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Changes in Trabecular Bone, Hematopoiesis and Bone Marrow Vessels in Aplastic Anemia, Primary Osteoporosis, and Old Age: A Comparative Histomorphometric Study

R. BURKHARDT[1,2], G. KETTNER[2], W. BÖHM[1,2], M. SCHMIDMEIER[1,2], R. SCHLAG[1], B. FRISCH[3], B. MALLMANN[1,2], W. EISENMENGER[4] and TH. GILG[4]

[1] *Abteilung für Knochenmarksdiagnostik, Medizinische Klinik Innenstadt der Universität, München, FRG,* [2] *Arbeitsgruppe für Hämatomorphologie, Gesellschaft für Strahlen- und Umweltforschung mbH, München, FRG,* [3] *Institute of Hematology, Ichilov Hospital, Tel Aviv Medical Centre, Tel Aviv, Israel,* [4] *Institute für Rechtsmedizin der Universität, München, FRG.*

Address for correspondence and reprints: Prof. Dr. Rolf Burkhardt, Abt.f.Knochenmarksdiagnostik, Med.Klinik Innenstadt d.Universität, Ziemssenstr.1a, D-8000 München 2, FRG.

Abstract

Retrospective histologic analyses of bone biopsies and of post mortem samples from normal persons of different age groups, and of bone biopsies of age- and sex-matched groups of patients with primary osteoporosis and aplastic anemia show characteristic age dependent as well as pathologic changes including atrophy of osseous trabeculae and of hematopoiesis, and changes in the sinusoidal and arterial capillary compartments. These results indicate the possible role of a microvascular defect in the pathogenesis of osteoporosis and aplastic anemia.

Key Words: Aplastic Anemia–Bone Marrow Biopsy–Bone Marrow Vessels–Osteopenia–Osteoporosis

Introduction

Osteoporosis and aplastic anemia exhibit different clinical aspects, though they have three things in common: unexplained atrophy in most cases, localization in the axial skeleton and manifestation of organic changes—osteopenia and bone marrow atrophy—usually found in old age. This coincidence was emphasized by Pommer in 1925 (Pommer, 1925) in his first description of osteoporosis. Previous observations in iliac crest biopsies of simultaneous atrophy of hematopoiesis and of trabecular bone in aplastic anemia as well as in primary osteoporosis stimulated the present study, undertaken to investigate the possibility of a circulatory basis common to all these disturbances.

Material

553 out of 32.000 iliac crest biopsies were used for this study, selected according to the following criteria:

a) osteopenia (n = 293):
1. technical preparation of sufficient quality for morphometric analysis; and a surface area of at least 40mm^2;
2. hematologic and radiologic data available; comprising complete blood count and x-rays of the axial skeleton;
3. exclusion of neoplastic, inflammatory and metabolic disorders;
4. trabecular bone volume less than 18 vol%

b) bone marrow atrophy (n = 260):
1., 2., and 3. as above
4. More than 30 vol% fat in the biopsy.

481 additional biopsies were studied for comparison.

Group 1: 400 specimens of iliac crest, sternal bone, second lumbar vertebra, calcaneus, and distal radius were taken with the myelotomy trephine between 2 and 12 h post mortem of 79 victims of fatal accidents, who had no history or necropsy signs of organic disease, divided into 6 age groups from 1 to 98 years, each with equal numbers of males and females (except in the first and last groups).

Group 2: 81 iliac crest biopsies without evidence of pathology, grouped according to the patients' ages 1 to 10 years (n = 20); 11 to 20 years (n = 24); 30 to 50 years (n = 30); and over 70 years (n = 7), each with equal numbers of males and females except the first and last groups (these biopsies were taken in the course of clinical investigations for a variety of conditions).

Methods

All biopsies were embedded in methacrylate without prior decalcification, and 3 micron sections were obtained as described previously (Burkhardt, 1981). Light microscopic evaluation was done by at least two independent investigators at magnifications of 50 to 250 times, using sections stained by Gallaminblue-Giemsa (Burkhardt, 1981). Forty-three clinical and 42 histological parameters were registered; those used for this study are given in **Tables 1 and 2.** Osseous parameters were defined by accepted criteria (Merz and Schenk, 1970); the following vascular compartments were counted: arteries, arterioles, capillaries, sinusoids (Burkhardt, 1970), see **Figure 1,** for their characteristic morphologic features. Ramifications within a vascular compartment were counted only once; ramifications belonging to other compartments were registered separately. BMDP-computer programs were used for statistical evaluation including the students t-test, the Pearson x^2-test and the Fisher test according to Breslow and Mantel-Cox (Mantel, 1966; Breslow, 1970; Dixon and Brown, 1979). This evaluation included all cases. The following biopsy groups were used for discriminative analysis:

Table I. Clinical data used for evaluation of biopsies

Age at biopsy
Sex
Clinical diagnosis
Indication for biopsy
Blood sedimentation rate
Blood cell counts/mm³
Hemoglobin g%
Values of routine biochemical screeing
Radiologic status of axial skeleton
Survival (months) from time of biopsy

1) Primary osteoporosis = 30 cases of both sexes from collective a) with confirmed clinical and radiologic diagnosis of severe disease;
2) Aplastic anemia = 30 cases of both sexes from collective b) with pancytopenia (erythrocytes < 3,5 millions, WBC < 4000/mm³, and platelets < 100,000/mm³), typical history and confirmed clinical diagnosis
3) 30 cases of both sexes, normal adults
4) 7 cases of both sexes, normal senile persons; 3) and 4) from group 2).

Results

Significance of morphometric measurements

The overall statistic error of volumetric measurements of trabecular bone is about 7% (Delling, 1974). In repeated evaluations of the same sections by two different investigators the values in this study differed by between 5 and 10%. The vascular branches were clearly distinguished (Fig. 1); except for minor sinusoids (Burkhardt and Gabel, 1969) which were not counted. The numbers of the sinusoids in the necropsy cases exceeded those in the biopsies by about 20%, probably due to post mortem hypostasis. Nevertheless similar proportions of age-related changes were observed in both groups.

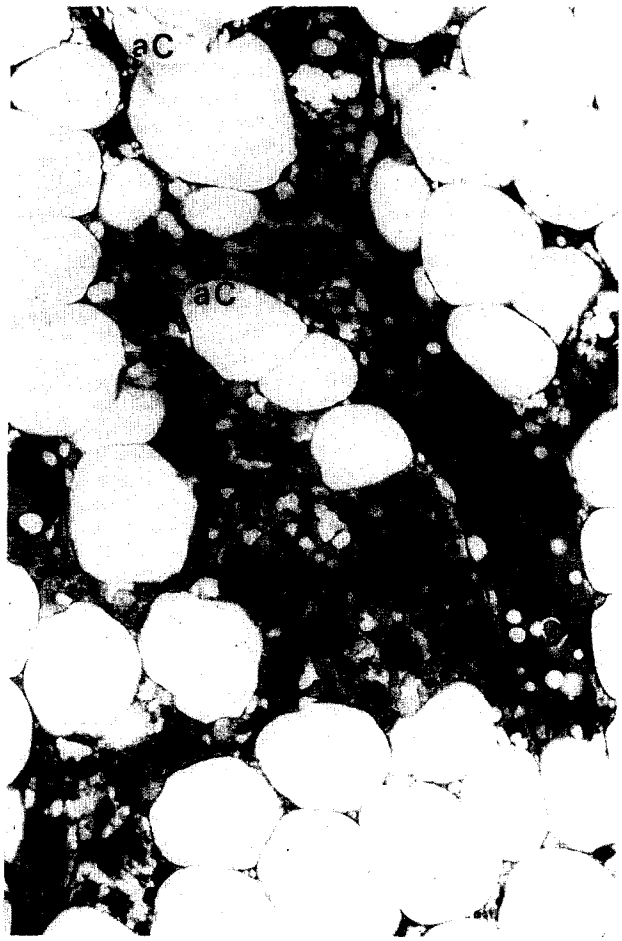

Fig. 1. Cross sections of bone marrow vessels in biopsy section. Aplastic anemia, female patient, 30 years old. Magnification ×250; Giemsa stain. A = arteriole; aC = arterial capillaries; S = sinusoids (used synonymously with the venous capillaries).

Table II. Histological parameters evaluated in each biopsy

Bone marrow tissues	
Hematopoiesis	(vol%)*
Adipose tissue	(vol%)*
Osseous tissues	
Trabecular bone	(vol%)*
Osteoid	(vol%)*
Specific trabecular surface	(mm^2/mm^3)†
Osteoblastic index	(Nobl/mm^2)†
Osteoclastic index	(Nocl/mm^2)†
Blood vessels	
Arteries	/100mm^2§
Arterioles	/100mm^2‡
Arterial capillaries	/100mm^2‡
Sinusoids	/100mm^2‡
Trabecular sinusoids	/100mm^2 Specific trabecular surface)†

* evaluated at magnification 100:1 using eyepiece with pointed grid in at least 20 biopsy fields.
† evaluated at magnification 250:1 using eyepiece with lines in at least 20 biopsy fields.
‡ counted at magnification 250:1 in at least 20 bone marrow fields.
§ counted at magnification 50:1 all over biopsy section.

Significance of the iliac crest biopsy for changes in trabecular bone and haematopoiesis

1. The results of the post mortem study show that the volumes of trabecular bone, osteoid, fat, and hematopoiesis are subject to similar age-related changes in all parts of the skeleton investigated **(Table 3),** though in different proportion. The axial skeleton contains more red marrow, and this difference is maintained throughout life. The numbers of osteoblasts and osteoclasts correspond with the volume of hematopoiesis, except in the geriatric period, when an increase in osteoclasts is accompanied by a decrease in marrow and in bone.
2. Correlation of osteopenia and osteoporosis. Clinical and radiologic manifestations of severe osteoporosis were absent in only 18% of 293 patients with osteopenia of <18 vol% **(Table 4).**
3. Correlation of fatty marrow with peripheral cytopenia **(Table 5).** Of 260 patients with <30 vol% of hemato-

Table III. Changes with age in different parts of skeleton (post-mortem biopsies of victims of fatal accidents)

	Age groups†	Adipose tissue vol%	Hematopoiesis vol%	Trabecular bone vol%	Osteoid vol%	Osteoblasts /mm²	Osteoclasts /mm²
Iliac	2–19	12.8	61.8	22.0	6.51	1116	423
crest	20–39	27.9	47.5	21.4	2.67	362	180
(anterior)	40–59	33.8	43.1	20.5	1.40	215	173
	60–99	37.7	43.8	15.3	2.02	220	257
Sternum	2–19	14.6	64.5	16.9	4.58	797	261
	20–39	23.0	58.4	15.2	1.98	294	159
	40–59	34.6	49.4	13.5	0.59	135	106
	60–99	36.1	45.4	14.8	1.47	132	232
2nd Lumbar	2–19	14.1	64.7	17.4	4.66	755	234
vertebra	20–39	21.6	57.0	18.2	2.18	317	175
	40–59	26.5	54.9	16.1	1.07	111	165
	60–99	33.2	52.1	11.5	1.46	97	231
Radius	2–19	62.0	9.2	24.4	8.25	1671	361
(right side)	30–39	77.9	0.3	19.6	0.58	34	47
	40–59	78.1	0.5	18.8	0.30	18	36
	60–99	76.5	0.5	16.6	0.47	15	75
Calcaneus	2–19	67.6	7.5	22.1	4.82	863	304
(right side)	20–39	75.1	0.4	22.1	1.03	81	63
	40–59	78.7	0.7	18.9	0.16	10	42
	60–99	80.3	0.3	17.8	1.16	55	99

† 20–24 individuals, equal numbers of both sexes, in each group.

poietic marrow in the biopsy, only 16% had no peripheral cytopenia; while 48% of those with <10 vol% had pancytopenia, or aplastic anemia. The difference in survival of patients with subtotal or with partial hematopoietic atrophy **(Fig. 2),** was significant at the 75% level.

Correlations between trabecular osteopenia and hematopoietic marrow in the groups with osteopenia and the groups with bone marrow atrophy

The quantities of trabecular bone and fatty marrow in the osteopenia group are plotted against each other in **Figure 3;** while **Figure 4** shows the same for the group with atrophic bone marrow in aplastic anemia. In both groups osteopenia corresponds significantly with replacement of hematopoiesis by fat.

Table IV. Atrophy of bone trabeculae in biopsy (osteopenia) and osteoporosis (clinical and radiologic data)

	Volume of trabecular bone (biopsy) <10% n = 227 mean age 60.5 ± 17.7	10–18% n = 66 mean age 54.8 ± 16.1	Total n = 293
Osteoporosis (clin. + x-rays) n = 200	70	62	68
Osteoporosis plus vertebral fracture(s) n = 42	15	12	15
Normal bone* radiology n = 51	15	26	17
Total percent	100%	100%	100%

* Osteopenia in biopsy, without manifest osteoporosis.

Numerical changes of bone marrow vessels with age

The numbers of cross-sectioned vessels per 100 mm²/section are represented by cubes of corresponding size **(Fig. 5).** During infancy and adolescence, when hematopoiesis is most active, the overall number of capillaries and of sinusoids is higher than in the adult period (p = 0.0001, resp. 0.03), primarily due to a decrease in arterial capillaries. The geriatric group (n = 7) shows an increase in arterial capillaries (though not significant), and a significant decrease in sinusoids (p = 0.01), and markedly higher counts of arterioles as well as arteries (p = 0.01). The proportion of sinusoids to arterial capillaries differed

Table V. Atrophy of hematopoiesis in biopsy and aplastic anemia

	Volume of hematopoietic tissue (biopsy) <10% n = 154 mean age 46.8 ± 21.3	10–30% n = 105 mean age 54.6 ± 15.8	Total n = 259
Blood counts			
Pan-cytopenia*	48	17	35
Erythro-*	6	15	10
Granulo-*	8	18	12
Thrombo-	2	5	4
E.-Gran.-	5	9	7
E.-Thr.-	6	4	5
Gran.-Thr.-	13	9	11
Normal	12	23	16
Total percent	100%	100%	100%
75% survival (months) n = 144	8,7	32,2	p = 0,01

* Pancytopenia = erythrocytes < 3.5 millions/, leukocytes < 4000/mm³ and thrombocytes < 100,000/ml blood; Erythrocytopenia = erythrocytes < 3.5 millions/mm³ Granulocytopenia = leukocytes < 4000/mm³ Thrombocytopenia = thrombocytes < 100.000/ml blood.

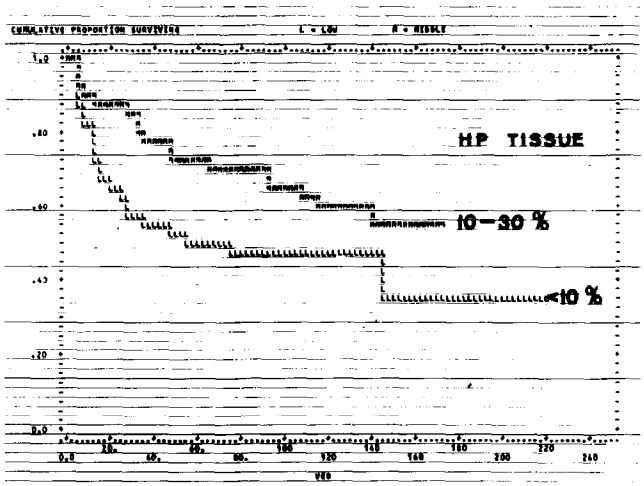

Fig. 2. Life tables of two patient groups showing mild and severe atrophy of hematopoiesis, respectively.

only slightly in the youngest, adolescent and geriatric groups (4,5; 5,4; 5,0, respectively), whereas in adults the value was 7,8. Similar proportions were found in the necropsy cases: 6,4; 3,8; 5,7 and 7,8. The vol% of the trabecular bone diminished parallel to the decrease in capillaries, and the volume of marrow fat increased with age.

Correlation of histomorphometric data of patients with aplastic anaemia, or with primary osteoporosis, with data derived from normals

The volumes of trabecular bone and marrow adipose tissue on one hand, and vascular counts on the other, were compared in aplastic anemia, primary osteoporosis, and normal groups of corresponding and old age respec-

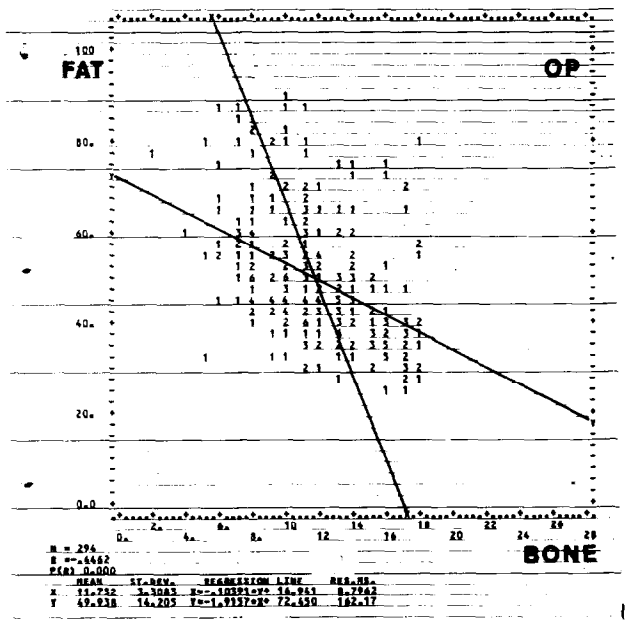

Fig. 3. Correlation of volumes of trabecular bone and of fat in osteopenia (OP).

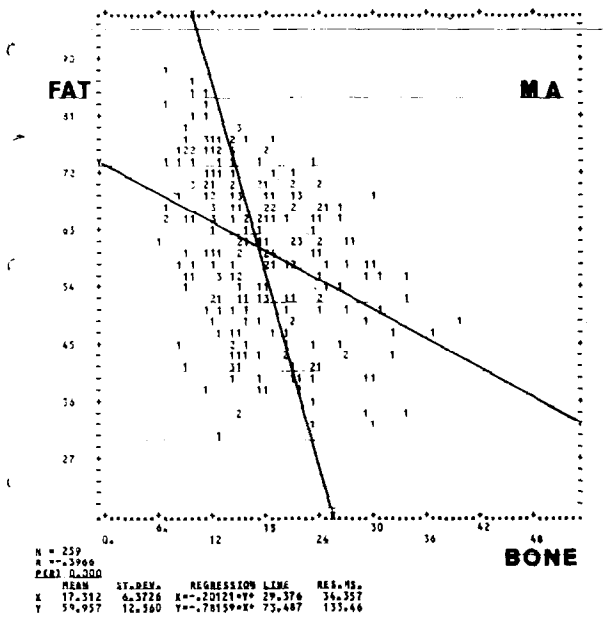

Fig. 4. Correlation of volume of trabecular bone and of fat in bone marrow atrophy (MA).

tively **(Table 6).** Different grades of atrophic changes of bone marrow and trabecular bone in aplastic anemia on one side, and primary osteoporosis and senile osteopenia on the other have in common different grades of diminution of bone marrow sinusoids. The severest depletion of sinusoids in aplastic anemia is combined with a unique increase in arterial vessels, whereas both the other conditions share an exclusively venous defect of capillarization. The histology of the geriatric group is generally similar to the primary osteoporotics. The values of the normal adolescent group were: trabecular bone 20,5 vol%; adipose tissue 18.0 vol%; arteries 6,3; arterioles 29; arterial capillaries 340; sinusoids 1543/100mm^2.

Special aspects of capillaries and sinusoids

Similar proportions of arterial capillaries and sinusoids were found in adolescent and geriatric normals and in primary osteoporosis **(Table 7).** The proportions in aplastic anemia and in normal adults were different, representing maximum arterial or venous capillarization, respectively.

Further marked differences became manifest by the quotient of the number of sinusoids directly in contact with the trabecular surface, and the dimension of this surface in relation to trabecular volume, the so-called specific trabecular surface. The highest value was found in the adolescent group, the lowest in primary osteoporosis. The other groups were not significantly different. The endothelial cells of paratrabecular sinusoids differ from their centrally located counterparts by intracytoplasmatic accumulation of PAS-positive droplets, as noted earlier (Burkhardt et al., 1984), and again in this study. The amount of glycoprotein in these endothelial cells corresponds with osteoblastic osteoid deposition.

On the other hand, in many cases of (possibly early) primary osteopenia, the atrophy of trabecular bone and the surrounding hematopoietic and capillary tissues contrasted with the cellularity of the central marrow spaces

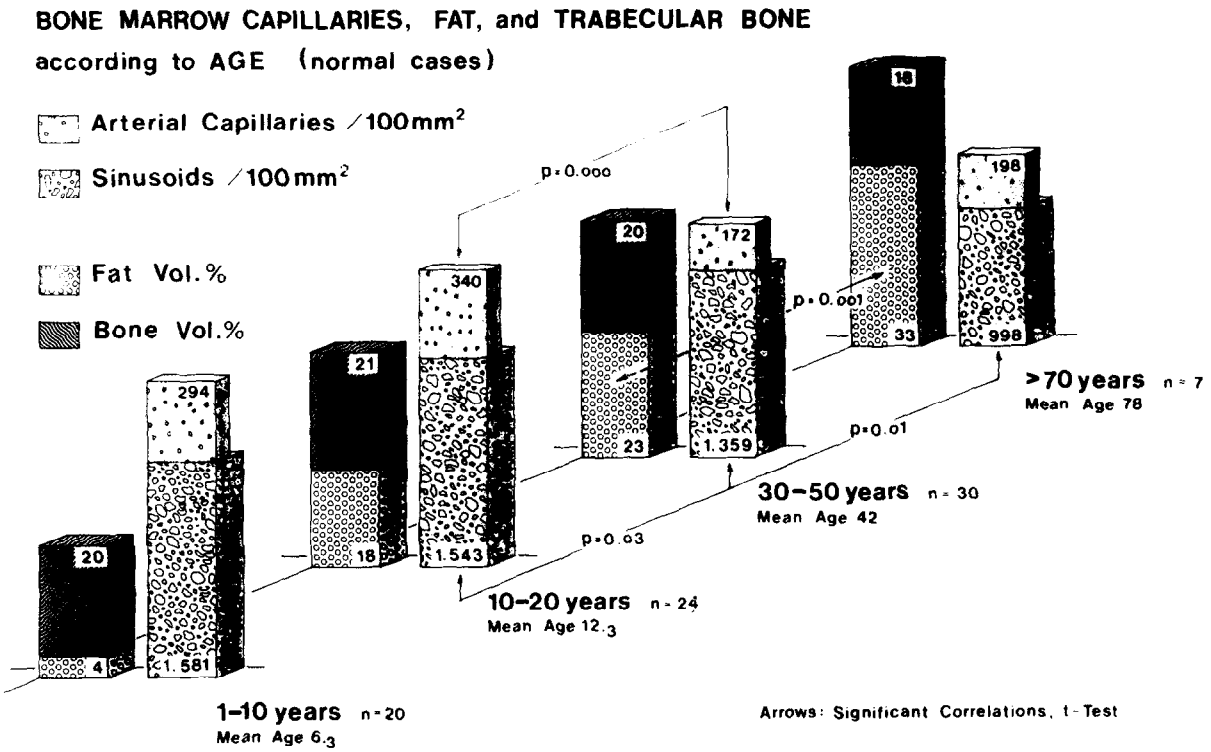

Fig. 5. Bone marrow vessel counts in four different age groups (biopsies of normal cases).

(Fig. 6a). A different role for these regions is also indicated by the preferentially paratrabecular localization of cellular proliferation, e.g. in some lymphoma groups **(Fig. 6b).**

Discussion

The results of the necropsy studies confirm that the amounts of bone and marrow found in iliac crest biopsies are likely to represent roughly those of the axial skeleton (Byers, 1977; Kerndrup et al., 1980; Chavassieux et al., 1985). Regression of hematopoiesis and trabecular bone with age is also well established (Whitehouse, 1977; Kerndrup et al., 1980), and likewise confirmed by the necropsy study. In addition concordant results of both biopsy and necropsy studies show the practicability of studying large patient groups thereby eliminating the high individual variance in morphometric parameters (Byers, 1977). The validity of the results is also supported by the congruence of clinical and biopsy data, which suggest that atrophic changes of bone and of marrow not only reflect the process of aging, but also aplastic anemia and osteoporosis; in both these conditions osseous and hematopoietic atrophy were significantly correlated, confirming earlier observations (Meunier et al., 1971; Burkhardt, 1974); moreover negative correlations of these components and of resorption surfaces have been found in transiliac biopsies of patients with hip fractures, suggesting a relationship between osseous remodeling and hematopoiesis (Lips et al., 1985).

The atrophy of the main structural components in three different conditions encouraged the search for a common, perhaps circulatory denominator. There have been few attempts so far to evaluate counts of bone marrow vessels in spite of the acknowledged importance of the specialized vascularization of this organ (Rhinelander et al., 1979; Burkhardt et al., 1984). This can be attributed mainly to technical reasons. After plastic embedding the different vascular compartments were clearly identified and counting errors reduced by adequate size, equal thickness and overall quality of the sections. Two obstacles however were not eliminated: irregular localization and spatial distribution of the larger arteries and existence of countless sinusoidal clefts in various stages of filling. Different blood filling of sinusoids due to postmortem hypostasis increased the counts by about 20%, however, without changing the proportions within the age groups. Nevertheless, the vascular figures of the necropsy cases were not included in the comparative evaluation; and major hypostasis was not observed in the biopsies. Minimal sinusoids, as seen in serial sections (Burkhardt and Gabel, 1969) and ultramicroscopy (Weiss and Chen, 1975) had to be excluded in spite of their essential function. The figures for sinusoids in this study therefore do not reflect the genuine extent of the bone marrow sinusoidal system, and the variance of the numbers is high; however significant differences among the tested groups require explanation.

Vascular supply is one of the most important requisites for biologic activity (including that of the flat bones), and low capillarization is generally taken as a sign of minor vitality (Rhinelander et al., 1979; Burkhardt et al., 1984). The age dependent diminution of the bone marrow sinusoids supports this assumption. The essential role of capillaries in hematopoiesis, in the release of blood cells, and in morphogenesis of trabecular bone has frequently been demonstrated, for example, by the influence of experimentally varied oxygenation on hematopoiesis and on bone formation (Rutishauser et al., 1960; Rhinelander et al., 1979), by

Table VI. Correlation of trabecular bone (vol%), adipose tissue (vol%), and vessel counts in biospies of aplastic anemia, primary osteoporosis, and two normal groups

Case numbers	Apl. anemia 30 ♂:♀ = 1:1	Pr. osteoporosis 30 ♂:♀ = 1:1	Normal groups 30 ♂:♀ = 1:0,5	7 ♂:♀ = 1:2,5
Age range years	18–60	27–52	30–52	70
Mean age (years)	34	45	42	78
Trabecular bone (vol%)	16.0	11.0	20.3	17.8
	S ← 0.0001 → S			
	S → 0.005 → S			
		S → 0.0001 → S		
		S → 0.004 → S		
Adipose tissue (vol%)	71.0	53.0	23.0	33.0
	S ← 0.0001 → S			
	S ← 0.0001 → S			
	S ← 0.0001 → S			
		S ← 0.0001 → S		
		S ← 0.001 → S		
			S → 0.001 → S	
Arteries /100mm²	11.6	7.4	6.6	14.9
	S ← 0.005 → S			
	S ← 0.05 → S			
		S → 0.001 → S		
			S → 0.01 → S	
Arterioles /100mm²	60	37	34	52
	S ← 0.0001 → S			
	S ← 0.003 → S			
Arterial capillaries /100mm²	385	186	172	198
	S ← 0.0001 → S			
	S ← 0.0001 → S			
	S ← 0.02 → S			
Sinusoids /100mm²	589	940	1359	998
	S → 0.0001 → S			
	S → 0.0001 → S			
	S → 0.0001 → S			
		S → 0.0001 → S		
			S ← 0.01 → S	

S ——— x → S = Significant difference; p-values (t-test).

Table VII. Correlation of arterial capillaries and sinusoids, and trabecular sinusoids in aplastic anemia, primary osteoporosis, and three normal groups

Case numbers	Apl. anemia 30 ♂:♀ = 1:1	Pr. osteoporosis 30 ♂:♀ = 1:1	24 ♂:♀ = 1:0.8	Normal groups 30 ♂:♀ = 1:0.5	7 ♂:♀ = 1:2.5
Age range (years)	18–60	27–52	10–20	30–52	70
Mean age (years)	34	45	12	42	78
Relation of art. capillaries /sinusoids	1:1.5	1:5.1	1:4.5	1:7.9	1:5.0
Trabecular sinusoids /100mm*	10.4 ± 6.5	5.2 ± 3.0	15.2 ± 7.8	8.4 ± 3.9	6.1 ± 1.9
	S ← 0.0003 → S				
	S → 0.02 → S				
		S → 0.0001 → S			
		S → 0.0006 → S			
			S ← 0.0005 → S		
			S ← 0.0001 → S		

* Sinusoids adjacent to trabecular surface; number/100mm specific trabecular surface (mm²/mm³)

Fig. 6. (a) Paratrabecular increase in fat cells; hematopoiesis confined to central bone marrow spaces, 75-year-old female with osteoporosis. ×50, Giemsa stain. **(b)** Paratrabecular infiltration in plasmacytoma with increase in fat cells in central bone marrow areas, ×50, Giemsa stain.

the hyperplasia of the sinusoidal system in polycythemia vera and by the common atrophy of the bone and marrow following obstructive, inflammatory, or degenerative circulation disturbances (Burkhardt, 1980). Our results show further that the relative numbers of sinusoids compared with the arterial capillaries are highest in early adult age, a period with steady bone and marrow functions, and that diminution of the sinusoids is common in geriatric and primary osteopenia, both accompanied by a decrease in hematopoiesis and a corresponding increase in fat cells. This observation underlines the generally accepted close relationship of these conditions.

Some additional light is shed by comparison of normal, primary osteoporosis, and aplastic anemia groups of corresponding average ages. Both osteoporosis and aplastic anemia differ from the normals by diminution of sinusoids; and in both the diminution of the trabecular bone volume and increase of adipose tissue are significantly correlated, though in different proportions. This difference is characterized by a unique ratio of arterial capillaries and sinusoids in the aplastic group. On the other hand the number of trabecular sinusoids in relation to specific trabecular surface is lowest in primary osteoporosis, and highest in the growth period. We therefore assume that a high proportion of sinusoids to arterial capillaries may be essential for hematopoiesis, and a lower proportion at a certain quantitative level for the maintenance of the trabecular bone, the increase and decrease of which are marked by corresponding changes in the paratrabecular sinusoidal branches. It is now widely accepted that there is some coordination of hematopoietic, stromal, and osseous compartments of trabecular bone, controlling reciprocal functions of regeneration and maintenance (Burkhardt, 1974), and circumscribed as "internal organization" (Frost, 1985). It may be worth while to reconsider the role of microvascularization in this context, in order to elucidate the pathogenesis of aplastic anemia and primary osteoporosis, two different disorders with a similar histologic aspect.

Acknowledgment: This work is dedicated to Professor Dr. Wolfgang Spann on occasion of his 65th birthday.

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