed for evidence of a previous hematologic examination at ABCC (Appendix Table A). Those patients reported in either of the earlier ABCC preleukemic studies were excluded from this report.[18,19] The routine hematologic studies performed at the time of each health examination consisted of hemoglobin and hematocrit determinations, erythrocyte count, and total and differential leukocyte counts. Peripheral blood smears and blood count records obtained from more than 1 to 10 years prior to the date of diagnosis of leukemia were identified for 44 patients. Most of the patients in the study had been in close proximity to the hypocenter of the A-bomb so that they had been exposed to appreciable amounts of ionizing radiation. The number of patients in the study by type of leukemia, city, age, and exposure status are shown in Tables 1-3. The study included 26 male and 18 female patients. Most of the acute nonlymphocytic leukemias were granulocytic, monocytic, or myelomonocytic in type. Several of the acute leukemias in adults which were difficult to classify because of their extreme degrees of undifferentiation also were included in the nonlymphocytic group.

急性または慢性白血病の発病をみた全患者の臨床記録を調べて，ABCCでそれまでに血液検査を受けたかどうかを調べた（付録表A）．前記のABCC前白血病調査で報告された患者は本報告からは除外した．[18,19] 定期検診時に行われた通常の血液検査では，ヘモグロビン値，ヘマトクリット値，赤血球数，白血球数，白血球分類が測定された．44人の患者について，白血病の診断が確立される1年以上前から10年前までの末梢血液塗抹標本および血球数算定記録が確認された．本調査に含まれる患者の大部分は，いずれかの市において至近距離で原爆に被爆しており，従ってかなりの量の電離放射線を受けた．白血病型，都市，年齢および被曝状態別対象者数は表1－3に示す．本調査には男26人と女18人が含まれていた．急性非リンパ球性白血病の大部分は骨髄性，単球性または骨髄単球性であった．極度の未分化のために分類困難であった成人白血病数例も非リンパ球性群の中に入れた．

TABLE 1 NUMBER OF PATIENTS BY TYPE OF LEUKEMIA & CITY, 1947-62
表1　症例数：白血病の病型および都市別，1947－62年

| Type of Leukemia | Hiroshima | Nagasaki | Total |
|---|---|---|---|
| Acute nonlymphocytic* | 13 | 10 | 23 |
| Acute lymphocytic | 7 | 2 | 9 |
| Chronic granulocytic | 11 | 1 | 12 |
| Total | 31 | 13 | 44 |

**Includes 10 patients with acute granulocytic, 7 patients with monocytic or myelomonocytic, and 6 patients with undifferentiated leukemia.*

TABLE 2 DISTRIBUTION OF LEUKEMIA BY AGE AT ONSET & CITY, 1947-62
表2　白血病の分布－発病時年齢および都市別，1947－62年

| Age at Onset | Hiroshima | Nagasaki | Total |
|---|---|---|---|
| 10 – 19 | 7 | 6 | 14 |
| 20 – 29 | 8 | 4 | 12 |
| 30 – 39 | 4 | 1 | 6 |
| 40 – 49 | 3 | 0 | 4 |
| 50 + | 9 | 2 | 8 |
| Total | 31 | 13 | 44 |

TABLE 3 EXPOSURE STATUS OF LEUKEMIA PATIENTS BY CITY OF ONSET, 1947-62

表 3　白血病症例の被曝状態—発病時居住都市別，1947—62年

| T65 Dose * | Hiroshima | Nagasaki | Total |
|---|---|---|---|
| 200+ rad | 18 | 9 | 27 |
| 100–199 | 4 | 3 | 7 |
| 50– 99 | 2 | 0 | 2 |
| 1– 49 | 5 | 1 | 6 |
| 0 | 1 | 0 | 1 |
| No estimate | 1 | 0 | 1 |
| Total | 31 | 13 | 44 |

**Milton, Shohoji*[56]

The peripheral blood smears for each patient with leukemia were controlled with peripheral blood smears from at least one and usually two other individuals who were matched by sex and as closely as was possible by age, exposure history, and time of examination.

Most peripheral blood smears had been carefully stored so that it was possible to perform an intensive morphologic reevaluation of each blood smear coded in accord with a single blind study protocol procedure. Mean values for the various cells identified on the smears were determined by years prior to the onset of leukemia for each type of leukemia. The actual number of blood smear examinations performed for each cell type, however, depended on the number of patients examined at any particular time as well as the availability, and the state of preservation of the blood smears. Table 4 shows the total number of blood smear examinations for both the acute and chronic leukemia patients and their controls.

A 200 cell differential leukocyte count was performed on each blood smear. In order to improve the accuracy of basophil counting the number of basophils was identified in a separate 1000 cell leukocyte count of each smear. The absolute number of each cell type per $mm^3$ was calculated as the product of the total leukocyte count per $mm^3$ and the percent of each cell type divided by 100.

The presence of significant lymphocyte morphologic changes was determined by means of an additional examination of each smear. At least 100 lymphocytes were identified and classified as normal (large or small without atypical features), abnormal (large

各白血病患者の末梢血液塗抹標本は，少なくとも１人，普通は２人の出来るだけ年齢，被爆歴および検査時に差のない同性の対照者の末梢血液塗抹標本と比較した．

大部分の末梢血液塗抹標本はよく保存されていたので，単一盲目調査法に従ってコードされた各血液塗抹標本について徹底的に形態学的再検討を行うことが出来た．塗抹標本上で確認された各種細胞の平均値は，各型の白血病について白血病発病前の年数別に示した．しかし各細胞型について行われた実際の血液塗抹検査数は，ある特定時点の受診患者数，ならびに血液塗抹標本の有無およびその保存状態によって定めた．表４は急性および慢性の白血病患者並びにその対照例の血液塗抹検査総数を示す．

各血液塗抹標本について200個の白血球の分類を行った．好塩基球数算定の精度を上げるために，各塗抹標本について別に1000個の白血球の算定を行い好塩基球数を確認した．各細胞型の $1\ mm^3$ 当たりの絶対数は $1\ mm^3$ 当たりの総白血球数と各細胞型の百分率の積を100で割った値として計算した．

著明なリンパ球の形態的変化の有無は各塗抹標本の追加検査で決定した．少なくとも100箇のリンパ球が確認され，正常(異型性のない大型または小型のもの)，異常

TABLE 4 TYPE OF TEST & NUMBER OF BLOOD SMEARS EXAMINED, HIROSHIMA PLUS NAGASAKI, 1947-62

表 4　血液塗抹検査の種類と数，広島・長崎合計，1947－62年

| Type of Test | Blood Smears Examined | |
|---|---|---|
| | Leukemia Patients | Controls |
| Differential leukocyte count | 91 | 146 |
| Basophil count | 91 | 146 |
| Lymphocyte study | 70 | 142 |
| Neutrophil nuclear appendage count | 76 | 140 |
| Neutrophil nuclear lobe count | 79 | 140 |
| Platelet surface area | 64 | 132 |
| Platelet morphology | 64 | 132 |

cytoplasmic granules, nuclear fissures or cleft, or bilobed nuclei), or atypical (plasmacytoid, nucleolated, or Downey types I or III). The absolute value for each cell type was determined as the product of the total number of lymphocytes per $mm^3$ and the percent of each cell type divided by 100. Each of the three classes of lymphocytes was expressed as number of cells per $mm^3$.

The number of nuclear lobes and nuclear appendages was determined for 500 consecutive polymorphonuclear leukocytes on each blood smear. Individual lobes were counted only if they were clearly attached to one another by a fine filament. The average number of nuclear lobes per polymorphonuclear leukocyte was calculated for each smear. Nuclear appendages were classified as drumsticks, clubs, and nodules.[20,21] The results of each appendage count were expressed as the total number of appendages per 500 neutrophils. During this examination the polymorphonuclear leukocytes also were checked for morphologic abnormalities such as Pelger or pseudo-Pelger transformation, or stages of maturation earlier than that of the band.

Platelet size comparisons were made on the basis of average platelet surface area. The maximum and minimum platelet diameters for 100 representative platelets which were clearly isolated on each smear were measured using a microscope eyepiece micrometer. The diameter recorded for each platelet was the average of the two values. The average platelet diameter for each blood smear was used to calculate average platelet surface area as expressed in $\mu^2$ according to the formula $A = \pi r^2$. The measured platelets also were evaluated for their morphologic characteristics. Each platelet was classified as

（大型細胞質顆粒，核溝ないし核裂，または分葉核），または異型（形質細胞様，仁核，または Downey Ⅰ型かⅢ型）に分類した．各細胞型の絶対値は 1 $mm^3$ 当たりのリンパ球総数と各細胞型の百分率の積を100で割ったものであるとした．3群のリンパ球はそれぞれ 1 $mm^3$ 当たりの細胞数で表わした．

各血液塗抹標本の500個の連続多形核白血球について，核分葉および核付属物の数を求めた．核分葉は細いフィラメントで相互に明らかに接続しているものだけを計算した．多形核白血球1個当たりの核分葉の平均値は塗抹標本毎に計算した．核付属物は太鼓桴，棍棒体，小結節に分類した．[20,21] 各付属物数算定の結果は500個の好中球当たりの付属物総数として表わした．この検査中の Pelger または pseudo-Pelger 変体またはバンド期以前の熟成期等の多形核白血球の形態学的異常についても検討した．

血小板の大きさの比較は平均血小板表面積に基づいて行った．各塗抹標本毎に，はっきりと分離している100個の典型的な血小板について，顕微鏡接眼部レンズマイクロメーターを用いて最大と最小の血小板直径を測定した．この二つの値の平均を血小板直径として記録した．各血液塗抹標本の平均血小板直径は，公式 $A = \pi r^2$ に従って $\mu^2$ 単位で表わされる平均血小板表面積の計算に用いた．測定した血小板はその形態学的特徴についても検討した．

Type I (normal size without abnormal morphologic features), Type II (normal size with increased vacuoles or abnormal granules), Type III (large without abnormal morphologic features), or Type IV (large with increased vacuoles, abnormal granules, or unusual shape). The relative number of platelets in each category was compared for the leukemic patients and their controls by year prior to onset of leukemia.

Variance and statistical differences between mean values for leukemic and control subjects were determined for each parameter studied by type of leukemia and years prior to onset of leukemia. The small number of cases for comparison required careful selection of the appropriate statistical tests.

## RESULTS

Individual preleukemic absolute values for each type of peripheral blood leukocyte are plotted by year prior to onset of leukemia along with the mean values for patients and controls in Figures 1-3. The control range was established as ±2 SD from the mean of all control determinations for each cell type. The mean absolute values for each type of peripheral blood leukocyte by year prior to onset of leukemia and by type of acute leukemia are shown in Appendix Tables B and C.

The total leukocyte counts for the acute leukemia patients during the preleukemic period were not significantly different from those of the controls by parametric and nonparametric tests. Consistent and possibly significant differences were noted for certain cell types, however. Several patients had a modest polymorphonuclear leukocytosis during the year preceding the development of either acute lymphocytic or acute nonlymphocytic leukemia. There was no consistent trend in the earlier blood counts and in some instances a moderately left-shifted polymorphonuclear leukocytosis was associated with either bacterial or parasitic infection. Periodic eosinophilia was frequently noted, but in most instances this was traced to the presence of intestinal parasites, especially during the period of the late 1940's and early 1950's. Four patients who subsequently developed acute granulocytic leukemia (AGL) each had a single immature leukocyte form of uncertain type in the differential count between 1 and 2 years prior to establishment of the diagnosis of leukemia. Neither leukopenia nor neutropenia (total leukocyte count less than 3000/mm$^3$ or neutrophil count less than 2500/mm$^3$) were

血小板はⅠ型(正常大，形態学的異常なし)，Ⅱ型(正常大，空胞または異常顆粒の増加を伴う)，Ⅲ型(大型，形態学的異常なし)，Ⅳ型(大型，空胞，異常顆粒，または異常形態の増加を伴う)に分類された．各分類における血小板の相対数は白血病患者およびその対照者について，白血病発病前の年数別に比較した．

白血病患者と対照者の平均値の相違および統計的差を白血病の型ならびに白血病発病前の年数別に調べた各パラメーターについて求めた．比較する症例数が少なかったので適切な統計的検定の選択には慎重を期した．

## 結　果

各型の末梢血液白血球について，個人の前白血病期絶対値を，患者および対照者の平均値とともに，白血病発病前の年数別に図1－図3にプロットした．対照値の範囲は，各細胞型について，全対照測定値の平均±2 SDと設定した．白血病発病前の年数別および急性白血病の病型別の末梢血液白血球各型の平均絶対値を付録表BとCに示す．

パラメーターおよび非パラメーター検定では，急性白血病患者の前白血病期の白血球総数と対照者の白血球総数の間に有意の差は認められなかったが，特定の細胞型については一定で有意と思われる差が認められた．数名の患者に，急性リンパ球性または急性非リンパ球性白血病の発病前年にわずかな多形核白血球増多症が認められた．初期の血球数に一定の傾向はなく，いくつかの例では細菌性感染または寄生虫感染のいずれかに関係のある中等度の左方移動多形核白血球増多症が認められた．周期性の好酸球増多症もしばしば認められたが，大部分の例では，特に1940年代後期から1950年代の初期までの期間のものにおいては，これは腸内寄生虫症によるものであったことが判明した．急性骨髄性白血病の発病をみた4人の患者には，白血病の診断の確立前1年ないし2年の間に，それぞれ1個の分類不明の幼若白血球が認められた．前白血病期中，急性白血病患者に白血球減少症も好中球減少症(総白血球数3000／mm$^3$以下または好中球数2500／mm$^3$

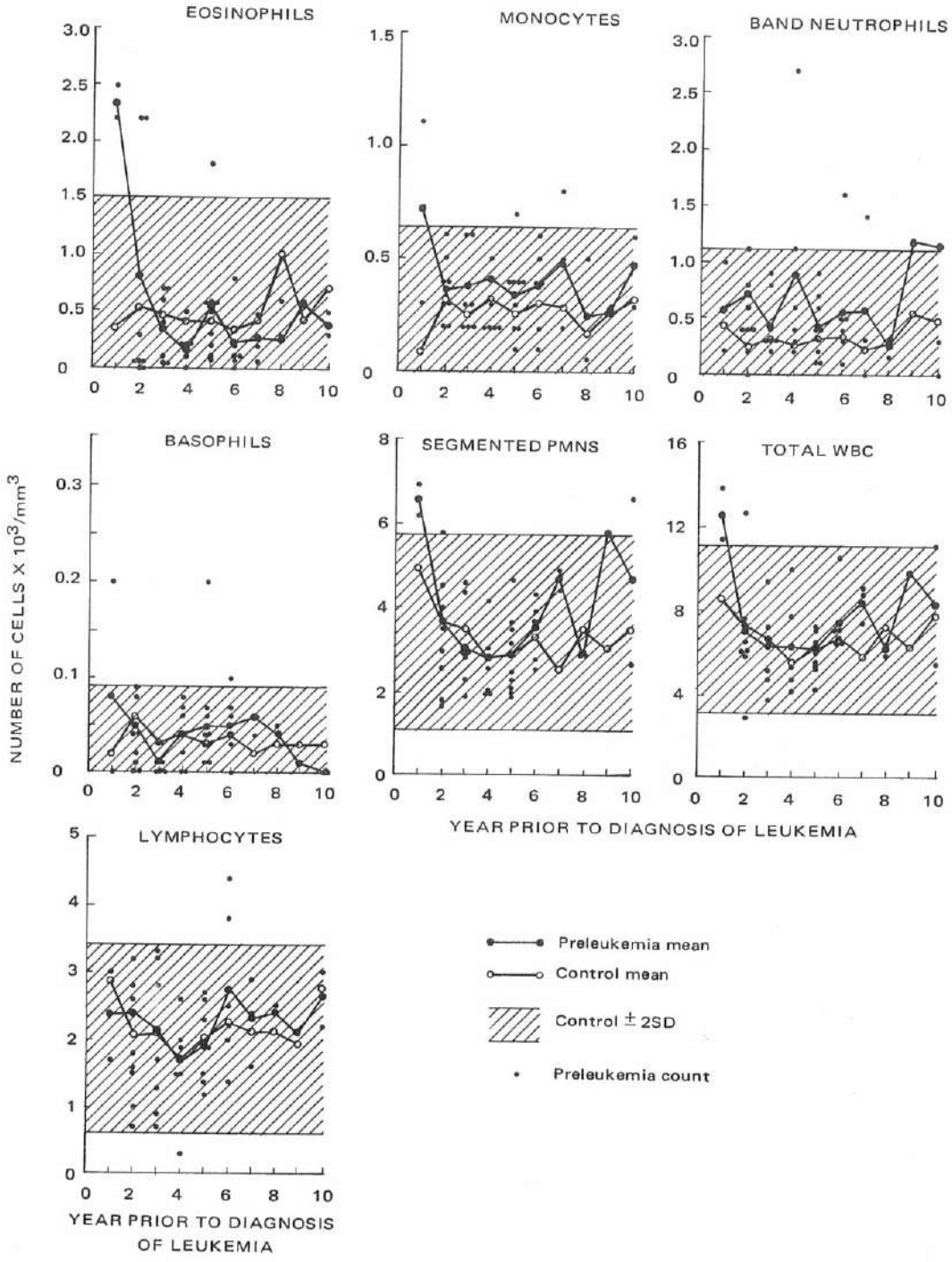


*Figure 1 Peripheral blood leukocytes, individual and mean values by year prior to the diagnosis of acute nonlymphocytic leukemia, Hiroshima and Nagasaki, 1947-62*

図1　急性非リンパ球性白血病診断前の年数別末梢血白血球数の個人値および平均値，広島・長崎，1947－62年

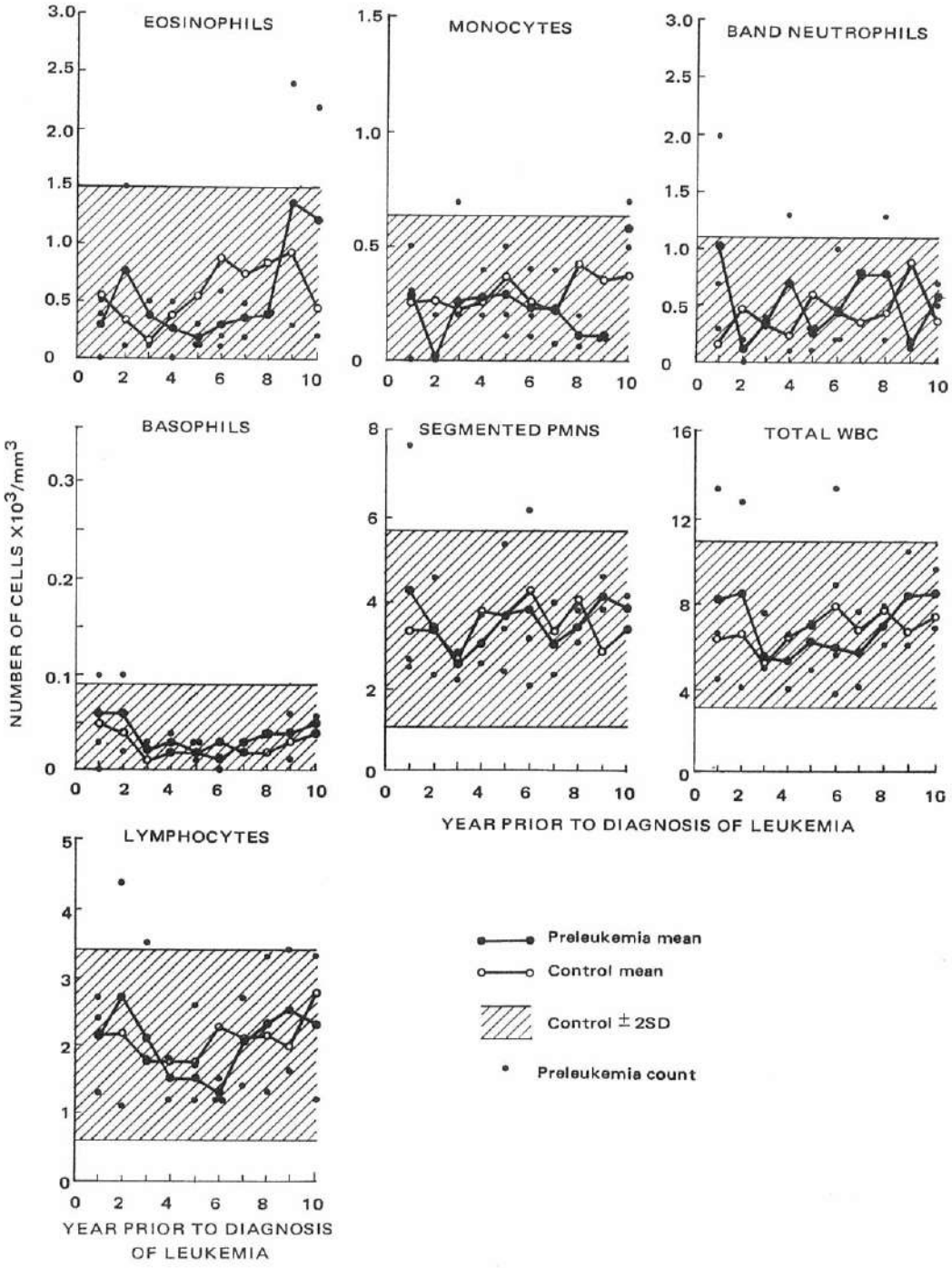


*Figure 2 Peripheral blood leukocytes, individual and mean values by year prior to the diagnosis of acute lymphocytic leukemia, Hiroshima and Nagasaki, 1947-62*

図 2　急性リンパ球性白血病診断前の年数別末梢血白血球数の個人値および平均値，広島・長崎，1947－62年

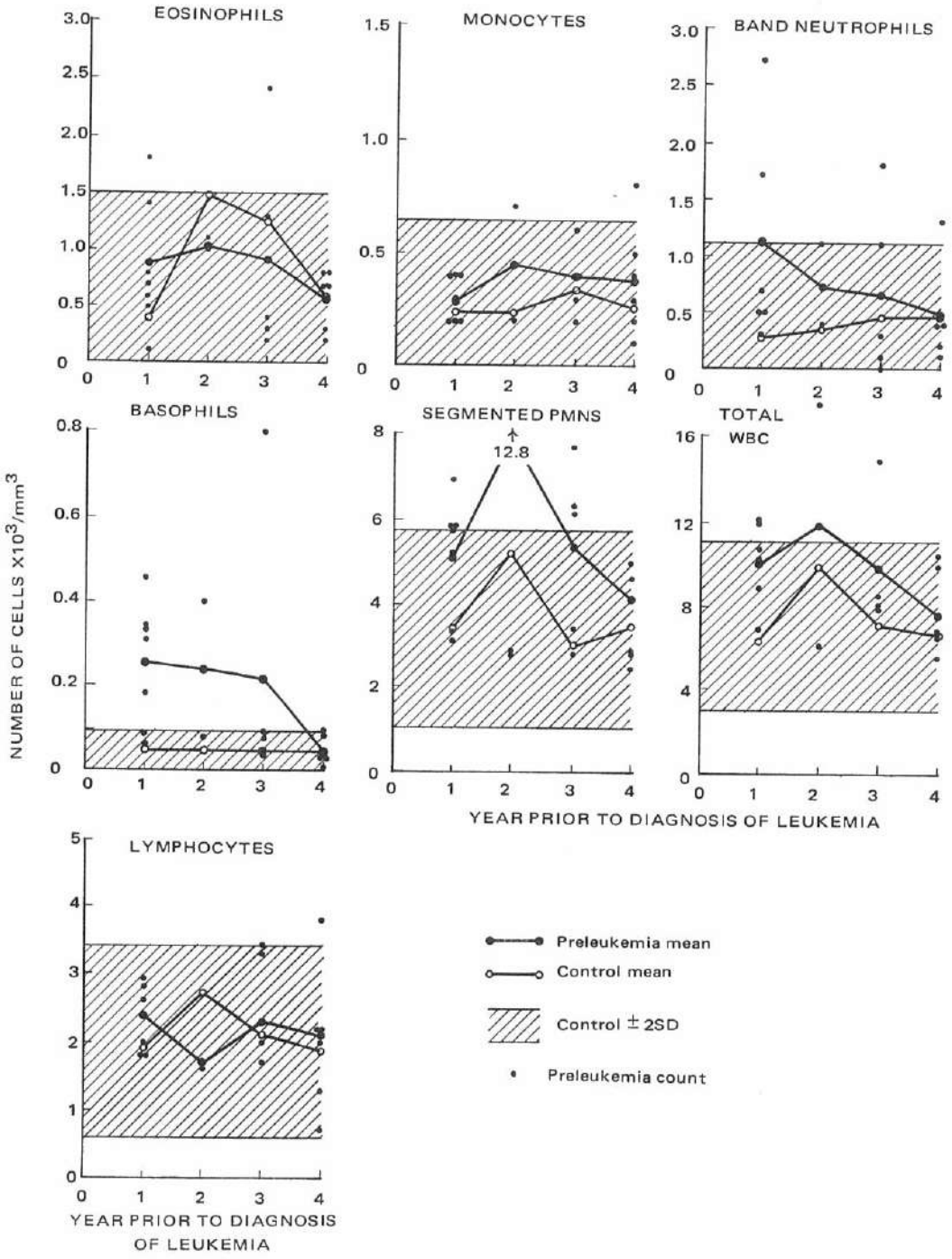


*Figure 3 Peripheral blood leukocytes, individual and mean values by year prior to the diagnosis of chronic granulocytic leukemia, Hiroshima and Nagasaki, 1947-62*

図3　慢性骨髄性白血病診断前の年数別末梢血白血球数の個人値および平均値，広島・長崎，1947－62年

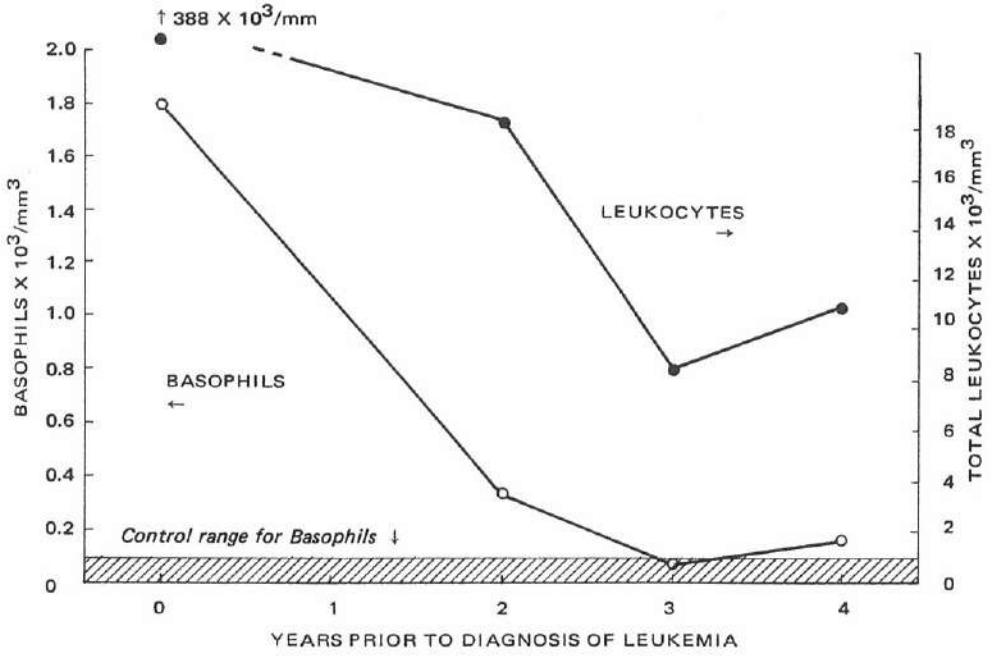


*Figure 4 Total leukocyte and basophil counts in a patient with chronic granulocytic leukemia during the 4 years prior to establishment of the diagnosis of leukemia*

図 4　慢性骨髄性白血病患者における白血病診断前 4 年間の総白血球数および好塩基球数

observed in any of the acute leukemia patients during the preleukemic period.

One of the significant findings for CGL was the occurrence of borderline polymorphonuclear leukocytosis during the preceding year and occasionally 2 or 3 years prior to establishment of the diagnosis of leukemia. In every instance, 3 years or less prior to diagnosis of leukemia, there was a moderate left shift of the granulocyte series with increased numbers of band forms and in five of seven instances cells younger than band forms were observed. Perhaps the most important observation was that the leukocytosis in all seven of these patients was associated with basophilia (>125 basophils/mm$^3$) and that basophilia always was associated with moderate to marked leukocytosis. Basophilia was not found in any of the controls. One patient (MF [redacted]) had borderline leukocytosis and basophilia 4 years prior to diagnosis of leukemia (Figure 4). The following year his total leukocyte and basophil counts were within the control range, but the year after (2 years prior to diagnosis) he again demonstrated leukocytosis and marked basophilia. The early leukocytosis probably was due to his chronic otitis media rather than his leukemia, but it is of interest that he had modest basophilia with his infection long before leukemia was

以下）も認められなかった．

慢性骨髄性白血病の著明な所見の一つは，白血病の診断確立の前年および場合によっては 2 年または 3 年前に，軽度の多形核白血球増多症が認められたことであった．各例において，白血病診断前 3 年以内に顆粒球の中等度の左方移動およびバンドの増加を認め，さらに 7 人中 5 人においてはバンドよりも幼若な細胞が認められた．この 7 人の患者全員における白血球増多は好塩基球増多（好塩基球 125／mm$^3$ 以上）と関係があり，また好塩基球増多は常に中等度から高度の白血球増多と関係があったということが，おそらく最も重要な所見であろう．好塩基球増多はどの対照例にも認められなかった．1 人の患者（MF # [redacted]）には白血病診断の 4 年前に軽度の白血球増多と好塩基球増多が認められた（図 4）．翌年，この患者の総白血球数と総好塩基球数は対照値の範囲内にあったが，その翌年（診断の 2 年前）には白血球増多と高度の好塩基球増多が再び認められた．初期の白血球増多は白血病によるよりもむしろ慢性中耳炎によるものと思われるが，白血病診断のかなり前にこの感染症と同時に軽度の好塩基球増多があったことは興味深い．慢性骨髄性

diagnosed. No other significant changes in leukocyte concentrations were noted during the preleukemic phase of chronic granulocytic leukemia. None of the patients had an absolute neutrophil count less than 2500/mm$^3$ at any time during the preleukemic period. The physical findings invariably were negative at the time of all preleukemic blood counts, and it was not possible to establish the diagnosis of CGL by the usual criteria. Unfortunately, leukocyte alkaline phosphatase (LAP) and chromosome studies were not performed on these patients during the preleukemic period.

Absolute values for each type of lymphocyte are shown by year prior to onset of leukemia for each leukemia patient along with the mean patient and control values in Figures 5-7. The control range was established as ±2 SD from the mean of all control determinations for each type of lymphocyte. The mean absolute values for each type of peripheral blood lymphocyte by year prior to onset of leukemia are shown for all acute and chronic leukemia and by type of acute leukemia in Appendix Tables D and E, respectively.

Patients with all types of acute leukemia had an increase over control values for abnormal and atypical lymphocytes for each of the 6 years prior to diagnosis. Significant values for abnormal lymphocytes were noted for years 1, 3, and 5 ($P < 0.01$). The presence of increased numbers of atypical and abnormal lymphocytes for several years prior to establishment of the diagnosis of CGL also was noted (Figure 7). Values for the year prior to diagnosis were significant for both atypical and abnormal lymphocytes ($P < 0.01$) although the trend was uniform and modestly significant for several other years. The absolute number of normal appearing lymphocytes in circulation remained within the control range for all types of leukemia. A rare bilobed lymphocyte was identified in the blood smear of two patients with acute lymphocytic leukemia at 1 and 2 years prior to diagnosis of leukemia. None was identified in the smears of any controls.

Occasional lymphocytes with nucleoli were identified in the peripheral blood smears of 6 of the 33 patients with acute leukemia sometime during the 4 years prior to diagnosis, but in none of 47 controls. The other abnormal lymphocyte feature of possible significance was the frequent appearance of lymphocyte nuclei with clefts or fissures in numbers greater than 100/mm$^3$ during the 4 years prior to diagnosis. This was observed in 13 of the 33 patients with acute leukemia and only 4 of 47

白血病の前白血病期中，白血球各型集団にその他の著明な変化は認められなかった．前白血病期のどの時期においても好中球絶対数が2500／mm$^3$ 以下であった患者は1人もいなかった．前白血病期の血球数算定時の診察所見はすべて正常であったので，通常の規準で慢性骨髄性白血病の診断を確立することは不可能であった．残念ながら，前白血病期中にこれらの患者について白血球アルカリホスファターゼ(LAP)および染色体の調査は行われなかった．

各白血病患者について，白血病発病前の年数別に各リンパ球型の絶対値を，患者および対照例の平均値と共に図5—図7に示す．対照値の範囲は各リンパ球型の全対照者測定値の平均±2 SDと設定した．白血病発病前の年数別各末梢血液リンパ球型の平均絶対値を付録表DおよびEに示す．付録表Dでは，急性および慢性白血病全例の値を示し，付録表Eは急性白血病の型別の値である．

すべての型の急性白血病患者は診断前の6年間に毎年対照値を超える異常および異型リンパ球の増加を示した．異常リンパ球について，有意な値が1年，3年，5年に認められた($P < 0.01$)．慢性骨髄性白血病の診断確立前の数年間にも異型および異常リンパ球の増加が認められた(図7)．異型および異常リンパ球の値は，診断の前年以前は一様の傾向を示しわずかに有意であったが，診断の前年には有意の値を示した($P < 0.01$)．すべての型の白血病において，循環中の正常と思われるリンパ球の絶対数は対照リンパ球数の範囲内にあった．白血病診断のそれぞれ1年および2年前に，急性リンパ球性白血病患者2人の血液塗抹標本中に，まれにしか認められない二分葉リンパ球が1個づつ認められた．対照例の塗抹標本には全然認められなかった．

診断前の4年間に，33人の急性白血病患者のうち6人の末梢血液塗抹標本中に核を有するリンパ球が時として認められたが，47人の対照例の標本中には全く認められなかった．有意と思われるもう一つのリンパ球の異常としては，診断前の4年間に100／mm$^3$ 以上の核溝又は核裂のあるリンパ球がしばしば出現したことであった．これは33人の急性白血病患者中の13人に認められたが対照例では47人中4人に認められたにすぎなかった．異型リンパ

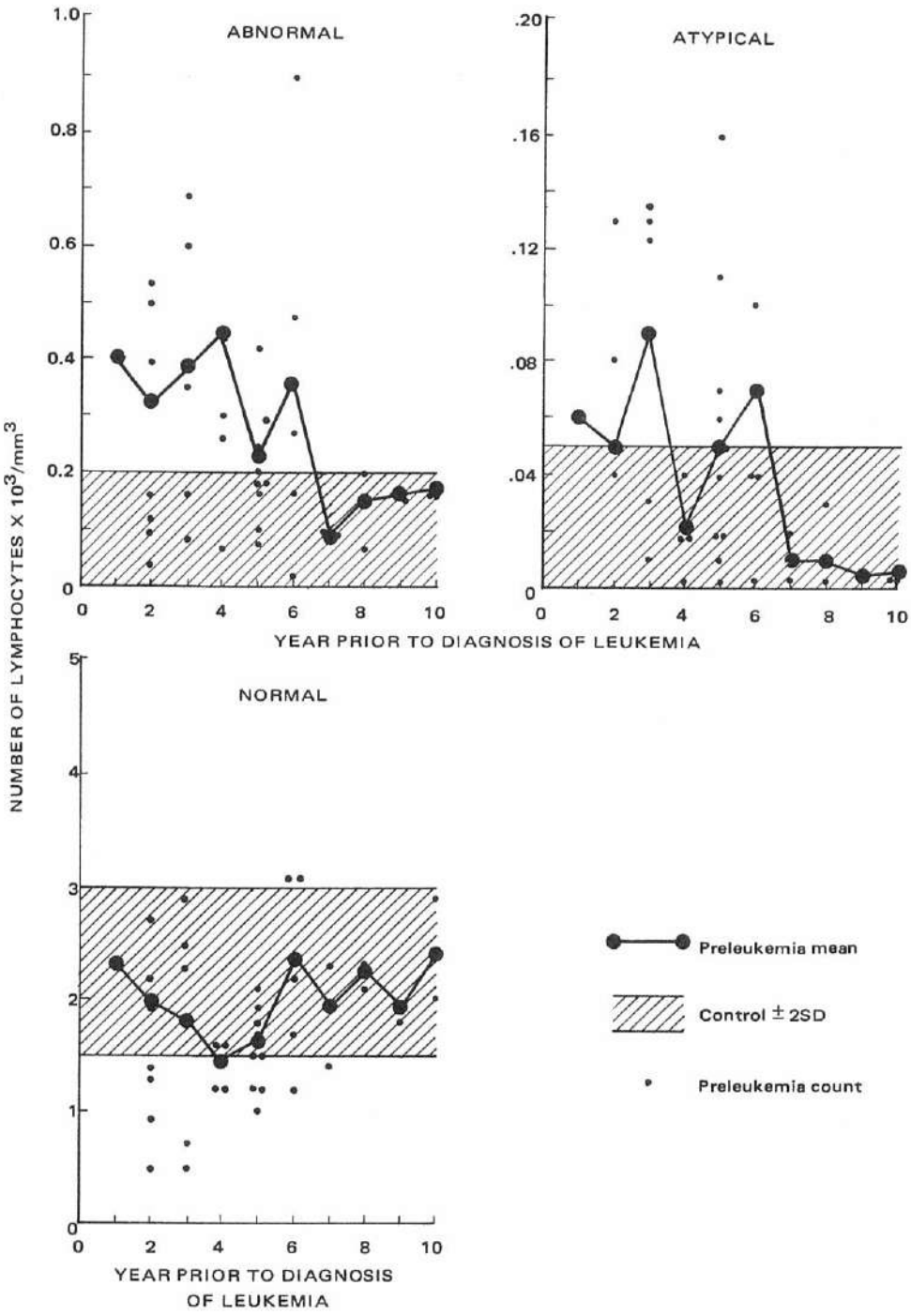


*Figure 5 Peripheral blood lymphocytes by year prior to the diagnosis of acute nonlymphocytic leukemia, Hiroshima and Nagasaki, 1947-62*

図5　急性非リンパ球性白血病診断前の年数別末梢血リンパ球数，広島・長崎，1947－62年

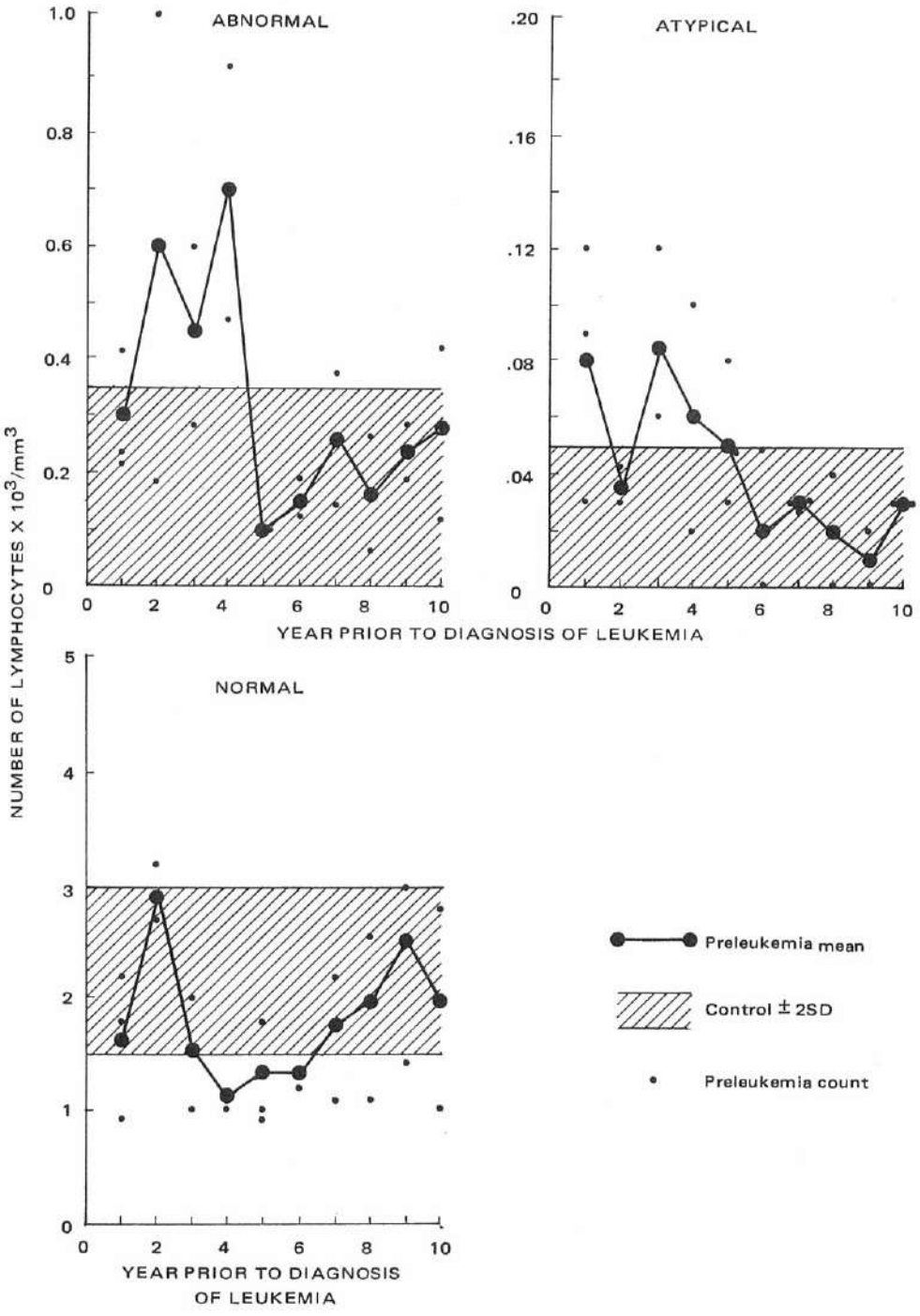


*Figure 6 Peripheral blood lymphocytes by year prior to diagnosis of acute lymphocytic leukemia, Hiroshima and Nagasaki, 1947-62*

図 6　急性リンパ球性白血病診断前の年数別末梢血リンパ球数，広島・長崎，1947－62年

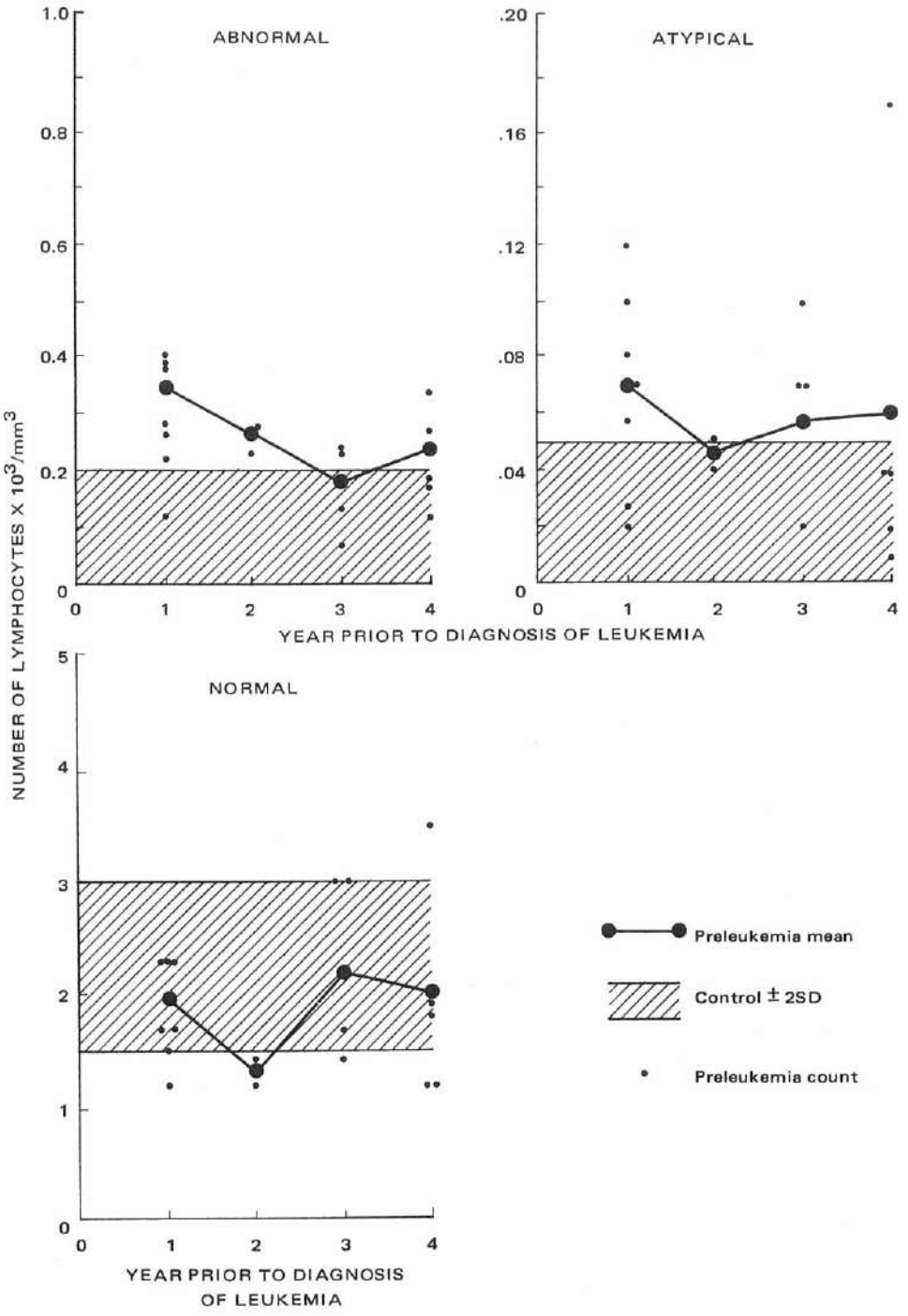


*Figure 7 Peripheral blood lymphocytes by year prior to diagnosis of chronic granulocytic leukemia, Hiroshima and Nagasaki, 1947-62*

図7 慢性骨髄性白血病診断前の年数別末梢血リンパ球数，広島・長崎，1947－62年

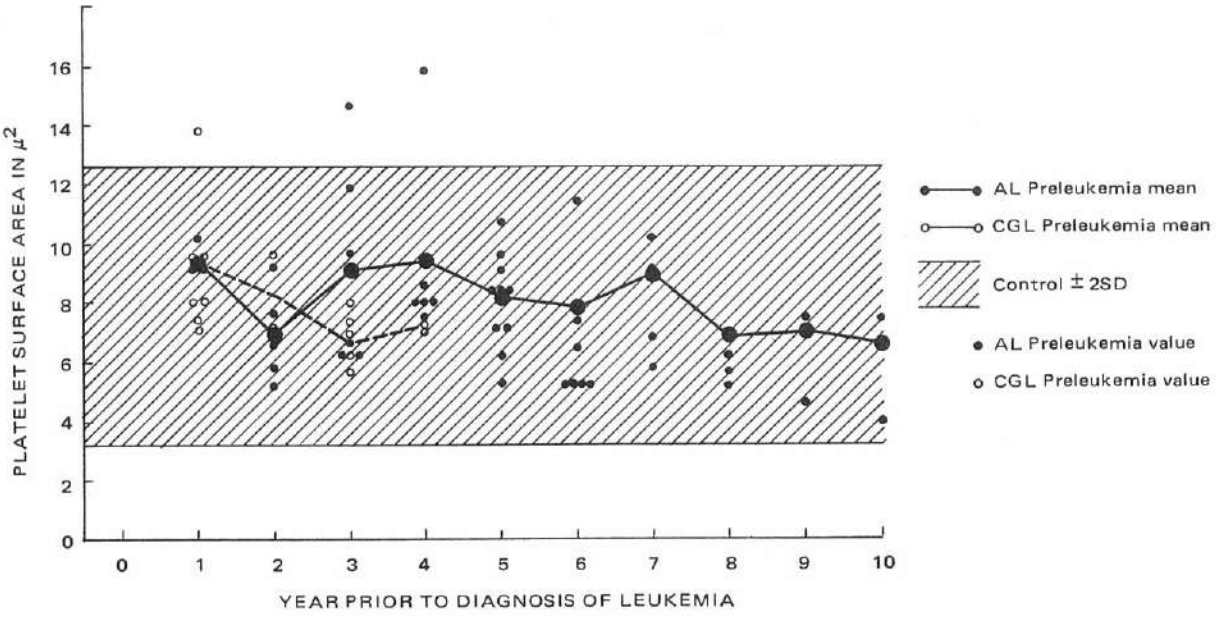


*Figure 8 Peripheral blood platelet surface area by year prior to diagnosis of leukemia, Hiroshima and Nagasaki, 1947-62*

図8 白血病診断前の年数別末梢血血小板表面積，広島・長崎，1947－62年

controls. Both the atypical and abnormal lymphocytes were about equally divided between the patients with acute lymphocytic and acute non-lymphocytic leukemia.

There was no significant difference in the average number of neutrophil nuclear lobes for either the acute or chronic leukemia patients in comparison to their controls (Appendix Table F).

The data for neutrophil nuclear appendages were analyzed for 2-year periods because of the small number of observations in each group when the sexes were separated (Appendix Table G). The only difference of possible importance in any of the parameters studied was an increase in average number of nuclear nodules in the male patients during the few years prior to the onset of acute leukemia. A similar trend also was observed in the blood of the patients with CGL. It was not possible to evaluate preleukemic drumstick counts in CGL since there was only one female patient in the study. In none of the smears were Pelger cells or pseudo-Pelger cell forms noted.

No significant differences in platelet surface area or platelet morphology were noted between the controls and the leukemia patients for any of the

球および異常リンパ球は共に急性リンパ球性白血病患者と急性非リンパ球性白血病患者においてほぼ同程度認められた．

急性または慢性白血病患者とその対照例との比較では，好中球核分葉の平均数に有意の差はなかった（付録表F）．

性別に分けると各群の観察数が少なくなるので，好中球核付属物に関する資料は2年分をまとめて解析した（付録表G）．調べたパラメーター中重要と思われる唯一の相違は，急性白血病発病前の2－3年間に男性患者にみられた核小結節の平均数の増加であった．同じ様な傾向が慢性骨髄性白血病患者の血液にも認められた．この調査では女性患者は唯1例だったので，慢性骨髄性白血病における前白血病性太鼓桴数を求めることは不可能だった．塗抹標本においては Pelger 細胞または pseudo - Pelger 細胞は認められなかった．

前白血病期のいずれにおいても，白血病患者と対照例の間には，血小板表面積または血小板形態に有意の差は認

preleukemic periods which were studied (Figure 8, Appendix Tables H and I).

Hemoglobin and hematocrit values, erythrocyte counts, and erythrocyte indices for both the acute and chronic leukemia patients showed no consistent change prior to the development of leukemia (Appendix Table J). Hematocrit values fluctuated considerably in the male subjects and tended to be low in the female patients during most of the 5 years prior to the development of acute leukemia. Anemia during these periods, however, usually was not substantiated by hemoglobin determinations and erythrocyte counts, and anemia was present in neither the male or female patients during the year preceding the diagnosis of leukemia. Preleukemic CGL erythrocyte values were analyzed only for the male subjects. No evidence of anemia was present in this group.

None of the control subjects has developed leukemia over a 12-year follow-up period. All of the patients with leukemia have expired.

## DISCUSSION

Acute leukemia (1) may occur abruptly with antecedent symptoms of only several days or several weeks duration, (2) may be preceded by one of many hereditary or constitutional disorders that is known to be associated with a high risk for leukemia,[15,22-25] (3) may be preceded for months or years by "smouldering leukemia",[26] or (4) may be preceded for months or years by one or more hematologic changes which are not diagnostic of acute leukemia, but have been defined as "preleukemia" or the "preleukemic syndrome".[1-16] There are wide differences of opinion regarding the frequency with which each of these presentations occurs.[14,15]

The preleukemic syndrome has been reported most frequently in elderly patients, many of whom ultimately develop acute granulocytic, monocytic, myelomonocytic, or stem cell leukemia. The most frequent presentation has been with pancytopenia, but many patients have anemia, leukopenia, or thrombocytopenia, alone, or in various combinations. The most frequently reported erythrocyte morphologic changes in the peripheral blood have been the presence of basophilic stippling, anisocytosis, poikilocytosis, macroovalocytosis, macrocytosis, and erythroblastemia. Immature myeloid forms, monocytosis, and Pelger-Hüet neutrophils also have been noted.[5,10,27,28] Bone marrow aspirates

められなかった(図8，付録表H，I)．

急性および慢性白血病患者のヘモグロビン値，ヘマトクリット値，赤血球数および赤血球指数は，白血病発病以前には一定の変化を示さなかった(付録表J)．ヘマトクリット値は急性白血病前のほぼ5年間にわたって，男性対象者においてはかなりの変動を示し，女性対象者においては低い傾向を示した．しかしこの期間中，貧血は通常ヘモグロビン測定値および赤血球数からは立証されず，白血病診断の前年には男性患者にも女性患者にも貧血はなかった．前白血病期の慢性骨髄性白血病における赤血球値は男性対象者についてのみ解析を行った．この群には貧血の所見はなかった．

12年間の経過観察調査期間中，対照例に白血病の発病はなかった．白血病患者は全員死亡している．

## 考　察

急性白血病とは(1)わずか数日または数週間の前駆症状で突然発病する，(2)白血病に対してリスクが高いと言われている多くの遺伝性または体質性疾患の一つが先行する，[15,22-25] (3)何か月または何か年か"潜在性白血病"が先行する，[26] または(4)急性白血病と診断できないが，"前白血病"または"前白血病性症候群"と定義されている血液学的変化が一つまたはそれ以上，何か月または何か年か先行する．[1-16] これらの状態がそれぞれどの位の頻度で認められるかについては意見が分かれている．[14,15]

前白血病的症候群についての報告は高年齢者に最も多くみられ，その多くは最終的には急性骨髄性，単球性，骨髄単球性または幹細胞性の白血病となる．最も多いのは汎血球減少症であるが，多くの患者は貧血，白血球減少症または血小板減少症が単独またはいろいろな組み合せでみられる．最も高い頻度で報告されている末梢血液の赤血球形態学的変化は好塩基性斑点，不同細胞症，異形赤血球増多症，巨大卵円形赤血球増加症，大赤血球増多症，赤芽球血症である．幼若な骨髄球，単球増多症，Pelger-Hüet好中球も認められている．[5,10,27,28] 穿刺骨

frequently are hyperplastic with atypical or immature morphologic characteristics of one or more of the marrow cell lines. Usually there is immature myeloid preponderance, but extreme erythroid hyperplasia with moderate megaloblastic change, and even severe marrow aplasia have been reported.[10] Diagnosis of the preleukemic syndrome implies that the marrow changes fall short of the requirements for establishing the diagnosis of leukemia. The similarities between the preleukemic syndrome and various myeloproliferative disorders has prompted the suggestion that the syndrome be referred to as myelodysplasia rather than "preleukemia".[11]

The frequency with which the preleukemic syndrome occurs probably depends a great deal on the characteristics of the clinical population at risk. Many patients with atypical hematologic findings are referred to major diagnostic centers so that incidence reports of preleukemia from these centers may be much higher than from general hospital hematology clinics where there is less selection. The true incidence of preleukemia is not known, however, and it is unlikely that it will become known unless determined by massive routine hematologic screening of an unselected population.

Another major problem in the study of preleukemia is one of definition. Many instances of preleukemia which have been described might be defined by others as aleukemic leukemia, smouldering leukemia, subacute leukemia, low percentage leukemia, or just early acute leukemia.[29-31] Dameshek and Gunz[29] have expressed the opinion that all "preleukemia" is a type of leukemia and that these patients have a small nidus of abnormally proliferating "foreign" cells growing within the normal marrow. They indicate that following a static period these abnormal proliferations may grow slowly or rapidly or may disappear. Interpretation of the clinical and laboratory findings is controversial, however, and a precise definition of the preleukemic syndrome and its transition to acute leukemia remains unclear. Morphologic and clinical criteria have prevailed over the years, but recently bone marrow chromosomal and culture techniques have been reported.[10,15,32-37] There is some evidence that the presence or absence of certain bone marrow chromosomal changes are of considerable value in predicting the likelihood of rapid transition to acute leukemia.[32,34] The predictive value of serum lysozyme and red cell enzyme changes in the identification of preleukemia remains uncertain at this time.[38-41]

Definition of a preleukemic syndrome becomes

髄液はしばしば増殖性であって一つまたはそれ以上の骨髄培養細胞株には異型または幼若な形態学的特徴がある．通常，幼若骨髄球が多いが，中等度の巨大赤血芽球様変化をともなう著しい赤血球増殖や高度の骨髄形成不全も報告されている．[10] 前白血病症候群の診断がなされるということは骨髄変化が白血病診断確立のための必要条件を満たしていないことを意味する．前白血病症候群が骨髄増殖性の諸疾患に類似しているところから，この症候群は"前白血病"よりもむしろ骨髄異形成と呼ぶべきであるという意見が出ている．[11]

前白血病症候群が出現する頻度はそのリスクを持つ臨床対象集団の特徴に大きく左右されると考えられる．非定型の血液所見を示す多くの患者は大きな診断センターへ照会されるので，このようなセンターにおける前白血病の発病率報告はそのような選択がなされる機会の少ない総合病院血液クリニックからの報告数よりもはるかに多いと思われる．しかし，前白血病の実際の発病率は明らかではない．そして，特別に選択の行われていない人口集団について大規模の集団通常血液検査によって確認されない限り明らかにすることはできないと思われる．

前白血病研究におけるもう一つ重要なことは定義の問題である．前白血病として報告されている多くの症例は別の研究者が定義すれば，非白血性白血病，潜在性白血病，亜急性白血病，低百分率白血病，あるいは単に初期の急性白血病等と定義されるかも知れない．[29-31] Dameshek および Gunz は全ての"前白血病"は白血病の一つの型であり，患者は正常な骨髄中に異常に増殖する"異種"細胞の小病巣をもっているという見解を明らかにしている．[29] 彼らはまた，この異常細胞はある静止期後，徐々にまたは急速に増殖したり，場合によっては消失することがあると述べている．しかし，臨床所見および検査所見の解釈には多くの異論があり，また前白血病症候群の明確な定義および急性白血病への移行の過程は明らかではない．従来，形態学的および臨床的基準が広く用いられていたが，最近は骨髄の染色体および培養技法が報告されている．[10,15,32-37] 特定の骨髄染色体の変化の有無が急性白血病への急速な移行の可能性を予測する上で，かなり重要であることを示す所見がある．[32,34] 前白血病を確認するための血清リゾチーム[38-40]および赤血球酵素の変化[41]の予報的価値は現在のところ明確ではない．

他の血液疾患から，急性白血病へ移行することもあるの

even more unclear when other hematologic disorders which occasionally transform into acute leukemia are considered. Included in this category are polycythemia vera and even multiple myeloma.[42]

A preleukemic syndrome for chronic granulocytic leukemia has not been clearly defined. In a sense CGL itself may be considered a preleukemic disorder since it frequently terminates in fulminating acute leukemia following a relatively benign chronic course of months or years. In a fashion similar to the preleukemic syndrome which precedes the development of certain types of acute leukemia, CGL preleukemia may be difficult to establish since it may not be possible to determine just when the transition to leukemia has occurred. A single patient with Philadelphia chromosome (Ph+) marrow cells and relatively normal peripheral blood was followed for about 5 years before terminating in acute myeloid leukemia.[43] Rarely is there an opportunity to define the "preleukemic" features of CGL, but changes very early in the course of the illness have been noted. Most noteworthy are the studies of Moloney and Lange[18,19] at ABCC. They have emphasized the moderate leukocytosis, left shift of the myeloid series, basophilia, and reduced LAP. Others also have noted reduced LAP in the early phases of CGL.[44,45] The presence of the Ph+ chromosome is an extremely important diagnostic feature of CGL, but the technique is such that it is not practical for screening purposes in large health study programs.[46]

The leukemia which has occurred in the A-bomb survivors of Hiroshima and Nagasaki has a clinical course which is similar to that of nonradiation induced leukemia.[47,48] Periodic health examination of a number of these leukemia patients during their preleukemic years has provided some valuable information relative to the early natural history of their illnesses. The most notable features of both CGL and acute leukemia of all types are the presence of increased numbers of abnormal and atypical lymphocytes for several years preceding the actual diagnosis of leukemia. There are various interpretations of these findings. One of the most attractive is that they represent early lymphocyte transformation in response to the presence of foreign tumor cell antigen.[49] Although they could be analogous to the in vitro transformed lymphocyte in response to a mitogen, they might be more closely related to the atypical lymphocytes which sometimes appear during the early phase of transplantation rejection. Another interpretation would be that of an atypical response to viral or other type of opportunistic infection in patients with

で，前白血病症候群の定義はさらに不明瞭になる．このような事例には真性多血球血症および多発性骨髄腫も含まれる．[42]

慢性骨髄性白血病の前白血病症候群は明確に定義されていない．慢性骨髄性白血病は数か月または数か年比較的良性の慢性経過の後，突然急性白血病に移行する場合が多いので，ある意味ではこれ自体が前白血病的疾患と言えるかも知れない．ある型の急性白血病の発病に先行する前白血病症候群と同様に，慢性骨髄性白血病が前白血病として，いつ白血病へ移行したかを確認することは不可能と思われるので，慢性骨髄性白血病を前白血病として確立することは困難であろう．フィラデルフィア染色体（Ph＋）骨髄細胞を有しながら比較的正常な末梢血液像を示した１人の患者が急性骨髄性白血病の転帰をとるまでの約５年間経過観察を行った．[43] 慢性骨髄性白血病の前白血病的特徴を確かめる機会はまれであるが，ごく初期における変化は認められている．最も注目に値する研究はABCCの Moloney および Lange のものである．[18,19] 彼らは中等度の白血球増多症，骨髄球の左方移動，好塩基症および白血球アルカリホスファターゼ（LAP）の低下について特に述べている．他にも慢性骨髄性白血病の初期におけるLAPの低下を認めた研究者がいる．[44,45] Ph＋染色体の存在は慢性骨髄性白血病の診断上極めて重要な特徴であるが，その技法は大規模な健康調査計画におけるスクリーニングの検査としては実用的ではない．[46]

広島，長崎の被爆者に発現した白血病の臨床経過は非放射線誘発白血病の臨床経過に類似している．[47,48] これらの白血病患者のうち数名について，数年間の前白血病期における定期検診からこの疾病の初期の自然史に関係のある貴重な資料が若干得られた．慢性骨髄性白血病およびあらゆる型の急性白血病の最も目立つ特徴は，白血病の診断がなされる以前の数年間に異常リンパ球や異型リンパ球の増加がみられることである．この所見についてはいろいろの解釈がある．そのうち最も興味を引かれるものの一つは，それが異種腫瘍細胞抗原に対して初期リンパ球転換の反応を示すということである．[49] もっともこれらの所見は mitogen に対する試験管内で変換したリンパ球の反応に似てはいるが，移植拒絶の初期に現われることのある異型リンパ球とより密接な関係があるかも知れない．別の解釈としては感染に対し異常な抵抗を示す患者におけるウイルス感染またはその他の偶発的感染に対する非定型反応であるということができる．しかし，これらの患者は通常諸感染によく対応できること，リンパ

some abnormal resistance to infection. This seems quite unlikely, however, since these patients usually handle infections without difficulty, the lymphocyte changes are of long duration, and there is no evidence for chronic viral or other atypical infection. There are many other possible explanations one of which is that the changes are entirely nonspecific and of no significance, but the consistency and nature of the findings strongly suggest some perturbation of immune mechanisms.

Bilobed lymphocytes have been observed in the peripheral blood smears of cyclotron personnel.[50] These cells are not specifically radiation induced and rarely are found in association with viral and other types of infection.[51] A few of these cells were identified in the peripheral blood smears of several patients with acute leukemia during the preleukemic period, but their numbers were small and little significance is attached to this sporadic finding.

One of the most striking features of the acute leukemia studies has been the absence of those preleukemic findings which have been defined previously. Even the patients with myelomonocytic leukemia failed to demonstrate significant monocytosis prior to the development of leukemia. These negative observations indicate that an appreciable number of acute leukemia patients do not develop the peripheral blood changes which have been described in the preleukemic syndrome during any of the several years preceding the clinical evolution of their leukemias. In our patients with acute leukemia the clinical manifestations of disease developed acutely without previous warning. On the other hand, the presence of abnormal or atypical lymphocytes in the peripheral blood may be indicative of some smouldering immunologic challenge in response to emerging clones of tumor cells which are the forerunner of acute leukemia in most patients with this disorder. Those acute leukemia patients who present with various types of myeloid dysplasia which has been categorized as the preleukemic syndrome have a different form of acute leukemia which must be less common. Without systematic study of large numbers of acute leukemia patients during the preleukemic period from the standpoint of bone marrow morphology, chromosome changes and culture characteristics, it is not possible to define a preleukemic syndrome for the majority of the patients with this disease.

Observations in patients with CGL indicate that the actual onset of disease is difficult to define and probably should have been diagnosed 1 or 2 years

球の変化が長期に亘ってみられること，また慢性のウイルス感染またはその他の非定型感染の徴候がないことなどから，この解釈は該当しないと考えられる．その他多くの可能性が考えられるが，その中の一つとして，各種変化は全く非特異性のものであるので意義がない，という説明もあるが，所見の一貫性および性質は免疫機序の何らかの混乱を強く示唆している．

二分葉リンパ球がサイクロトロン関係作業員の末梢血液塗抹標本中に認められている．[50] この細胞は特に放射線により誘発されるものではなく，ウイルス感染およびその他の感染に伴って認められることもまれにある．[51] 数名の急性白血病患者の前白血病期末梢血液塗抹標本中に，この細胞が少数認められたが，数が少なくこの散発性所見に意義はない．

急性白血病研究における最も著しい特徴の一つは，先に明らかにした前白血病所見の欠如である．骨髄性単球性白血病患者でさえも白血病発病以前に著明な単球増多を示さなかった．この陰性の観察所見はかなりの数の急性白血病患者にその臨床的進展以前の数年間に前白血病症候群として記述されている末梢血液変化を起こしていないことを示している．当所で調査した急性白血病患者ではその臨床的発現には前兆がなく急であった．一方，末梢血液中の異常または異型リンパ球はほとんどの急性白血病患者において認められる前駆症状である腫瘍細胞クローンの出現に対する潜在性免疫学的反応を示しているかも知れない．前白血病症候群に含まれている幾つかの型の骨髄様異形成を呈する急性白血病患者は比較的珍しい異った型の急性白血病に罹っている．骨髄の形態，染色体変化および培養特性の面から多数の急性白血病患者をその前白血病期中において系統的に研究しなければ，急性白血病患者の大多数について前白血病症候群を定義することは不可能である．

慢性骨髄性白血病患者の観察から，実際の発病の時期を明確に定めることは困難であるが，我々の患者の若干のものについてはもう1年ないし2年前に診断が下される

earlier in some of our patients. Basophilia did not occur without accompanying mild leukocytosis and usually was associated with moderate left shift in the neutrophilic cells. Sustained leukocytosis invariably was accompanied by basophilia. These changes occurred prior to the development of any signs or symptoms of the disease. Not only is there reason to believe that basophilia accompanies the early phase of CGL, there is much to suggest that leukocytosis without basophilia may have negative diagnostic implications. The combination of leukocytosis (with moderate left myeloid shift), basophilia, reduced LAP and positive Ph+ chromosome are the most important diagnostic features, but none of these by itself is completely diagnostic. The Ph+ chromosome has been described in patients with polycythemia vera.[52] Basophilia occurs in certain hypersensitivity reactions and occasionally is observed in myxedema, ulcerative colitis, polycythemia vera, tuberculosis, diabetes, systemic mast cell disease, hemolytic anemias, carcinoma, and several other disorders.[53] Reduced LAP may be observed in infectious mononucleosis, myeloid metaplasia, paroxysmal nocturnal hemoglobinuria, primary sideroblastic anemia, hereditary hypophosphatasia, and several other conditions.[54] The antecedent abnormal and atypical lymphocytes disappeared in our patients with the onset of leukocytosis and basophilia. The nonspecific nature of the lymphocyte changes is such that they appear to have little diagnostic value in CGL. It is unfortunate that it was not possible to determine whether or not there was a change in the number of neutrophil nuclear drumsticks occurring during the preleukemic phase of CGL. Tomonaga et al[21] have observed reduced drumstick forms in CGL during relapse.

Qualitative changes in peripheral blood platelets and neutrophils during the preleukemic phase of either acute or chronic leukemia were not striking. A trend towards larger platelets as one approaches the onset of clinical disease has been noted previously.[1,10] A preponderance of large and bizarre appearing platelets has been reported in the preleukemic syndrome.[55] Abnormal marrow megakaryocytes without significant platelet changes have been observed in childhood preleukemia.[13] There was no evidence of increased neutrophilic nuclear hypersegmentation during the preleukemic phase as a possible peripheral blood manifestation of relative bone marrow $B_{12}$ or folate deficiency due to competition for substrate in a hyperproliferative state. Other important negative findings during the preleukemic period of both acute and chronic leukemia include absence of anemia and change in erythrocyte indices. These findings again do not

べきであったと思われる．好塩基症は，軽度の白血球増多症を伴わずに発現されることはなく，通常好中球細胞の中等度の左方移動があった．持続性の白血球増多症は例外なく好塩基症を伴なっていた．これらの変化はこの疾患の兆候または症状の発現する以前にすでに生じていた．好塩基症は慢性骨髄性白血病の初期に起こると信ずべき理由があるばかりでなく，好塩基症を伴なわない白血球増多症は診断上陰性的な意味をもつことを示唆する多くの理由がある．白血球増多症(中等度の骨髄球左方移動を伴なう)，好塩基症，白血球アルカリホスファターゼの低下，陽性 Ph＋染色体の組み合わせは最も重要な診断上の特徴であるが，これらはいずれも単独では完全な診断のきめ手とはならない．Ph＋染色体は真性多血球血症患者に認められている．[52] 好塩基症はある種の過敏症反応では認められるが，時には粘液水腫，潰瘍性大腸炎，真性多血球血症，結核，糖尿病，全身性肥胖細胞疾患，溶血性貧血，癌，その他数疾患においても認められる．[53] 白血球アルカリホスファターゼの低下は感染性単核細胞増加症，骨髄様異形成，発作性夜間血色素尿症，原発性シデロブラスト性貧血，遺伝性低燐酸酵素症，その他数疾患に認められる．[54] 本調査の対象患者においては，白血球増多および好塩基症の出現に伴い前駆性の異常リンパ球および異型リンパ球の消失が認められた．この非特異性リンパ球変化は慢性骨髄性白血病においては診断的価値はほとんどないようである．慢性骨髄性白血病の前白血病期中に出現する好中性有核太鼓桴の数に変化があったか否かを調べることができなかったことは残念である．朝長らは慢性骨髄性白血病の再発において太鼓桴の減少を認めている．[21]

急性または慢性白血病の前白血病期中の末梢血液における血小板および好中球の質的変化は顕著ではなかった．以前，臨床的発病が近ずくにつれて血小板が大きくなる傾向が認められた．[1,10] 前白血病症候群においては，大形で異形の血小板が優勢を占めることが報告されている．[55] 小児前白血病において著明な血小板変化を伴わない異常骨髄巨大細胞が認められている．[13] 末梢血液の症状としての相対的骨髄 $B_{12}$ あるいは過増殖状態での基質の争奪による葉酸塩不足発現のような前白血病期中の好中球核過分割増加の徴候はみられなかった．急性および慢性白血病の前白血病期中のその他の重要な陰性所見としては，貧血がなく，赤血球指数の変化がないことである．これらの所見も赤血球造血要因の絶対的あるいは相対的

suggest either absolute or relative deficiency in erythropoietic factors, or the occurrence of other types of impaired erythropoiesis prior to the development of leukemia.

The results of our study suggest that the "preleukemic syndrome", as previously described, may be uncommon in early acute leukemia. Furthermore, there is little sound basis for describing the extremely heterogenous clinical and hematologic changes that precede the obvious clinical onset of certain types of acute leukemia as a "syndrome". It is more likely that these changes represent early leukemia in a variety of subclinical forms. This philosophy is consistent with our finding of abnormal or atypical lymphocytes in the peripheral blood of many patients with both acute and chronic leukemia during the preleukemic phase of their clinical illnesses. These findings suggest a possible longstanding host response to underlying clones of leukemic cells with foreign surface antigens. The release of some trigger mechanism or variations in host resistance factors could result in the emergence of the full clinical disease. In most instances, it would be difficult if not impossible to date the onset of leukemia.

不足，あるいは白血病発病以前にみられる別の型の赤血球造血障害の出現を示唆しない．

本調査の結果は，初期の白血病においては前述の"前白血病症候群"が通常認められないことを示唆しているようである．さらに，ある種の急性白血病の発病が臨床的に明らかになる前に認められる非常に異質な臨床的および血液学的変化を一つの"症候群"であると記述する確実な根拠はない．これらの変化は様々な準臨床的形態をもった初期白血病である可能性の方が強い．この考え方は前白血病期中の多数の急性および慢性白血病患者の末梢血液中に異常または異型リンパ球を認めた我々の所見と一致する．これらの所見は，異質な表面抗原をもつ潜在白血病細胞のクローンに対する長期にわたる宿主反応のあることを示唆する．引金となるような機転が働いた場合または宿主抵抗要因における変化により，臨床的に認められる疾患が出現することもある．ほとんどの症例において，白血病発病の時期を予知することは不可能でないにしても困難であると思われる．

## APPENDIX
## 付　録

TABLE A LIST OF LEUKEMIA PATIENTS STUDIED, HIROSHIMA AND NAGASAKI, 1947-62
表A　調査対象白血病患者一覧表，広島・長崎，1947－62年

| MF No. | Diagnosis | | Sex | T65 Dose rad | Diagnosis |
|---|---|---|---|---|---|
| | Year | Age | | | |
| | | | Hiroshima | | |
| [redacted] | 1957 | 51 | M | 730 | AGL |
| | 52 | 32 | F | 946 | CGL |
| | 59 | 19 | M | 513 | ALTU |
| | 49 | 12 | F | 348 | ALL |
| | 53 | 16 | M | 950 | CGL |
| | 52 | 51 | M | 44 | CGL |
| | 51 | 29 | M | 1 | CGL |
| | 58 | 30 | M | 154 | AML |
| | 50 | 17 | M | 653 | ALTU |
| | 55 | 17 | M | 350 | CGL |
| | 56 | 54 | M | 228 | AGL |
| | 52 | 59 | F | 72 | CGL |
| | 59 | 27 | M | 0 | AGL |
| | 58 | 64 | M | 238 | CGL |
| | 52 | 44 | M | 326 | CGL |
| | 52 | 50 | M | 265 | CGL |
| | 59 | 27 | F | 82 | ALTU |
| | 57 | 25 | F | 126 | ALL |
| | 54 | 43 | M | 312 | CGL |
| | 59 | 29 | F | 118 | AML |
| | 59 | 23 | F | 29 | ALL |
| | 60 | 23 | M | 19 | ALL |
| | 53 | 32 | F | 537 | AMML |
| | 51 | 24 | F | 828 | ALL |
| | 57 | 49 | F | 448 | AGL |
| | 58 | 76 | M | 867 | AGL |
| | 52 | 17 | M | 595 | ALL |
| | 59 | 18 | M | (No est.) | CGL |
| | 55 | 54 | F | 9 | ALL |
| | 58 | 51 | M | 344 | ALTU |
| | 60 | 33 | M | 182 | AGL |
| | | | Nagasaki | | |
| | 1960 | 35 | M | 127 | AGL |
| | 58 | 56 | M | 611 | AGL |
| | 52 | 25 | F | 936 | AGL |
| | 59 | 29 | F | 175 | ALTU |
| | 61 | 19 | F | 539 | AMML |
| | 55 | 25 | M | 2 | AMML |
| | 58 | 19 | M | 485 | AGL |
| | 56 | 29 | F | 256 | ALL |
| | 58 | 68 | M | 163 | AMML |
| | 55 | 13 | M | 463 | CGL |
| | 50 | 15 | F | 581 | AMoL |
| | 57 | 13 | M | 276 | ALL |
| | 54 | 13 | F | 539 | ALTU |

TABLE B MEAN PERIPHERAL BLOOD LEUKOCYTE COUNTS (per $mm^3$) BY YEAR PRIOR TO ONSET AND CHRONICITY OF LEUKEMIA, HIROSHIMA AND NAGASAKI, 1947-62

表B　白血病発病前の年数および急性・慢性別平均末梢血白血球数（$mm^3$ 当たり），広島・長崎，1947－62年

| Years Prior to Onset | No. of Subjects | | Total WBC | | Segmented Neutrophils | | Band Neutrophils | | Lymphocytes | | Monocytes | | Eosinophils | | Basophils | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | L | C | L | C | L | C | L | C | L | C | L | C | L | C | L | C |
| Acute (All Types) | | | | | | | | | | | | | | | | |
| 1 | 5 | 6 | 9955 | 6808 | 5211 | 3502 | 845 | 208 | 2218 | 2266 | 463 | 228 | 1101 | 497 | 70 | 45 |
| 2 | 10 | 15 | 7238 | 6918 | 3374 | 3628 | 641 | 297 | 2082 | 2095 | 328 | 296 | 663 | 483 | 42 | 51 |
| 3 | 9 | 14 | 6224 | 6348 | 2995 | 3309 | 395 | 313 | 2132 | 2031 | 349 | 255 | 352 | 409 | 15 | 28 |
| 4 | 8 | 14 | 6134 | 5819 | 2883 | 3066 | 692 | 258 | 1598 | 1715 | 384 | 303 | 200 | 415 | 39 | 38 |
| 5 | 12 | 22 | 6206 | 6346 | 3103 | 3199 | 370 | 397 | 1899 | 1952 | 335 | 294 | 446 | 464 | 42 | 29 |
| 6 | 9 | 15 | 6994 | 7208 | 3604 | 3719 | 516 | 381 | 2245 | 2268 | 338 | 284 | 253 | 561 | 38 | 32 |
| 7 | 5 | 9 | 7370 | 6219 | 4065 | 2948 | 380 | 285 | 2208 | 2115 | 385 | 259 | 297 | 585 | 44 | 24 |
| 8 | 4 | 8 | 6594 | 7549 | 3178 | 3793 | 520 | 342 | 2349 | 2150 | 183 | 306 | 329 | 930 | 39 | 28 |
| 9 | 3 | 6 | 8883 | 6567 | 4703 | 3015 | 493 | 435 | 2377 | 1976 | 175 | 335 | 1115 | 762 | 27 | 32 |
| 10 | 4 | 8 | 8419 | 7619 | 4249 | 3437 | 368 | 417 | 2462 | 2787 | 532 | 356 | 808 | 578 | 26 | 32 |
| Chronic Granulocytic | | | | | | | | | | | | | | | | |
| 1 | 7 | 11 | 10043 | 6288 | 5130 | 3405 | 1060 | 237 | 2355 | 1995 | 297 | 228 | 855 | 390 | 255 | 46 |
| 2 | 2 | 3 | 11800 | 9975 | 7855 | 5170 | 709 | 366 | 1667 | 2668 | 442 | 220 | 1012 | 1475 | 241 | 47 |
| 3 | 5 | 6 | 9800 | 7118 | 5294 | 3002 | 661 | 439 | 2276 | 2057 | 400 | 326 | 909 | 1280 | 221 | 48 |
| 4 | 6 | 6 | 7683 | 6671 | 4147 | 3457 | 489 | 467 | 2046 | 1854 | 375 | 270 | 561 | 588 | 51 | 48 |

*L: Leukemia*　　*C: Control*

TABLE C MEAN PERIPHERAL BLOOD LEUKOCYTE COUNTS (per $mm^3$) BY YEAR PRIOR TO ONSET AND TYPE OF ACUTE LEUKEMIA, HIROSHIMA AND NAGASAKI, 1947-62

表C　白血病発病前の年数および急性病型別平均末梢血白血球数（$mm^3$ 当たり），広島・長崎，1947－62年

| Years Prior to Onset | No. of Subjects | | Total WBC | | Segmented Neutrophils | | Band Neutrophils | | Lymphocytes | | Monocytes | | Eosinophils | | Basophils | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | L | C | L | C | L | C | L | C | L | C | L | C | L | C | L | C |
| Acute Nonlymphocytic | | | | | | | | | | | | | | | | |
| 1 | 2 | 1 | 12550 | 8600 | 6552 | 4902 | 596 | 430 | 2366 | 2838 | 722 | 86 | 2316 | 344 | 83 | 17 |
| 2 | 8 | 11 | 8173 | 7031 | 3706 | 3733 | 733 | 235 | 2372 | 2064 | 362 | 310 | 811 | 537 | 49 | 56 |
| 3 | 7 | 11 | 6384 | 6671 | 3097 | 3479 | 414 | 313 | 2148 | 2103 | 375 | 262 | 343 | 473 | 13 | 33 |
| 4 | 6 | 10 | 6413 | 5547 | 2795 | 2772 | 887 | 274 | 1630 | 1694 | 420 | 316 | 195 | 424 | 39 | 44 |
| 5 | 9 | 16 | 6164 | 6085 | 2887 | 2997 | 408 | 322 | 1931 | 2026 | 349 | 260 | 531 | 436 | 49 | 33 |
| 6 | 6 | 9 | 7442 | 6652 | 3492 | 3331 | 552 | 339 | 2720 | 2286 | 392 | 306 | 230 | 352 | 51 | 36 |
| 7 | 3 | 5 | 8392 | 5775 | 4684 | 2630 | 581 | 224 | 2317 | 2147 | 487 | 289 | 263 | 452 | 55 | 24 |
| 8 | 2 | 4 | 6150 | 7150 | 2917 | 3488 | 250 | 268 | 2422 | 2166 | 256 | 184 | 276 | 1014 | 40 | 33 |
| 9 | 1 | 2 | 9925 | 6300 | 5757 | 3082 | 1191 | 535 | 2084 | 1936 | 298 | 283 | 596 | 434 | 10 | 30 |
| 10 | 2 | 4 | 8338 | 7825 | 4707 | 3474 | 138 | 488 | 2640 | 2788 | 466 | 328 | 388 | 731 | 0 | 29 |

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Table C Continued

| Years Prior to Onset | No. of Subjects | | Total WBC | | Segmented Neutrophils | | Band Neutrophils | | Lymphocytes | | Monocytes | | Eosinophils | | Basophils | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | L | C | L | C | L | C | L | C | L | C | L | C | L | C | L | C |
| Acute Lymphocytic | | | | | | | | | | | | | | | | |
| 1 | 3 | 5 | 8225 | 6450 | 4318 | 3321 | 1011 | 163 | 2120 | 2151 | 291 | 256 | 291 | 528 | 62 | 51 |
| 2 | 2 | 4 | 8500 | 6606 | 3400 | 3341 | 272 | 469 | 270 | 2180 | 10 | 257 | 790 | 335 | 12 | 37 |
| 3 | 2 | 3 | 5663 | 5167 | 2639 | 2688 | 331 | 313 | 2075 | 1764 | 259 | 231 | 383 | 171 | 22 | 12 |
| 4 | 2 | 4 | 5300 | 6500 | 3148 | 3800 | 106 | 220 | 1504 | 1769 | 278 | 270 | 264 | 395 | 28 | 21 |
| 5 | 3 | 6 | 6333 | 7042 | 3749 | 3738 | 256 | 600 | 1804 | 1752 | 294 | 384 | 190 | 538 | 24 | 19 |
| 6 | 3 | 6 | 6100 | 8042 | 3830 | 4302 | 445 | 444 | 1295 | 2242 | 231 | 250 | 300 | 876 | 13 | 27 |
| 7 | 2 | 4 | 5838 | 6775 | 3137 | 3346 | 79 | 362 | 2044 | 2075 | 231 | 223 | 348 | 751 | 28 | 23 |
| 8 | 2 | 4 | 7038 | 7948 | 3439 | 4098 | 791 | 417 | 2276 | 2134 | 111 | 428 | 383 | 845 | 39 | 24 |
| 9 | 2 | 4 | 8363 | 6700 | 4176 | 2981 | 145 | 385 | 2524 | 1996 | 114 | 361 | 1375 | 927 | 35 | 33 |
| 10 | 2 | 4 | 8500 | 7413 | 3791 | 3400 | 599 | 346 | 2285 | 2787 | 599 | 383 | 1128 | 426 | 51 | 36 |

*L: Leukemia* *C: Control*

TABLE D MEAN PERIPHERAL BLOOD LYMPHOCYTE COUNTS (per $mm^3$) BY YEAR PRIOR TO DIAGNOSIS AND CHRONICITY OF LEUKEMIA, HIROSHIMA AND NAGASAKI, 1947-62

表D 白血病発病診断前の年数および急性・慢性別平均末梢血リンパ球数（$mm^3$ 当たり），広島・長崎，1947—62年

| Years Prior to Onset | No. of Subjects | | Normal Lymphocytes | | Abnormal Lymphocytes | | Atypical Lymphocytes | |
|---|---|---|---|---|---|---|---|---|
| | L | C | L | C | L | C | L | C |
| Acute (All Types) | | | | | | | | |
| 1 | 4 | 6 | 1877 | 2124 | 398** | 137 | 75 | 5 |
| 2 | 9 | 12 | 1714 | 1971 | 350 | 143 | 43 | 13 |
| 3 | 7 | 14 | 1755 | 1849 | 407** | 123 | 86 | 12 |
| 4 | 6 | 15 | 1352 | 1655 | 267 | 130 | 31 | 3 |
| 5 | 12 | 22 | 1574 | 1803 | 237** | 109 | 53 | 14 |
| 6 | 7 | 12 | 2078 | 2158 | 345 | 176 | 53 | 9 |
| 7 | 4 | 7 | 1842 | 1954 | 178 | 210 | 18 | 9 |
| 8 | 4 | 8 | 2106 | 2004 | 154 | 142 | 15 | 11 |
| 9 | 4 | 5 | 2154 | 1832 | 218* | 104 | 4 | 18 |
| 10 | 4 | 8 | 2206 | 2562 | 241 | 211 | 15 | 14 |
| Chronic Leukemia | | | | | | | | |
| 1 | 7 | 10 | 1962 | 1785 | 323** | 139 | 70** | 6 |
| 2 | 2 | 3 | 1369 | 2550 | 256 | 196 | 43 | 11 |
| 3 | 4 | 6 | 2373 | 1940 | 165 | 113 | 64* | 12 |
| 4 | 5 | 6 | 2001 | 1746 | 253* | 98 | 63* | 10 |

*Mann-Whitny U-test* **P: ≤ .01 *P: .05-.01*
*L: Leukemia* *C: Control*

TABLE E MEAN PERIPHERAL BLOOD LYMPHOCYTE COUNTS (per $mm^3$) BY YEAR PRIOR TO DIAGNOSIS AND TYPE OF ACUTE LEUKEMIA, HIROSHIMA & NAGASAKI, 1947-62

表E　急性白血病診断前の年数および病型別平均末梢血リンパ球数（$mm^3$ 当たり），広島・長崎，1947－62年

| Years Prior to Onset | No. of Subjects | | Normal Lymphocytes | | Abnormal Lymphocytes | | Atypical Lymphocytes | |
|---|---|---|---|---|---|---|---|---|
| | L | C | L | C | L | C | L | C |
| | | | Acute Nonlymphocytic Leukemia | | | | | |
| 1 | 1 | 1 | 2251 | 2524 | 425 | 284 | 61 | 28 |
| 2 | 7 | 7 | 1995 | 1959 | 406 | 135 | 45 | 4 |
| 3 | 5 | 10 | 1844 | 1995 | 387 | 130 | 88 | 10 |
| 4 | 4 | 10 | 1448 | 1523 | 145 | 124 | 18 | 3 |
| 5 | 9 | 16 | 1654 | 1854 | 277 | 74 | 53 | 15 |
| 6 | 5 | 8 | 2375 | 2027 | 418 | 161 | 66 | 8 |
| 7 | 2 | 3 | 1926 | 2069 | 97 | 219 | 8 | 16 |
| 8 | 2 | 4 | 2265 | 2055 | 145 | 119 | 13 | 7 |
| 9 | 1 | 2 | 1918 | 1746 | 167 | 155 | 0 | 35 |
| 10 | 2 | 4 | 2436 | 2531 | 204 | 240 | 0 | 18 |
| | | | Acute Lymphocytic Leukemia | | | | | |
| 1 | 3 | 5 | 1652 | 2044 | 290 | 108 | 79 | 0 |
| 2 | 2 | 5 | 2900 | 1994 | 600 | 159 | 34 | 26 |
| 3 | 2 | 4 | 1535 | 1484 | 456 | 103 | 83 | 16 |
| 4 | 2 | 5 | 1160 | 1985 | 690 | 146 | 58 | 5 |
| 5 | 3 | 6 | 1335 | 1668 | 110 | 74 | 50 | 10 |
| 6 | 2 | 4 | 1335 | 2421 | 164 | 205 | 23 | 14 |
| 7 | 2 | 4 | 1759 | 1867 | 258 | 204 | 28 | 5 |
| 8 | 2 | 4 | 1946 | 1953 | 163 | 166 | 19 | 15 |
| 9 | 2 | 3 | 2273 | 1890 | 243 | 71 | 5 | 6 |
| 10 | 2 | 4 | 1977 | 2593 | 278 | 183 | 29 | 11 |

*L: Leukemia*　　*C: Control*

TABLE F MEAN BLOOD NEUTROPHIL NUCLEAR LOBE COUNTS BY YEAR PRIOR TO DIAGNOSIS AND CHRONICITY OF LEUKEMIA, HIROSHIMA & NAGASAKI, 1947-62

表F　白血病診断前の年数および急性・慢性別平均好中球核分葉数，広島・長崎，1947－62年

| Years Prior to Onset | Leukemia | | Control | | U-Test P |
|---|---|---|---|---|---|
| | No. | Mean | No. | Mean | |
| | Acute Leukemia | | | | |
| 1 | 4 | 2.7 | 6 | 2.7 | NS |
| 2 | 9 | 2.6 | 11 | 2.5 | NS |
| 3 | 8 | 2.6 | 13 | 2.5 | NS |
| 4 | 6 | 2.6 | 14 | 2.5 | NS |
| 5 | 12 | 2.6 | 22 | 2.5 | * |
| 6 | 7 | 2.6 | 15 | 2.5 | NS |
| 7 | 4 | 2.5 | 9 | 2.4 | NS |
| 8 | 4 | 2.6 | 8 | 2.4 | NS |
| 9 | 3 | 2.7 | 5 | 2.4 | * |
| 10 | 3 | 2.4 | 8 | 2.5 | NS |

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Table F Continued

| Years Prior to Onset | Leukemia | | Control | | U-Test P |
|---|---|---|---|---|---|
| | No. | Mean | No. | Mean | |
| | | Chronic Leukemia | | | |
| 1 | 7 | 2.5 | 10 | 2.6 | NS |
| 2 | 2 | 2.6 | 3 | 2.6 | NS |
| 3 | 3 | 2.6 | 6 | 2.5 | NS |
| 4 | 5 | 2.5 | 6 | 2.5 | NS |

*P: .05-.01*

TABLE G MEAN NUMBER OF NUCLEAR APPENDAGES PER 500 NEUTROPHILS BY SEX, YEARS PRIOR TO DIAGNOSIS, AND CHRONICITY OF LEUKEMIA, HIROSHIMA AND NAGASAKI, 1947-62

表G 性，白血病診断前の年数，および急性・慢性別平均核付属物数，好中球500個当たり，広島・長崎，1947－62年

| Appendage | Years Prior to Onset | Acute Leukemia | | | | | Chronic Leukemia | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Leukemia | | Control | | U-test | Leukemia | | Control | | U-test |
| | | No. | Mean | No. | Mean | P | No. | Mean | No. | Mean | P |
| | | | | | Male | | | | | | |
| Nodules | 1-2 | 6 | 7.2 | 9 | 3.2 | NS | 7 | 12.9 | 12 | 4.3 | NS |
| | 3-4 | 11 | 12.0 | 22 | 6.9 | ** | 8 | 7.2 | 12 | 5.1 | NS |
| | 5-6 | 12 | 9.2 | 25 | 6.0 | * | | | | | |
| | 7-8 | 4 | 6.3 | 12 | 5.4 | NS | | | | | |
| | 9-10 | 3 | 4.7 | 6 | 4.5 | NS | | | | | |
| Clubs | 1-2 | 6 | 98.3 | 9 | 77.8 | NS | 7 | 101.1 | 12 | 95.4 | NS |
| | 3-4 | 11 | 94.3 | 22 | 102.8 | NS | 8 | 96.8 | 12 | 84.0 | NS |
| | 5-6 | 12 | 112.0 | 25 | 101.1 | NS | | | | | |
| | 7-8 | 4 | 68.0 | 12 | 94.8 | NS | | | | | |
| | 9-10 | 3 | 92.7 | 6 | 78.5 | NS | | | | | |
| | | | | | Female | | | | | | |
| Nodules | 1-2 | 6 | 44.7 | 8 | 41.5 | NS | | | | | |
| | 3-4 | 3 | 30.0 | 5 | 47.5 | NS | | | | | |
| | 5-6 | 6 | 35.3 | 12 | 41.4 | NS | | | | | |
| | 7-8 | 3 | 27.3 | 5 | 35.0 | NS | | | | | |
| | 9-10 | 3 | 35.3 | 7 | 33.3 | NS | | | | | |
| Clubs | 1-2 | 6 | 53.5 | 8 | 58.9 | NS | | | | | |
| | 3-4 | 3 | 40.0 | 5 | 55.0 | NS | | | | | |
| | 5-6 | 6 | 54.2 | 12 | 51.8 | NS | | | | | |
| | 7-8 | 3 | 35.7 | 5 | 38.4 | NS | | | | | |
| | 9-10 | 3 | 23.0 | 7 | 50.3 | NS | | | | | |
| Drumsticks | 1-2 | 6 | 9.0 | 8 | 7.5 | NS | | | | | |
| | 3-4 | 2 | 6.0 | 5 | 5.8 | NS | | | | | |
| | 5-6 | 6 | 5.3 | 12 | 5.3 | NS | | | | | |
| | 7-8 | 3 | 4.3 | 5 | 5.2 | NS | | | | | |
| | 9-10 | 3 | 5.0 | 7 | 3.1 | NS | | | | | |

***P: ≤.01* **P: .05-.01*

TABLE H PLATELET SIZE AND MORPHOLOGY BY YEAR PRIOR TO DIAGNOSIS FOR ACUTE LEUKEMIA, HIROSHIMA AND NAGASAKI, 1947-62

表H　急性白血病診断前の年数別血小板の大きさおよび形態，広島・長崎，1947－62年

| Years Prior to Onset | No. of Subjects | Platelet Type (%) | | | | Average Platelet Diameter $\mu$ | Average Platelet Surface Area $\mu^2$ |
|---|---|---|---|---|---|---|---|
| | | I | II | III | IV | | |
| | | Leukemia | | | | | |
| 1 | 3 | 64.3 | 22.5 | 8.0 | 5.6 | 3.5 | 9.5 |
| 2 | 6 | 66.6 | 17.6 | 11.1 | 4.5 | 2.9 | 6.9 |
| 3 | 6 | 58.0 | 26.0 | 8.1 | 7.9 | 3.4 | 9.2 |
| 4 | 7 | 62.0 | 23.0 | 8.7 | 6.3 | 3.4 | 9.3 |
| 5 | 10 | 57.8 | 26.0 | 8.8 | 7.4 | 3.2 | 8.1 |
| 6 | 5 | 70.4 | 21.0 | 5.6 | 3.0 | 2.9 | 6.7 |
| 7 | 4 | 68.0 | 18.5 | 8.0 | 5.5 | 3.1 | 7.9 |
| 8 | 3 | 65.2 | 31.6 | 1.6 | 1.6 | 2.7 | 5.7 |
| 9 | 3 | 73.2 | 14.6 | 7.6 | 4.6 | 2.8 | 6.0 |
| 10 | 2 | 73.0 | 22.0 | 2.0 | 3.0 | 2.6 | 5.7 |
| | | Control | | | | | |
| 1 | 4 | 71.8 | 18.2 | 7.0 | 3.0 | 2.7 | 5.6 |
| 2 | 9 | 59.0 | 24.8 | 8.3 | 7.9 | 3.2 | 8.3 |
| 3 | 11 | 66.3 | 21.1 | 9.1 | 3.5 | 3.3 | 8.5 |
| 4 | 16 | 57.9 | 25.1 | 11.6 | 5.4 | 3.2 | 8.8 |
| 5 | 20 | 62.0 | 21.5 | 10.5 | 6.0 | 3.2 | 7.3 |
| 6 | 15 | 63.0 | 20.7 | 10.7 | 5.6 | 3.2 | 8.5 |
| 7 | 9 | 63.2 | 21.2 | 8.7 | 6.9 | 3.2 | 10.4 |
| 8 | 8 | 66.7 | 19.0 | 9.0 | 5.3 | 3.2 | 8.0 |
| 9 | 7 | 65.4 | 19.6 | 9.6 | 5.4 | 2.9 | 6.8 |
| 10 | 8 | 67.6 | 18.6 | 9.3 | 4.5 | 2.9 | 6.8 |

TABLE I PLATELET SIZE AND MORPHOLOGY BY YEAR PRIOR TO DIAGNOSIS FOR CHRONIC LEUKEMIA, HIROSHIMA AND NAGASAKI, 1947-62

表I　慢性白血病診断前の年数別血小板の大きさおよび形態，広島・長崎，1947－62年

| Years Prior to Onset | No. of Subjects | Platelet Type (%) | | | | Average Platelet Diameter $\mu$ | Average Platelet Surface Area $\mu^2$ |
|---|---|---|---|---|---|---|---|
| | | I | II | III | IV | | |
| | | Leukemia | | | | | |
| 1 | 7 | 56.9 | 28.4 | 8.7 | 6.0 | 3.4 | 9.2 |
| 2 | 2 | 67.0 | 11.0 | 7.8 | 1.5 | 3.3 | 8.3 |
| 3 | 3 | 68.0 | 15.3 | 12.0 | 5.3 | 2.9 | 6.6 |
| 4 | 2 | 67.5 | 25.5 | 6.5 | 4.0 | 3.1 | 7.3 |
| | | Control | | | | | |
| 1 | 10 | 65.0 | 22.4 | 8.7 | 3.9 | 3.1 | 7.7 |
| 2 | 3 | 62.0 | 24.0 | 10.0 | 4.6 | 3.6 | 10.1 |
| 3 | 5 | 63.0 | 24.0 | 8.0 | 4.2 | 3.3 | 8.6 |
| 4 | 6 | 65.9 | 21.8 | 10.7 | 5.0 | 3.2 | 8.1 |

TABLE J MEAN VALUES FOR RED BLOOD COUNT, HEMOGLOBIN, HEMATOCRIT, MCV, MCH, AND MCHC BY YEAR PRIOR TO DIAGNOSIS FOR ACUTE AND CHRONIC LEUKEMIA, HIROSHIMA AND NAGASAKI, 1947-62

表J　急性・慢性白血病診断前の年数別赤血球数，ヘモグロビンおよびヘマトクリットの平均値ならびに平均血球容積，平均血球血色素量，平均血球血色素濃度，広島・長崎，1947－62年

| Years Prior to Onset | Sex | | Acute Leukemia | | | | | | Chronic Leukemia | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | RBC | Hb | Ht | MCV | MCH | MCHC | RBC | Hb | Ht | MCV | MCH | MCHC |
| 1 | Male | N | 1 | 1 | 1 | 1 | 1 | 1 | 7 | 7 | 6 | 6 | 7 | 6 |
| | | $\bar{x}$ | 4.44 | 13.1 | 41.5 | 93.5 | 29.5 | 31.6 | 4.96 | 15.3 | 47.9 | 96.8 | 30.9 | 32.1 |
| | Female | N | 3 | 4 | 3 | 3 | 3 | 3 | | | | | | |
| | | $\bar{x}$ | 4.23 | 12.4 | 37.7 | 89.5 | 28.1 | 31.6 | | | | | | |
| 2 | Male | N | 2 | 4 | 1 | 1 | 2 | 1 | 1 | 2 | 1 | 1 | 1 | 1 |
| | | $\bar{x}$ | 4.04 | 12.8 | 42.5 | 95.2 | 30.0 | 32.6 | 4.20 | 12.8 | 40.0 | 95.3 | 28.6 | 30.0 |
| | Female | N | 6 | 7 | 6 | 6 | 6 | 6 | | | | | | |
| | | $\bar{x}$ | 4.31 | 11.3 | 34.8 | 82.9 | 25.7 | 31.2 | | | | | | |
| 3 | Male | N | 5 | 7 | 4 | 4 | 5 | 4 | 5 | 5 | 5 | 5 | 5 | 5 |
| | | $\bar{x}$ | 4.31 | 12.2 | 40.4 | 90.9 | 28.8 | 31.7 | 4.48 | 13.5 | 43.0 | 96.1 | 30.0 | 31.3 |
| | Female | N | 2 | 2 | 2 | 2 | 2 | 2 | | | | | | |
| | | $\bar{x}$ | 3.70 | 11.2 | 34.3 | 92.9 | 30.3 | 32.8 | | | | | | |
| 4 | Male | N | 3 | 7 | 3 | 3 | 3 | 3 | 8 | 8 | 8 | 8 | 8 | 8 |
| | | $\bar{x}$ | 4.24 | 11.9 | 41.2 | 96.8 | 29.6 | 30.5 | 4.57 | 12.9 | 41.9 | 91.7 | 28.1 | 30.7 |
| | Female | N | 3 | 3 | 2 | 2 | 3 | 2 | | | | | | |
| | | $\bar{x}$ | 3.69 | 10.8 | 36.0 | 94.5 | 29.4 | 31.5 | | | | | | |
| 5 | Male | N | 7 | 8 | 6 | 6 | 7 | 6 | 2 | 2 | 2 | 2 | 2 | 2 |
| | | $\bar{x}$ | 4.53 | 13.20 | 42.4 | 94.8 | 29.3 | 31.1 | 4.66 | 14.2 | 42.3 | 90.9 | 30.2 | 33.3 |
| | Female | N | 6 | 6 | 6 | 6 | 6 | 6 | | | | | | |
| | | $\bar{x}$ | 3.92 | 11.2 | 34.9 | 90.3 | 28.5 | 31.6 | | | | | | |
| 6 | Male | N | 5 | 6 | 5 | 5 | 5 | 5 | | | | | | |
| | | $\bar{x}$ | 4.44 | 12.9 | 41.8 | 94.4 | 29.1 | 30.8 | | | | | | |
| | Female | N | 2 | 3 | 2 | 2 | 2 | 2 | | | | | | |
| | | $\bar{x}$ | 4.04 | 12.2 | 39.5 | 88.0 | 30.2 | 30.8 | | | | | | |
| 7 | Male | N | 3 | 3 | 3 | 3 | 3 | 3 | | | | | | |
| | | $\bar{x}$ | 4.38 | 12.2 | 40.2 | 91.8 | 27.8 | 30.3 | | | | | | |
| | Female | N | 1 | 2 | 1 | 1 | 1 | 1 | | | | | | |
| | | $\bar{x}$ | 4.21 | 11.8 | 41.0 | 97.5 | 28.2 | 28.9 | | | | | | |
| 8 | Male | N | 4 | 4 | 4 | 4 | 4 | 4 | | | | | | |
| | | $\bar{x}$ | 4.23 | 12.6 | 38.9 | 92.1 | 29.7 | 32.3 | | | | | | |
| | Female | N | 1 | 1 | 1 | 1 | 1 | 1 | | | | | | |
| | | $\bar{x}$ | 4.28 | 12.1 | 40.1 | 93.8 | 28.3 | 30.2 | | | | | | |
| 9 | Male | N | 1 | 1 | 1 | 1 | 1 | 1 | | | | | | |
| | | $\bar{x}$ | 3.85 | 11.0 | 34.0 | 88.3 | 28.7 | 32.5 | | | | | | |
| | Female | N | 2 | 2 | 2 | 2 | 2 | 2 | | | | | | |
| | | $\bar{x}$ | 4.30 | 13.0 | 39.3 | 91.6 | 30.4 | 32.6 | | | | | | |
| 10 | Male | N | 2 | 2 | 2 | 2 | 2 | 2 | | | | | | |
| | | $\bar{x}$ | 3.85 | 12.2 | 36.4 | 95.0 | 31.7 | 33.4 | | | | | | |
| | Female | N | 2 | 2 | 2 | 2 | 2 | 2 | | | | | | |
| | | $\bar{x}$ | 3.92 | 11.6 | 36.1 | 94.1 | 30.1 | 32.3 | | | | | | |

## REFERENCES
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