Bone Marrow Infarction in Sickle Cell Anemia: Correlation With Hematologic Profiles

By Paul F. Milner and Mark Brown, with the technical assistance of George A. Yoder

Bone marrow infarction was investigated by $^{99m}$Tc-sulfur colloid imaging in 42 patients with sickle cell anemia (SS) over a period of 2 yr. Marrow defects were demonstrated in 28 patients (66.6%), and in 15 (aged 19–52 yr), they were matched by roentgenographic evidence of medullary bone infarction. Repeated images showed no change in the size or site of these defects. Among 13 patients (aged 6–32 yr), all in crisis when initially examined, marrow defects were not associated with roentgenographic changes, and in many cases, repeated images showed resolution or decrease in size of the defects in 3–6 mo, even if the limb had been swollen and the marrow defect large. Among 14 patients (aged 18–36 yr), all asymptomatic at the time of study, no defects were found. Comparison of hematologic variables revealed a higher mean hemoglobin and hematocrit level among those with marrow infarcts ($p < 0.001$). High levels of HbF, or the presence of $\alpha$-thalassemia, did not protect against marrow infarction. Pulmonary fat embolism was not observed. $^{99m}$Tc-sulfur colloid marrow imaging was considered to provide more useful information in the initial management of bone pain and swelling in sickle cell crisis than either roentgenographs or conventional $^{99m}$Tc-methylidiphosphate bone images.

Although bone marrow infarction is a well recognized complication of sickle cell disease, there is little information as to the frequency of its occurrence or its relationship to the more easily detected infarction of bone. Cortical infarction of the diaphyses of the long bones, a well documented complication of sickle cell anemia in children, leads to gross roentgenographic changes that marrow infarcts may heal, with regression of the reticuloendothelial tissue.9-13 There is recent evidence from bone marrow scintigraphy that marrow infarcts may heal, with regeneration of the reticuloendothelial tissue.9,10 It is not clear, however, how frequently this happens, whether it depends on the extent of the lesion, or whether endosteal reconstruction may also be involved in the process of repair without medullary sclerosis developing. It may be that initial marrow infarcts heal, but repeated ischemic insults in the same area result in sclerosis. Do all patients suffer from these marrow-obliterating events, or are some patients exempt and, if so, how does the prevalence of other vascular events, such as priapism and proliferative retinopathy, correlate with bone marrow lesions? Is there a difference in the hematologic and clinical profile between patients who develop marrow infarcts and those who do not? Is there always a marrow infarct when the bone is painful and tender? Is there also a bone infarct when the limb is swollen or can marrow infarction alone produce this? Lastly, is there a relationship between marrow infarction and salmonella osteomyelitis and the rare, but usually fatal, complication of marrow and fat embolization?11-13

The present study was prompted by a desire to find answers to these questions about the significance of marrow infarction in sickle cell disease.

MATERIALS AND METHODS

Patients and Laboratory Methods

The 42 patients who participated in the study were considered to be homozygous for the HbS gene (SS), based on hemoglobin electrophoresis in alkaline and acid media, a positive centrifuged insolubility test (Sickle quick. General Diagnostic, Morris Plains, N.J.), $\text{HbA}_2$, measured by microcolumn chromatography (Isolab Inc., Drawer 4350, Ohio), consideration of red cell indices measured by a Coulter Model S electronic cell counter, appearance of stained blood smears, and in many cases, family studies, globin chain synthesis, and DNA analysis. The patients, ranging in age from 6 to 52 yr, had been followed for several years and seen in an ambulatory clinic on many occasions. Patients were selected for study who had severe pain in an extremity, especially if accompanied by swelling. Some patients in crisis with multiple pain sites were also included. Asymptomatic patients were selected at a routine clinic visit after their informed consent had been obtained. HbF was measured by a microchromatographic technique14 using commercial columns (Quick-sep Sickle Cell F-test. Isolab Inc., Drawer 4350, Ohio). The values are about 25% higher than values measured by alkali denaturation. F cells were evaluated in smears examined after an acid elution technique15 using commercial reagents (Bio-Dynamics/bmc, Indianapolis, Ind.) and by an immunologic procedure.16 Irreversibly sickled cells (ISC) were counted on coverslip smears of venous blood

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Table 1. Hematologic and Clinical Profiles of SS Patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>Hb (g/dl)</th>
<th>PCV (%)</th>
<th>MCV (fl)</th>
<th>MCH (pg)</th>
<th>MCHC (g/dl)</th>
<th>Ratios (%)</th>
<th>ISC (%)</th>
<th>HbF (%)</th>
<th>Clinical Course, Complications, Sites of Bone Marrow Defects in Roentgenographs</th>
</tr>
</thead>
</table>

**Group I. Patients with defects in marrow images matched by roentgenographic changes**

1. 19 M 7.8 23 82 28 34 11.4 23 4.4 1 Frequent crises and bone pain; marrow defects and bone infarcts in all long bones. Recent salmonella osteomyelitis lower R tibia.
2. 20 F* 8.2 23 91 33 36 11.1 20 6.8 Asymptomatic now; crises in past. Marrow defects and bone infarcts shaft R R tibia, lowe L tibia.
3. 20 F 8.5 25 90 31 35 12.7 24 4.1 1 Frequent crises and bone pain; marrow defects and bone infarcts in all long bones.
4. 23 F* 8.5 25 89 30 34 11.0 20 1.1 Asymptomatic now; crises in childhood. Marrow defects and bone infarcts distal L both tibiae.
5. 23 F* 8.3 26 67 21 31 5.5 8 0.5 Frequent crises. AVN R femoral head. Marrow defects and bone infarcts in all long bones.
6. 24 M* 8.8 25 81 28 33 8.2 8 2.0 Asymptomatic now; crises in past. Marrow defects and bone infarcts in all long bones.
7. 26 F 9.4 28 94 32 34 13.0 15 2.2 1 Frequent bone pain. Marrow defects and bone infarcts lower R femur, distal L both tibiae.
8. 26 M 9.5 28 80 27 33 7.7 5 2.2 1 Fractures. Marrow defects and bone infarcts shaft R femur, both distal femora, proximal R tibia and distal L tibia. ASMN humeral heads.
9. 27 M 9.6 28 95 32 33 12.0 9 6.2 1 Frequent bone crises and bone pain. Marrow defects and bone infarcts in all long bones.
10. 27 F* 7.1 26 98 33 34 14.7 13 4.5 1 Asymptomatic. ASN femoral heads; protheses. Marrow defects and bone infarcts proximal femora, proximal and distal R tibia.
11. 28 M* 8.4 26 75 24 32 10.4 14 0.5 1 Frequent pain crises and bone pain. ASN femoral heads and humeral heads. Marrow defects and bone infarcts R humerus, both femora, and R tibia.
12. 28 F* 10.1 31 87 28 34 7.3 3 6.8 1 Frequent bone pain. Multiple sites healed osteomyelitis. Marrow defects and bone infarcts L humerus, both femora, both tibiae. Recent salmonella osteomyelitis L humerus. Functioning spleen.
13. 29 F* 8.4 25 85 28 34 9.6 14 1.6 1 Frequent crises and bone pain. ASN femoral heads, L protheses. Marrow defects and bone infarcts both humeri, shaft L femur, and L tibia.
14. 35 M* 8.9 27 94 31 33 10.5 7 11.0 1 Asymptomatic now; crises in past. Marrow defects and bone infarcts R humerus, both distal femora, and both tibiae.
15. 52 F* 7.0 20 88 33 35 8.3 20 4.0 1 Asymptomatic now; crises in past. Marrow defects and bone infarcts proximal L femur, both distal femora, both proximal tibiae, and shaft L tibia.

**Group II. Patients with fresh marrow defects associated with bone pain**

16. 6 M 6.3 19 80 25 31 25.0 25.0 4.0 Infarcts shaft R humerus, shaft R femur, distal L femur. Functioning spleen, recent blood transfusion. 11 mo: all defects resolved.
17. 15 F 9.1 26 92 32 34 12.6 15 12.2 Small defects both humeri, mid shaft, and distal R femur, entire L tibia. Distal L femur. 3 mo: defects both femora resolved; defect L tibia smaller.
18. 17 M 9.1 26 91 32 34 7.8 14 16.0 Defects both proximal femora and distal R femur, proximal R tibia. 6 mo: AVN R femoral head. 8 mo: all defects resolved. Prisapram. Necrosis R femoral head.
19. 17 F 6.6 20 81 27 33 10.7 20 2.0 Pain distal L tibia. Small defect distal L tibia. 12 mo: recurrent pain L tibia. 5 mo: larger defect L tibia. 24 mo: defect still present; no x-ray changes.
20. 19 M 7.4 22 82 27 33 10.1 15 2.4 Marrow defect shaft L humerus, proximal L tibia; frequent bone pain. 6 mo: resolution L humerus; new defects distal R humerus, shafts of both tibiae. 12 mo: resolution of all defects.
21. 20 F 10.2 30 91 31 34 7.0 8.7 Defect mid-shaft R humerus. 5 mo: no change, normal bone on x-ray.
22. 22 F 10.4 23 67 23 34 3.3 2 11.2 Defect in L tibia. 12 mo: large defects both distal femora and proximal tibiae. 24 mo: all defects resolved. Functioning spleen.
24. 26 M 10.1 30 84 28 33 7.4 10 2.3 1 Defects in shaft L femur, proximal R, and L tibiae. 14 mo: all defects resolved.
25. 26 F 9.2 27 84 28 34 6.3 8 2.5 1 Defect in proximal and distal R femur, distal left femur, both proximal tibiae. 12 mo: resolution typical defects, decreased size of femoral defects. Functioning spleen.
26. 30 M 9.3 26 98 35 35 8.5 20 4.0 1 Defect shaft R humerus. 12 mo: decrease in this defect, new defects both tibiae. Prisapram.
27. 32 F 7.6 22 91 31 34 10.0 2 2.2 1 Defect proximal R tibial metaphysis, shafts both tibiae. 6 mo: resolution tibial metaphyses, no change in tibial shafts.
28. 32 F 7.4 22 91 30 33 11.4 9 1.7 1 Small defect mid R tibia. 4 mo: pain crises, defect lower R both tibiae. 8 mo: no change. No x-ray changes.

**Group III. Asymptomatic patients with no marrow defects or roentgenographic changes in the long bones**

29. 18 M 7.3 20 94 34 38 11.9 20 6.8 No crises; prisapram, ankle ulcers; no marrow defects; normal vertebral bodies.
30. 18 M 9.1 26 100 35 35 9.3 15 13.2 Frequent back and chest pain; no severe crises; no marrow defects; typical changes in vertebral bodies.
31. 21 F 7.8 23 96 33 34 13.4 15 5.1 Frequent pain complaints, analgesic usage. 1 Small defects mid-shaft both tibiae; no roentgenographic changes; normal vertebrae.
after oxygenation by rocking with room air for 5 min. All the counts were performed by the same observer. The values for all laboratory tests listed in Table 1 (except for patients 2, 16, and 21) are average figures of many investigations carried out during routine out-patient attendances over a period of more than 4 yr.

99mTc-Sulfur Colloid Marrow Imaging

Patients were injected intravenously with 8 mCi 99mTc-sulfur colloid, and after 20 min, the whole body images were obtained using a Picker 4/15/61 Dyna camera, an ultrafine collimator, and an Omniview 4 whole body imaging system set at 1.2 (a table speed of 7.2 in/min). A flexible lead shield was placed over the liver to reduce counts and scatter from this area. At least five high resolution images were also obtained, including the pelvis and both femora, knees, legs below the knees including ankles, and right and left arms bent at the elbow.

Roentgenographic Investigations

Standard roentgenographic views of the long bones and vertebral bodies were obtained. Bone changes, when present, were interpreted as bone infarcts when they had the characteristics of medullary bone infarction described in the literature.4-8

Statistical Methods

Student's t test was used to find the significance of differences between means for laboratory values among patients who had marrow infarcts and those who had not. MCHC values were also compared after correction for reticulocytes by the formula of Embury et al.13 

\[
\text{MCHC}_{\text{Corr}} = \text{MCHC}_{\text{Meas}} - \left( 29 \times \text{retic. fraction} \right) / (1 - \text{retic. fraction})
\]

Because values for reticulocytes and ISC do not form part of a normal distribution, log, of the figures (using the empirical constants of Hawker et al.),14 % retics + 1, % ISC + 10 were employed to assess significances of differences between means.

RESULTS

99mTc-sulfur colloid is removed from the blood by the reticuloendothelial elements of the bone marrow.10 In sickle cell anemia, as in other severe hemolytic anemias, the bone marrow is extended into the long bones, and the images obtained (Fig. 1) indicate the degree of this hypertrophy, which has a symmetrical distribution. Infarction of the reticuloendothelial tissue, or blockage of the blood supply to that tissue, produces an asymmetrical photon-deficient area referred to here as a defect in the marrow image. The extent of the defect was best judged in the high resolution images (Fig. 2), the whole body scans being used mainly to find areas of suspected defects.

The 42 patients, whose bone marrow integrity was assessed by 99mTc-sulfur colloid marrow imaging, can be divided into three groups (Table 1). In the first 15 patients (group I), 6 of whom were asymptomatic when initially studied, the marrow defects were matched by roentgenographic changes in the bones indicative of medullary infaracts. Repeat marrow images over a 2-yr period showed no change in the size or sites of the marrow defects. The 13 patients in group II, who were all studied during pain crises, showed large or small defects in the marrow in 99mTc-sulfur colloid images but did not have roentgenographic evidence of bone infarction. Repeat marrow imaging during the 2-yr study showed resolution, or a decrease in size, of most of the marrow defects, and roentgenographic changes did not develop. Group III was comprised of 14 patients who had no obvious marrow
defects in $^{99m}$Tc-sulfur colloid images and no roentgenographic evidence of infarction in their long bones.

$^{99m}$Tc-Sulfur Colloid Marrow Images

Extension of bone marrow into the skull, clavicals, acromial processes, ribs, spine, pelvis, and long bones of all four limbs was a prominent finding in all cases (Fig. 1). In the setting of extended marrow, defects in the marrow images of the long bones tended to stand out and were more clearly delineated in the high resolution views (Fig. 2). Heavy uptake of radionuclide at the metaphyses was frequently seen in adults as well as adolescents. Small defects were more easily seen in larger bones, and it was not always possible to be sure of the complete integrity of the marrow in the radii, ulnae, and fibulae. Decreased uptake of radionuclide in the region of a femoral head was sometimes seen in the absence of clinical or roentgenographic evidence of avascular necrosis. Hepatomegaly was commonly observed, but a spleen image was seen in only four patients: a 6-yr-old child with gross splenomegaly and hypersplenism (patient 16), who had recently had a blood transfusion, and three adults who had a high level of HbF and/or genes for concomitant $\alpha$-thalassemia (patients 12, 22, 25).

Patients With Defects in Marrow Images

Bone marrow defects were found in 28 of the 42 patients studied (66.6%). Ten asymptomatic patients and 5 who were in a pain crisis when initially studied...
had defects that were matched by roentgenographic bone changes (group I). Six of the 15 patients in this group were restudied on several occasions over 2 yr without a change in the appearance of the $^{99m}$Tc-sulfur colloid images. Some of these patients were seen on numerous occasions with recurrent pain in bones that were known to be the sites of medullary infarcts, and two patients developed salmonella osteomyelitis in areas of old medullary infarction during the period of the study. Four had avascular necrosis of the head of the femur, bilateral in three cases, and sclerotic changes in the humeral heads were present in these three and two other patients.

**Patients With Recent Marrow Infarcts**

Thirteen patients (Table 1, group II) developed marrow defects during the period of observation. Some of these patients had previous $^{99m}$Tc-sulfur colloid images to compare with images taken during episodes of bone pain and swelling. Images were repeated during subsequent crises and frequently showed new lesions. $^{99m}$Tc-MDP and $^{67}$Ga images were also obtained on occasions when it was necessary to rule out osteomyelitis. Roentgenographs of bones in which marrow defects were present showed no localized changes initially or after intervals of up to 2 yr. Roentgenographic abnormalities, however, were sometimes present and included thinning of the cortex, osteopenic areas, and small areas of increased density, particularly in the cancellous bone of metaphyses and humeral and femoral heads, but these did not correspond to photopenic areas in the marrow images.

**Resolution of Marrow Defects**

Nine patients in group II (Table 1) showed complete or partial resolution of marrow defects. In some cases defects resolved in 3–6 mo, only to be succeeded by new defects either at the same site or elsewhere. Patient 20 (Table 1) illustrates this point. He had an initial $^{99m}$Tc-sulfur colloid marrow scan in March 1980, which showed a large defect involving almost the entire shaft of the left humerus and a smaller defect in the left tibia. Two months later, when he was no longer having any pain, there was no change in the size or site of the defects. In November 1980, during another crisis, the defect in the left tibia had resolved and that in the left humerus had almost resolved, but there was now a new defect in the distal right tibia. One month later, again in a crisis, another new defect was seen in the right humerus, and both tibiae showed multiple focal defects. He remained free of pain crises for the next 6 mo, and in June 1981, $^{99m}$Tc-sulfur colloid marrow images showed complete resolution of all defects. Both humeri appeared roentgenographically unremarkable at this time, but some increased density was noted in the proximal tibial epiphyses.

Resolution of marrow defects in some of these subjects is illustrated in Fig. 2. Avascular necrosis of the femoral head occurred in only one subject in this group (no. 17, Table 1). A photopenic area was seen in the right femoral head in initial $^{99m}$Tc-sulfur colloid images, made during a bone pain crisis, but symptoms did not develop in the hip joint until 4 mo later when roentgenographs confirmed early necrosis. Only 6 of the 13 patients in group II had the end-plate deformities of the femoral head, but in two of the six male patients in this group had experienced more than one episode of priapism, but none of the patients had ever had an ankle ulcer.

Among the 28 patients, marrow defects occurred in 36% of humeri, 61% of femora, and 80% of tibiae. Among those with roentgenographic evidence of infarction, 100% of tibiae were involved. However, resolution of marrow defects was observed in all 3 bones.

**Patients With No Marrow Defects**

Fourteen of the 24 patients (58%) who were asymptomatic at initial studies showed extended bone marrow throughout the long bones without any defects (Table 1, group III). Five were in the fourth decade, 7 were in the third decade, and 2 were 18 yr old. None of these patients had avascular necrosis of humoral or femoral heads or infarcts in those long bones examined. However, typical end-plate deformities of the vertebral bodies were present in 3, and 6 others showed osteosclerotic changes of increased trabeculation. One patient had severe proliferative retinopathy, 3 had recurrent priapism, and 4 had recurrent ankle ulceration. None of the patients in this group had a pain crisis involving localized bone pain since the $^{99m}$Tc-sulfur colloid images were recorded over a year ago.

**Variance in Hematologic Parameters**

Patients who had infarcted their marrow had a higher mean PCV and hemoglobin level (Table 2). The MCHC, however, tended to be lower in this group, and correcting for the difference in reticulocyte count did not alter the significance of this difference. The mean MCV and MCH were also lower among patients who had infarcts. The lower PCV and Hb level in the noninfarcted patients was due to increased hemolysis, as indicated by higher reticulocytes and ISC counts.

Among the patients with permanent infarcts and avascular necrosis (Table 1, group I), HbF was low, but among those in group II, there were 4 patients who had more than 10% HbF (patients 17, 18, 22, 25).
99mTc sulfur colloid images, in 5 had roentgenographic studies using 99mTc-methyldiphosphate, helps to resolve this difficulty. Additional scintillation with RE tissue. Among patients with recent infarcts, there were no statistically significant differences in PCV, Hb, MCV, MCH, or MCHC between groups I and II.

**DISCUSSION**

Bone marrow scintigraphy, using the reticuloendothelial (RE) labeling radionuclide 99mTc-sulfur colloid, is an easily performed practical procedure for demonstrating marrow infarction in sickle cell disease. The greatly expanded bone marrow shows up as a symmetrical increased uptake of radionuclide throughout the axial skeleton, the skull, the ribs, and all the long bones, often showing extension into the small bones of the wrists and feet. Infarcts are detected as photopenic areas with sharply defined borders. Distinction between old and new infarcts, however, cannot be made with a single study, but correlation with the roentgenographic appearances, plus repeated RE scintigraphy at a later date, helps to resolve this difficulty. Additional scintigraphic studies using 99mTc-methylidiphosphate (99mTc-MDP) may sometimes be helpful in distinguishing a fresh infarct from an old infarct.

Among the 28 patients with marrow defects in 99mTc sulfur colloid images, 15 had roentgenographic evidence of bone infarction and repair which, in some cases, may have dated back many years to lesions acquired in childhood. Repeat scans in 5 patients over a 2-yr period showed no change in marrow defects at these sites, and presumably the lesion precludes repopulation with RE tissue. Among patients with recent marrow infarcts, however, complete resolution of some of the defects was observed in about 3 mo, while other defects showed a decrease in size and were resolved in 6 mo to 1 yr. In those who are still showing marrow defects, no roentgenographic changes are at present apparent at these sites. It may be that calcification of these areas will ultimately occur. Very fresh lesions gave normal 99mTc-MDP bone images but showed increased uptake when repeated after about 7 days, indicating that damage to bone trabeculae probably frequently accompanies marrow infarction. However, osteosclerotic lines parallel with the endosteal surface, the so-called “bone within a bone” appearance, were observed in roentgenographs of bones in which marrow defects had completely resolved, indicating that damage to bone structure does not preclude marrow regeneration. Patches of increased density in metaphyseal areas, particularly at the knees and in humeral heads, were also seen in the absence of marrow defects.

Diaphyseal marrow infarcts tended to be more frequent at the proximal or distal thirds, i.e., adjacent to the metaphyses (Fig. 2). Diggs, in a description of the variety of pathologic changes that can be seen in the infarcted bones of adults with sickle cell disease, stated that he often found large areas of necrosis in the shafts of long bones that were not visible on roentgenograms. He also noted that this typically occurred in the proximal and distal thirds of the diaphysis, the remainder of the bone being filled with hypercellular marrow. Bohrer also noted a predilection for these sites, which he calls the intermediate segments, and suggested that there may be less collateral circulation from periosteal vessels there (endosteal bone) than at either the more central diaphysis (periosteal bone) or at the metaphys's (endochondral bone).

Closure of epiphyses is delayed in many patients with sickle cell disease, and hyperemia beneath the growth plate is responsible for an increased rate of growth at the ends of the long bones, resulting in the characteristic long, slender limbs and digits. At the time of closure of the epiphyses, the metaphyseal vessels from the nutrient artery penetrate the growth plate, and vascular connections are established between the epiphyseal and metaphyseal system of vessels. The intense uptake of all three radiopharmaceuticals, including 67Ga-citrate, by the metaphyseal areas may be due to increased bone perfusion in sickle cell disease. Metaphyseal infarcts were not as frequent in our material as infarcts in the diaphyses. The appearance of juxta-articular infarcts in 99mTc-sulfur colloid images has been described by Alavi et al. and, because of their proximity to the articular cartilage, are frequently associated with joint effusions.

Pain, tenderness, and even swelling sometimes

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**Table 2. Comparison of Hematologic Data Among Patients With and Without Marrow Infarcts**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Groups I and II (n = 28)</th>
<th>Group III (n = 14)</th>
<th>t</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g/dL)</td>
<td>8.58 ± 1.11</td>
<td>7.93 ± 0.81</td>
<td>4.12</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>PCV</td>
<td>25.2 ± 3.0</td>
<td>23.3 ± 3.1</td>
<td>3.74</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>MCV</td>
<td>86.5 ± 8.0</td>
<td>93.6 ± 8.2</td>
<td>5.66</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>MCH</td>
<td>30.3 ± 3.3</td>
<td>30.1 ± 3.4</td>
<td>2.72</td>
<td>p &lt; 0.01</td>
</tr>
<tr>
<td>MCHC</td>
<td>33.5 ± 1.1</td>
<td>34.5 ± 0.9</td>
<td>6.01</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>MCHC (±)</td>
<td>34.0 ± 1.3</td>
<td>35.3 ± 1.1</td>
<td>6.93</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>Log,(retics + 1)</td>
<td>2.36 ± 0.32</td>
<td>2.52</td>
<td>0.20</td>
<td>3.61</td>
</tr>
<tr>
<td>Log,(ISC + 10)</td>
<td>3.10 ± 0.31</td>
<td>3.22</td>
<td>0.27</td>
<td>2.5</td>
</tr>
</tbody>
</table>

Transformed values: *10.6%, †11.5%, ‡12.2%, §15.0%
occurred around bones known to show roentgenographic evidence of medullary bone infarction and, at such sites, corresponding marrow defects were always present in $^{99m}$Tc-sulfur colloid images. Bone imaging with $^{99m}$Tc-MDP and $^{67}$Ga images also showed corresponding, but usually smaller, defects indicating avascular areas. This is an important point because, when osteomyelitis develops in these areas, both of the latter scans usually show increased uptake of radionuclide around the infected infarct. Since the majority of cases of acute focal bone tenderness are caused by infarction alone, $^{99m}$Tc-sulfur colloid marrow imaging provides maximum information, and these procedures should initially take precedence over conventional roentgenographs. If osteomyelitis is suspected, further investigation with $^{67}$Ga imaging can often be helpful in deciding whether to perform surgical exploration.

The absence of marrow infarction in a subpopulation of patients aged 18–36 yr is in keeping with the wide spectrum of severity in this disease. Alavi et al. found that 9 of 17 asymptomatic patients (52.9%) did not have marrow defects, but their ages were not stated. Our patients were not selected in a random way and the numbers are too small to be of value in predicting prevalence in a larger sample, but 14 of 24 asymptomatic patients (58%) showed no defects in extended marrow in long bones. One might expect to find a high frequency of concomitant $\alpha$-thalassemia or high levels of HbF among this group (Table I) but, on the contrary, such patients were more common among the group who had suffered marrow infarction.

The group without infarcts had a significantly lower mean hemoglobin and PCV (Table 2), and their higher reticulocyte counts suggest a more severe hemolytic process as the reason for this. The MCHC was, surprisingly, lower in the group with infarcts than in those without infarcts, and the correction of Edbury et al. (MCHC$_{E.R}$) increased the difference. It would seem that MCHC reflects the ISC numbers in these circumstances, and correcting for reticulocytes only accentuates this effect. Mean MCV was smaller and MCH lower in the group with infarcts, probably reflecting the incidence of concomitant $\alpha$-thalassemia, which was indicated by globin chain synthesis in two of the patients in this group (patients 5 and 22).

Among patients who experienced multiple widespread marrow infarcts, there were 4 with HbF levels higher than 10% (Table 1, group II). Three of these, however, showed considerable resolution on follow-up studies. Among those with marrow defects associated with more permanent medullary infarction (group I), average HbF levels were lower, and 5 had avascular necrosis of the femoral and/or humeral heads, consistent with the observations of Hawker et al. that these lesions are more commonly associated with a high total hemoglobin level and a low fetal hemoglobin level. However, since HbF is unevenly distributed among the red cells in sickle cell disease, a group with a high level of HbF may encompass two subgroups: those in which the HbF is more evenly distributed (although not present in every red cell, as in the African type of HPFH) and those in which it is less evenly distributed. The former group is likely to be the one with the greatest protection against serious complications, as seems to be the case in sickle cell anemia among the Shiite Arabs. Such a subgroup has yet to be clearly defined among the black population, but was suggested by the F-cell smears in two patients in group III.

The bone marrow seems to be a very vulnerable tissue in sickle cell disease, which suggests that the microcirculation at this site may have special features. Very little is known about the terminal arterioles of the nutrient artery in human long bones or the way they connect with the sinusoids of the bone marrow. Studies in pigs, rats, and rabbits, however, suggest that the bone marrow sinususes receive arterial blood from two sources. The nutrient artery divides in the myeloid cavity and most of its branches enter the bony shaft as capillaries in the endocortical region, few supplying the marrow directly. The bone capillaries then turn back towards the myeloid cavity and form connections with the sinusoids of the marrow at the medullary–endocortical junction. The second source of arterial blood comes from the periosteal network of capillaries that penetrate the bone and run in the Haversian canals, anastomosing with the capillaries from the nutrient artery at the osteomyeloid junction. While the outer cortex is supplied exclusively by periosteal vessels, the endocortical bone has a dual blood supply by means of these anastomoses.

One can only speculate on the exact site or sites of microvascular blockage that cause marrow infarction in sickle cell disease. The bone capillaries that connect with the marrow sinususes are exceptionally small, and selective blockage could damage the marrow primarily, or damage both marrow and endocortical bone trabeculae. Moreover, blockage of microcapillary efferents distal to their periosteal capillary connections could interfere with the periosteal arterial drainage leading to periosteal edema and tissue swelling without necrosis of bone. It could be that in the young child, the periosteal circulation is less well developed in the outer cortex, which relies more on the supply from the nutrient artery, thus accounting for the more frequent cortical infarction described in children and produced in the long bones of immature animals by obliteration of the nutrient artery.
In venous sinusoids of the medullary cavity, with a rise in intramedullary pressure leading to necrosis in much the same way as in acute osteomyelitis. Because of the nature of the molecular substitution in the HbS molecule, it has always been taken for granted that sickling is an event that affects mainly the venous side of the circulation. The bone marrow may thus be like the corpora cavernosa in its vulnerability to deoxygenation and sickling. Recently, however, the finding of HbS polymer in red cells in the arterial circulation, sufficient to prevent their passage through the precapillary arterioles, has helped explain the occurrence of proliferative retinopathy in sickle cell disease and may also explain marrow infarction in the ribs and long bones.

This study has provided answers to some of our questions. Not all SS patients get marrow infarcts. Priapism and retinopathy were not prevalent among patients with marrow infarcts, but the study population was too small and selected for any conclusion to be drawn. A statistically significant difference was found in the hematocrit and hemoglobin level, those who escape marrow infarction tending to have a lower hematocrit and to show evidence of more severe hemolysis. In two instances 99mTc-sulfur colloid imaging failed to show a marrow defect in a painful tender bone, but this was exceptional. Severe pain and swelling were not incompatible with marrow infarction alone, as complete resolution occurred without the development of roentgenographic evidence of bone infarction. Although pulmonary infiltrates were commonly seen in patients who were having a severe pain crisis, no case of fatal or severe pulmonary embolism occurred despite multiple large marrow defects. Osteomyelitis occurred at sites of previous bone infarction, but not in patients with fresh marrow infarcts.

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