Bone and Bone-Marrow Blood Flow in Chronic Granulocytic Leukemia and Primary Myelofibrosis

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Blood flow in hematopoietic bone marrow and in nonhematopoietic bone has been measured with a Xe-133 washout method in 20 patients with chronic granulocytic leukemia (CGL) and in seven with primary myelofibrosis. Age-matched healthy persons served as controls. Bone-marrow blood flow in CGL was dependent upon the phase of the disease. In the metamorphosis phase, bone-marrow blood flow was high compared with that in the well-controlled phase. Apart from the initial phase, the mean values for bone blood flow in CGL were increased compared with the values of the healthy controls. In myelofibrosis the bone blood flow was also increased.

Bone-marrow blood flow in these diseases was dependent upon the cellularity of bone marrow as measured morphometrically.

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Although the measurement of mean blood perfusion of a mixed bone and the fraction of cardiac output flowing to the skeleton have been achieved (*1*,*2*), there is no method that can distinguish between the blood flow in bone marrow and that in other bony tissues. It has been proposed that the erythropoietic marrow and skeletal blood flow are similarly distributed (*3*). However, the effect of bone-marrow activity on bone blood flow is not known.

Recently, we proposed an intravenous Xe-133 injection method for measuring blood flow in bone (*4*). This method has the advantage of separating the blood flow between hematopoietic bone marrow and nonhematopoietic bone. The purpose of the present study was to measure blood flow in hematopoietic marrow and in nonhematopoietic tissues of bone in patients with chronic granulocytic leukemia or primary myelofibrosis. The studies demonstrated that the bone and bone-marrow blood flow depend on bone-marrow cellularity.

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MATERIALS AND METHODS

Patients. Twenty patients (7 males and 13 females) with chronic granulocytic leukemia (CGL) and seven patients (6 males and 1 female) with primary myelofibrosis were studied. The mean age of the CGL patients was 49 yr (range 25–75 yr) and that of the patients with myelofibrosis 68 yr (range 48–76 yr). The control material for the CGL patients consisted of 20 age-matched volunteers (mean age 51 yr, range, 25–77 yr) with no history of skeletal or hematological diseases according to the clinical and laboratory reports. The controls for the myelofibrosis group were also age matched. The mean age of the seven volunteers was 66 yr (range 50–77 yr).

Diagnosis and different phases of CGL. The diagnosis of the chronic phase of CGL was based on the characteristic blood and bone-marrow findings. The granulocytic count in peripheral blood was high, with cells in all stages of development. In all cases the bone marrow was hyperplastic. Eighteen patients had a Philadelphia (Ph′) chromosome and two were Ph′ negative.

Patients in the chronic phase of CGL were divided into three groups (*5*): Group I, patients before cytostatic therapy (one patient); Group II, symptomatic patients

after starting cytostatic therapy (three patients); and Group III, patients in the well-controlled phase of CGL (14 patients). The patients in Groups I and II were lumped together into a single group of "initial, uncontrolled CGL" owing to the very similar results in these groups. The duration of the cytostatic therapy in the initial, uncontrolled phase lasted less than 4 mo. In the well-controlled phase the time between diagnosis of the disease and the blood-flow measurements was 9–68 mo.

The diagnosis of the metamorphosis phase was based on the following symptoms and signs: malaise, weight loss, unexplained fever, splenomegaly, karyotype alteration, resistance to the chronic-phase treatment, and increasing immaturity of the granulocytes in the peripheral blood and bone marrow (*6*). The percentage of blast cells was more than 15% of the circulating leukocytes and/or more than 20% of the bone-marrow cells in eight of 12 patients studied during metamorphosis. Six patients were studied both in the chronic well-controlled phase and in the metamorphosis phase. None of the CGL patients started out with myelofibrosis.

Diagnosis of myelofibrosis. The patients with primary myelofibrosis had the following clinical and hematological findings: splenomegaly, leukoerythroblastic blood picture with abnormal red-cell morphology (including poikilocytosis and "tear drop" cells), and various degrees of myelofibrosis in bone-marrow biopsy samples. Based on Chelloul et al. (*7*) there are three different types of cases with myelofibrosis: those with hyperplasia (I), those with typical myelofibrosis (II), those with osteosclerosis and hypoplasia (III). One out of seven patients was classified as belonging to Group I, five patients to Group II, and one patient to Group III.

Blood and bone-marrow specimens. Red-cell and white-cell counts were determined by a Coulter counter, Model S. Peripheral blood and bone-marrow smears were stained with the May-Grünwald-Giemsa sequence (*8*) and studied with conventional methods.

Theoretical basis for blood-flow measurement. Blood flow in bone marrow and in nonhematopoietic bone tissue was determined from the greater trochanteric area of the femur using intravenous injection of Xe-133 (*4*). We have proposed that the rapidly falling segment of the biexponential washout curve represents blood flow in the hematopoietic bone marrow, while the slowly falling segment represents blood flow in nonhematopoietic bone (*9*). The mean bone blood perfusion F is obtained from the blood perfusions (f_i) of the components according to the equation

$$F(\text{ml}/100\text{g}/\text{min}) = \sum_{i=1}^{2} w_i f_i,$$

where w_i ($i = 1, 2$) is the fractional weight of the component of interest at time $t = 0$ (*10*). The fractional weight of a component can be obtained from

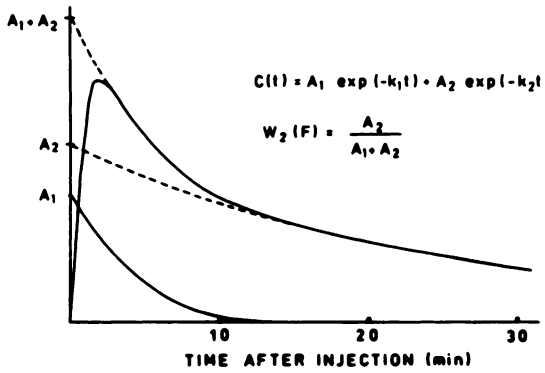

FIG. 1. Scheme of biexponential washout curve and derivation of fractional flow of nonhematopoietic component $w_2(F)$.

$$w_i(m) = \frac{A_i/f_i}{A_1/f_1 + A_2/f_2} \qquad (i = 1, 2).$$

The fractional flow through each component is defined as $w_i(F) = A_i/(A_1 + A_2)$. The initial quantities A_i of Xe-133 present in the components at $t = 0$ are presented in Fig. 1. The compartmental perfusion f_i is related to the washout rate constant k_i by

$$f_i\ (\text{ml}/100\ \text{g}/\text{min}) = \lambda_i k_i.$$

k_i may be calculated from the half-times $t_{1/2_i}$ of the activities of the components using the relation $k_i = (\ln 2)/t_{1/2_i}$. λ_i is the partition coefficient of Xe-133 between blood and the tissue component of interest.

Partition coefficient λ_1. The partition coefficient of the hematopoietic component was approximated by the partition coefficient of the concentrate of mature and immature white cells. A value of 0.8 ml/g was used for λ_1 (*11*).

Partition coefficient λ_2. The partition coefficient of the nonhematopoietic tissues of bone was determined using the approximate assumption that the nonhematopoietic tissue of bone consists of only two components: intraosseous fat and solid bone substance. The partition coefficient of the nonhematopoietic tissue of bone is then

$$\lambda_2 = m_F\lambda_F + m_B\lambda_B,$$

where m_F and m_B are the masses of intraosseous fat and solid bone substance as fractions of the total mass of nonhematopoietic bone tissue. λ_F (=13.6 ml/g) and λ_B (=1.7 ml/g) are the corresponding partition coefficients (*11*). To determine the fractional masses of intraosseous fat and solid bone substance, a morphometric quantification of bone-marrow biopsies was performed. Nine needle biopsies were taken from six patients with CGL, and three from three patients with myelofibrosis, with a Jamshidi needle (diam. 2 mm) at a time not exceeding 3 wk from the bone-perfusion measurement.

The biopsies were fixed in 10% neutral buffered formalin or nitric acid, then embedded in paraffin. Sections 6 μm thick were stained by the van Gieson hematoxylin

TABLE 1. VOLUMETRIC FRACTIONS AND FRACTIONAL MASSES (MEAN AND RANGE) OF HEMATOPOIETIC MARROW (VH), INTRAOSSEOUS FAT (VF), AND TRABECULAE (VB) IN BONE, IN CGL, AND IN MYELOFIBROSIS (MF)

Disease	Phase of disease	Number of patients	Volumetric fraction (%)			Fractional mass (%)		
			V_{VH}	V_{VF}	V_{VB}	M_{VH}	M_{VF}	M_{VB}
CGL	I	1	54.2	9.9	35.9	38.3	6.2	55.0
CGL	II	1	6.0	54.0	40.0	4.3	34.3	61.4
CGL	III	5	58.3 (33.4–82.0)	26.2 (3.0–38.1)	15.5 (7.2–24.5)	54.2 (27.1–70.2)	16.0 (2.3–39.7)	29.8 (4.6–30.9)
CGL	IV	2	8.1 (5.8–10.4)	68.0 (64.0–72.0)	23.9 (17.6–30.2)	6.8 (4.3–9.3)	50.9 (44.8–57.0)	42.3 (33.7–50.9)
MF	—	3	53.9 (43.8–66.9)	17.4 (14.2–23.2)	28.7 (18.9–34.3)	41.8 (32.5–55.8)	10.4 (5.6–15.2)	47.8 (33.7–57.4)

I = initial, uncontrolled phase.
II = well-controlled phase.
III = metamorphosis phase with hyperplastic bone marrow.
IV = metamorphosis phase with hypoplastic bone marrow (after cytostatic therapy).

method and were used for the morphometric studies of the different tissue components.

For the quantitation of the volumetric fractions of the tissue components, we used the point-counting method (magnification 143×, lattice with 120 points, 600–700 points per biopsy) (*12*). The volumetric fractions of hematopoietic marrow (V_{VH}) and the nonhematopoietic portion of bone marrow—consisting mainly of fatty marrow (V_{VF}) and bone trabeculae (V_{VB})—were changed into the fractional masses of the compartments (M_{VH}, M_{VF}, and M_{VB}), using the densities 1.028, 0.91, and 2.2 g/cm^3 (*13*) for the respective compartments. The calculation of $m_F = M_{VF}/(M_{VF} + M_{VB})$ and $m_B = M_{VB}/(M_{VF} + M_{VB})$ can then proceed.

Since the bone biopsies were not taken every time that the bone perfusion was measured, we developed an experimental way to determine the partition coefficient, λ_2. The method is based on the relation between the morphometrically determined λ_2 and the fractional flow $w_2(F)$ of the nonhematopoietic component. Intraosseous fat, with its large partition coefficient (*11*), is the important determinant of λ_2. Accordingly, the fractional flow of the nonhematopoietic component $w_2(F)$ is high when there is much fat in the bone marrow. Figure 1 shows the derivation of the fractional flow $w_2(F)$ from the biexponential washout curve.

We have shown morphometrically in healthy middle-aged persons that the fractional masses of hematopoietic marrow M_{VH}, intraosseous fat M_{VF}, and bone trabeculae M_{VB} in the trochanteric area of the femur are 19.9, 39.6, and 40.5% (*14*). The partition coefficient calculated according to the above equation would be then 7.52 ± 1.71 ml/g (1 s.d.). However, we showed previously (*11*) that λ_2 for the homogenized bone specimens in healthy persons of the same age was 4.91 ± 0.32 ml/g. For reasons that will be discussed later, it seems that the morphometric analysis overestimates the partition coefficient λ_2 by 53%. Therefore, the morphometrically determined partition coefficient λ_2 was corrected by a corresponding factor. The partition coefficients were then determined as functions of $w_2(F)$, which were calculated from the washout curves of the same patients. The partition coefficients λ_2 of the other patients were determined by means of their washout curves using this relationship.

Statistical calculations. Because of the small number of observations, a two-tailed randomization test for matched pairs was used to calculate the differences between the values of the initial phase of CGL and the controls. The same test was also applied to the data from patients with myelofibrosis.

A two-tailed Wilcoxon matched-pairs, signed-ranks *t*-test was applied when the values of the well-controlled phase and the metamorphosis phase of CGL were tested against the values of the controls.

A two-tailed Mann-Whitney U-test was used for the differences between the various groups of CGL.

RESULTS

Table 1 shows the morphometrically determined volumetric fractions and the fractional masses of hematopoietic marrow from the posterior iliac crest, in different phases of CGL and in myelofibrosis. The partition coefficient λ_2 calculated from the values of Table 1 correlated ($p < 0.05$) with the fractional flow of the second component $w_2(F)$ (Fig. 2). The figure also shows the corrected partition coefficient λ_2 used in the calculations.

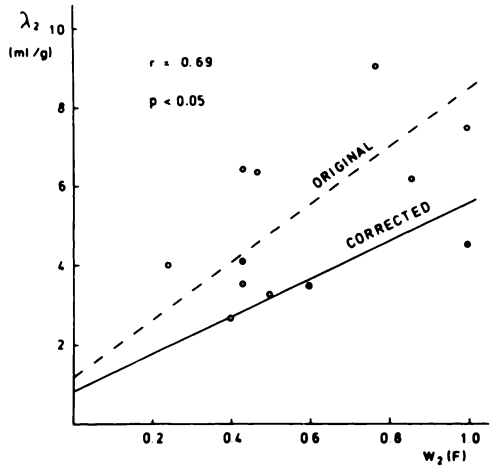

FIG. 2. Uncorrected and corrected partition coefficients λ_2 as a function of $w_2(F)$. Patients with CGL are shown as open circles and those with myelofibrosis as solid dots.

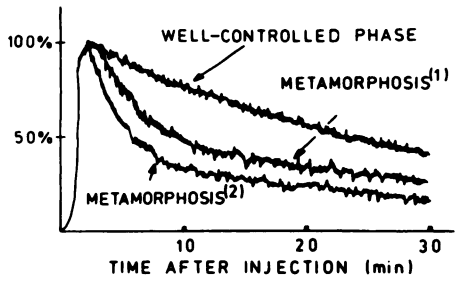

FIG. 3. Washout curves in well-controlled phase and in metamorphosis phase. In metamorphosis, (1) and (2), percentages of blast cells in bone marrow were 10 and 25, respectively.

Figure 3 presents the time-activity curves from one patient with CGL, in the well-controlled phase and in the metamorphosis phase. The rapidity of Xe-133 washout from bone was highest in the most active phase of the disease.

The compartmental blood perfusions and the mean bone perfusion in different phases of CGL in one patient are presented in Fig. 4. The most striking changes occurred in the perfusion of hematopoietic marrow.

Table 2 presents the compartmental perfusions f_1 and f_2 and rate constants k_1 and k_2, the mean bone perfusion F, the fractional flow $w_1(F)$, and weight $w_1(m)$ of the first component, all in different phases of CGL, in primary myelofibrosis, and in healthy controls. In the initial, uncontrolled phase of CGL, the bone-marrow perfusion appeared higher than that in the controls, but the difference was not statistically significant. The perfusion rate f_1 did not differ from the control value in the well-controlled phase, in which eight of 14 patients had no first component. In the metamorphosis phase the perfusion of the hematopoietic marrow was significantly higher than in the well-controlled phase and in the healthy controls ($p < 0.01$ in both cases).

There was a significant negative correlation between f_1 and the duration of the disease after initiation of busulfan therapy ($p < 0.05$). The bone-marrow perfusion correlated significantly with the volumetric fraction of the hematopoietic marrow ($p < 0.05$) (Fig. 5).

Changes of f_2 between different phases of CGL were small. In the well-controlled phase, however, f_2 was significantly higher than in the controls ($p < 0.01$).

Except for the initial phase of CGL, the mean blood perfusion F was higher than in healthy persons. The highest perfusion values were found in the metamorphosis phase.

The fractional flow $w_1(F)$ and the fractional weight $w_1(m)$ of the hematopoietic component were significantly higher in the metamorphosis phase than in the healthy controls.

The blood perfusions of the six patients who underwent a transition from the well-controlled phase to the metamorphosis phase are presented in Fig. 6.

In myelofibrosis the perfusion of nonhematopoietic tissues of bone and the mean bone perfusion were significantly higher than in the control material ($p < 0.05$ in both cases). In myelofibrosis the mean values of f_1, f_2, F, $w_1(F)$, and $w_1(m)$ were nearly the same as in the well-controlled phase of CGL (Table 2).

DISCUSSION

The perfusion values presented in this work depend on the accuracy of the estimation of the partition coefficients for the tissue compartments. The partition coefficient of the hematopoietic component (λ_1) was considered equal to the partition coefficient of white-cell concentrate containing mature and maturing white cells (*11*). The partition coefficient of erythroblasts is not known, but the partition coefficient of mature red cells is higher than that of white cells (*11*). Thus the partition coefficient of hematopoietic marrow may be too low when estimated from that of the white cells. Probably there is little difference between the real λ_1 and our ap-

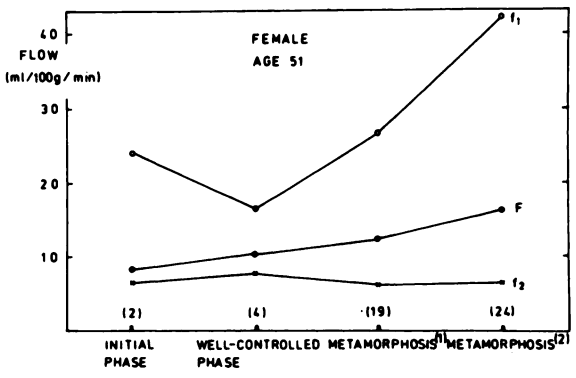

FIG. 4. Blood perfusions in hematopoietic marrow, in nonhematopoietic tissues of bone, and the mean bone perfusion in various phases of CGL. Numbers in brackets refer to time in months after diagnosis of CGL. For metamorphosis (1) and (2), see legend of Fig. 3.

TABLE 2. RESULTS FROM BONE CIRCULATION MEASUREMENTS IN CGL AND IN MYELOFIBROSIS

Phase of disease	Number of patients	Fast compartment f_1 (ml/100g/min)	Fast compartment k_1 (1/min)	Slow compartment f_2 (ml/100g/(min))	Slow compartment k_2 (1/min)	F (ml/100g/min)	$w_1(F)$	$w_1(m)$
Initial, uncontrolled phase	4	21.6† (19.1–24.3)*	0.24‡ (0.21–0.27)	6.6† (6.0–7.2)	0.016 (0.014–0.019)	9.6† (8.3–11.4)	0.44† (0.29–0.66)	0.20† (0.09–0.34)
Well-controlled phase	14	8.9‖ (0.00–21.0)	0.19 (0.15–0.24)	9.6¶ (6.4–17.1)	0.017 (0.010–0.030)	10.6¶ (6.4–17.1)	0.18‖ (0.00–0.52)	0.11‖ (0.00–0.34)
Metamorphosis phase	12	27.0¶ (15.6–42.2)	0.27 (0.16–0.41)	7.4‖ (4.0–10.8)	0.019 (0.012–0.027)	12.2¶ (7.2–16.3)	0.55¶ (0.23–0.74)	0.24¶ (0.15–0.34)
Controls	20	11.9 (0.00–24.1)	0.18 (0.12–0.25)	6.8 (5.4–9.0)	0.012 (0.008–0.013)	7.6 (5.4–10.7)	0.12 (0.00–0.32)	0.07 (0.00–0.21)
Myelofibrosis	7	9.3† (0.00–20.2)	0.15 (0.09–0.23)	10.6§ (6.8–14.2)	0.020 (0.011–0.031)	10.9§ (6.8–14.0)	0.19† (0.00–0.48)	0.17† (0.00–0.38)
Controls	7	2.8 (0.00–16.7)	0.18 (0.17–0.19)	7.2 (5.4–8.6)	0.011 (0.008–0.013)	7.4 (5.4–8.6)	0.03 (0.00–0.19)	0.02 (0.00–0.10)

* Range.
† Not significant (NS) by two-tailed randomization test for matched pairs.
§ $p < 0.05$.
‖ NS by Wilcoxon t-test.
¶ $p < 0.01$ "—"—".
‡ k_1 is shown for the patients with the rapidly falling segment in their washout curves.

proximation, because the mass of white cells is large compared with that of red cells in the bone marrow of CGL and primary myelofibrosis.

The most important determinant of the partition coefficient of the nonhematopoietic tissues of bone is intraosseous fat. In bone the amount of solid bone substance remains quite constant. In contrast, the amount of intraosseous fat decreases when the hematopoietic cellularity increases. The hypercellular marrow, with a high fractional flow $w_1(F)$ and a small $w_2(F)$, thus has a small value for λ_2. On the other hand, in the hypocellular marrow with a small hematopoietic component, both λ_2 and $w_2(F)$ are high. It is expected, therefore, that there is a relationship between λ_2 and $w_2(F)$ (Fig. 2). However, the morphometrically determined λ_2 was overestimated by 53%. The two probable reasons for the overestimation are intraosseous water and fibrous tissue, which we could not quantitate. In the morphometric analysis, intraosseous water (*11*) and fibrous tissue, both with lower partition coefficients than that of intraosseous fat, were included in the fat compartment. The validity of the determination of λ_2 in the manner presented is supported by the finding that λ_2 of healthy persons, determined using a widely accepted method of tissue ho-

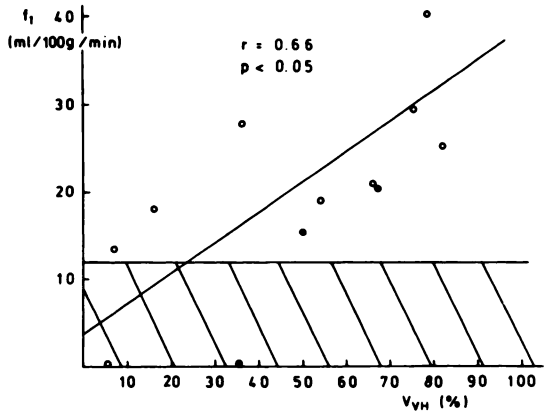

FIG. 5. Hematopoietic marrow perfusion as a function of morphometrically determined volumetric fraction of hematopoietic marrow. Shaded area represents region in which hematopoietic marrow perfusion cannot be calculated (*14*).

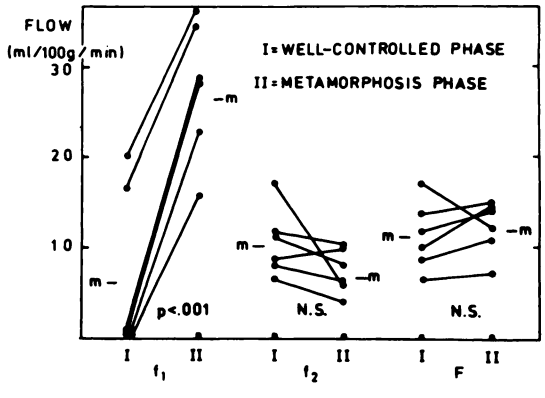

FIG. 6. Perfusion data for CGL patients in whom disease changed from well-controlled phase into metamorphosis phase.

mogenization (*15*), equals the λ_2 obtained on the basis of the corrected relationship between the morphometrically determined λ_2 and $w_2(F)$. The approach has the advantage that bone biopsies are not needed for the estimation of λ_2.

The rapidly falling component of the washout curves decreased as the time from the beginning of chronic-phase therapy progressed, and f_1 became zero in almost half of the patients. During metamorphosis the first component was greatly increased. Since the cellularity of hematopoietic marrow decreases during cytostatic therapy, and increases again during metamorphosis, it is probable that f_1 reflects blood flow dependent upon the cellularity of the hematopoietic marrow, as we have previously suggested (*9*). This view is also supported by the significant positive correlation between f_1 and the cellularity of hematopoietic marrow as determined from bone biopsies. Since the Xe-133 method is insensitive to a small first component (*14*) the points shown at zero in Fig. 6 may actually lie inside the limits 0 and 12 ml/100g/min.

Changes in the slow component of the washout curve were small. However, f_2 was significantly increased in the well-controlled phase of CGL and in myelofibrosis. Under these conditions, the amount of fibrous and fatty tissue in bone marrow, compared with hematopoietic tissue, is higher than in the initial, uncontrolled phase of CGL (Table 1). This finding suggests that the skeletal blood flow in myeloproliferative diseases may remain high although bone-marrow cellularity decreases. Nevertheless, the bone perfusion was normal in one case of myelofibrosis with hypoplastic bone marrow. This particular patient had the lowest bone perfusion in the present series.

The perfusion values in myelofibrosis and in the well-controlled phase of CGL were similar. Van Dyke et al. (*12*) have suggested that skeletal blood flow is markedly increased in myelofibrosis but is normal in CGL. Our results are not directly comparable with those of Van Dyke et al., owing to procedural differences.

Blood flow in human sternal marrow has been measured using the clearance rate of I-131 as a measure of blood flow (*17*). The clearance rate was increased in acute leukemia and in chronic lymphocytic leukemia but was within normal limits in CGL. Only the initial slopes of the clearance curves were recorded. Because of the different analyzing technique and the different measuring sites, these data are not comparable with our values. Neither Van Dyke et al. (*16*) nor Petrakis et al. (*17*) specify the phase of the disease on which the blood flow values are dependent.

Except in the initial phase of CGL, the mean bone blood perfusion in the greater trochanteric region in the femur was significantly increased. We believe that this is the case in the whole central skeleton. All patients with early metamorphosis (blast cells less than 20% in bone marrow) had greatly increased hematopoietic components, suggesting that cellularity in the proximal femur increases in the early phase of metamorphosis. This is in accordance with the clinical finding that patients with metamorphosis often have severe pains in the hip area. It is known that severe symptoms may persist for several months before the occurrence of metamorphosis can be verified by objective tests (*5*). Accordingly, Xe-133 monitoring of the blood flow in the marrow of the proximal femur may provide a valuable indication of the beginning of metamorphosis in CGL.

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