Orthopaedic Manifestations of Sickle-Cell Disease

MICHAEL H. HUO, M.D.,* GARY E. FRIEDELANDER, M.D.,b AND JAMES S. MARSH, M.D.©

*Resident in Orthopaedic Surgery and Rehabilitation, Yale University School of Medicine; bProfessor and Chairman, Department of Orthopaedics and Rehabilitation, Yale University School of Medicine; ©Assistant Professor, Department of Orthopaedics and Rehabilitation, Yale University School of Medicine, New Haven, Connecticut

Received January 12, 1990

Sickle-cell disease is a well-recognized clinical entity. The pathophysiology of this hemoglobinopathy has been described in detail by numerous investigators since the first case report appeared in 1910. Orthopaedic manifestations of sickle-cell disease account for much of the morbidity associated with this disorder, including pain, osteonecrosis, arthritis, and sepsis. Effective management of these bone and joint sequelae reflect accurate diagnosis, understanding of this disorder's pathophysiology, and knowledge of available medical and surgical treatment alternatives.

In this review, the authors summarize the major orthopaedic manifestations of sickle-cell disease with special emphasis placed upon osteonecrosis and osteomyelitis, since these conditions are the most disabling and serious complications in patients with sickle-cell disease.

INTRODUCTION

Prior to the first report in 1910 by Herrick of an anemic black medical student from Grenada, sickle-cell disease was misdiagnosed because its cardinal manifestations were common to other disorders [1]. Repeated juxta-articular pain resembled acute rheumatism. Jaundice and hemolysis were frequently seen in patients with malaria. Within three months of the original report, a second case of sickle-cell disease was described by Washburn, and during the next 30 to 40 years our understanding of this disease considerably expanded [2].

Vaso-occlusive phenomena were appreciated in the early 1930s when infarcts of the pulmonary and renal systems were discovered. Bone infarction and osteonecrosis of the femoral head were described in the 1940s by Danford [3]. In 1949, Pauling and his colleagues found that all the hemoglobin in patients with sickle-cell disease showed an abnormal electrophoretic pattern [4]. This discovery was the most significant milestone in understanding the pathogenesis and pathophysiology of this disease.

ETIOLOGY AND PATHOPHYSIOLOGY

There are few disorders of man whose etiology can be traced to as basic a level as sickle cell disease. In 1957, Ingram elucidated the biochemical defect in sickle-cell disease by digesting hemoglobin with trypsin and studying the peptides by electrophoresis and chromatography [5]. Sickle hemoglobin results from substitution of thymine...
for adenine in the glutamic acid codon of DNA which, in turn, results in a substitution of valine for glutamic acid in the beta-6 position of the hemoglobin molecule [6].

The hemoglobin molecule consists of four subunits, two alpha and two beta. The interaction between these subunits is dependent upon forces such as hydrogen bonding and covalent cross-linkages between the side chains of the amino acids in the subunits. Hemoglobin molecules also exist in an oxygenated and a deoxygenated state. It has been shown that deoxygenated hemoglobin S molecules have a high tendency to aggregate.

Electron microscopy had shown that hemoglobin S molecules will aggregate into microtubules. The exact nature of these microtubules has not been determined, but a solid structure of fourteen strands is the most widely accepted hypothesis [7]. Sickling is initially reversible with correction of the adverse conditions that have precipitated the event. When a cell sickles and unsickles repeatedly, however, its membrane is permanently altered. These end-stage cells are primarily responsible for the clinical manifestations seen in patients with sickle-cell disease [8]. Although the primary defect in sickle-cell disease is clearly in the hemoglobin molecule, secondary alterations in red cell metabolism and cell membrane structure and function also occur. For example, ionic imbalance and changes in the surface charges at the cell membrane may contribute to the vaso-occlusive phenomenon in sickle-cell crisis [9].

DIAGNOSIS

The inheritance pattern of sickle-cell disease is autosomal recessive, and major genotypes are SS (homozygous), SC (sickle-hemoglobin C), and sickle-beta thalassemia disease. The incidence of sickle-cell trait (SA) has been estimated to be approximately eight to ten percent among American blacks while the homozygous population is in the range of 0.2 to 0.5 percent of this same group. Sickle-cell trait may reach a 20 percent incidence in Western Africa [10].

Diagnosis of the major genotypes of sickle-cell disease is relatively simple, but differentiation of the various subtypes is more complex, requiring a variety of sophisticated laboratory procedures. The difference in migration patterns of normal and hemoglobin S seen during electrophoresis is due to the two fewer negative charges resulting from the substitution of valine for glutamic acid in the abnormal molecule.

BONE AND JOINT MANIFESTATIONS

Sickle-cell disease presents clinically as a multi-system disorder. One of the major organ systems involved and one that has contributed to much of the morbidity is the musculoskeletal system [11].

Bony changes seen in the sickle-cell disease can be grouped into two major types: those due to bone marrow hyperplasia secondary to the profound and prolonged anemia, and those changes due to ischemic necrosis of bone and its complications. One must also realize that the bony manifestations of sickle-cell disease are extremely variable and represent a wide spectrum of changes. Different individuals will follow different clinical courses, and, in any one person, the radiographic and pathological manifestations change over time as well.

It is now recognized that the thinned bony cortices, diminution and coarsening of the medullary trabeculae, and widened marrow cavities in the tubular bones of sickle-cell patients are all manifestations of increased erythropoiesis secondary to anemia [12–14]. This pattern is primarily seen in children. The demand for increased erythropoies-
sis leads to an expanded marrow distribution within individual bones and a spread of this activity to bones not normally occupied by productive marrow. In adults with sickle-cell disease, red marrow continues to fill the medullary cavities of long bones. This condition is in contrast to normal adults, where the active marrow is limited mainly to the axial skeleton.

Microscopically, the bone marrow is hypercellular and contains little fat. All cell lines are increased, including the erythroid, granulocytic, and megakaryocytic systems. Red marrow may even extend into the Haversian and Volkmann canal systems of the long bone cortices. This extension accounts for many of the radiographic changes observed. Enlargement of the marrow-containing medullary canal can produce a squared metacarpal. In the skull, the diploic space is widened, and there may be a loss of definition of the outer table and an hair-on-end appearance. This striking radiographic finding is seen in approximately 5 percent of patients. A loss of the normal concave margin of the distal femur can result in the so-called flask-shaped deformity. Nutrient foramina may be enlarged secondary to the hyperdynamic circulation, extreme cortical thinning may lead to spontaneous pathologic fractures, and acetabular protrusio may be present in some older patients [13-15].

Marrow expansion in the vertebrae leads to a characteristic radiolucency and prominence of the remaining vertical trabeculae. Smooth biconcave and step-like depressions are seen in the vertebral bodies, which are often flattened with an increased width-to-height ratio and an apparent enlargement of the pedicles. Some have attributed vertebral body deformities to weight bearing on osteoporotic and infarcted bones [16] (Fig. 1). Sections of the vertebrae, however, do not show any evidence of infarction. An alternative theory of limited growth of the central area due to impaired nutrient artery flow caused by marrow expansion in conjunction with normal growth of the vertebral margins supplied by the metaphyseal arteries seems a more plausible explanation. These vertebral changes have been reported in patients as young as nine months of age, and in most series reached a 40 percent incidence in older patients [16-18].

Changes reflecting bone marrow hyperplasia are usually asymptomatic and can be seen in other forms of anemia as well as sickle-cell disease. Chronic anemia causes alterations in bone marrow distribution and a distorted bony architecture secondary to marrow hyperplasia. Although these changes are not directly related to the development of ischemic osteonecrosis, they probably play a role in determining the sites, distribution, and late bone changes observed following medullary and cortical infarcts.

Infarction

Any portion of a long bone can be the site of ischemic infarction, and several locations in the same bone may be involved at the same time (Fig. 2). Some knowledge of bone circulatory dynamics is important in understanding the pathogenesis and healing of bone infarcts and the different manifestations of bone ischemia that occur at different ages and in various portions of the bone [19,20].

Most authors agree that there are four important sources of blood supply to the tubular bones: (1) Nutrient arteries supply the medullary bone and the endosteal aspect of the cortex. (2) Periosteal vessels perforate the cortex throughout its length and circumference supplying the outer cortex. (3) Metaphyseal perforators are branches of the periosteal system; they supply the peripheral portion of the metaphysis and the growth plate. (4) The epiphyseal arteries supply the epiphysis.
Each long bone can be divided into five sections: a large central segment, two small metaphyseal segments, and two meta-diaphyseal or intermediate zones. The most common sites of acute infarcts in sickle-cell patients are at the intermediate segments. Potential circulation to the cortex is the greatest at the metaphysis. It has been demonstrated that the periosteal blood flow can be reversed in the case of nutrient artery interruption; this procedure may protect the diaphyseal cortex from infarcts. In the intermediate zone, collateral circulation from the perforating metaphyseal vessels may be either insufficient or compromised in sicklers, thus leading to infarction. Localized infarcts occur primarily in younger children in whom the periosteal source of collateralization has not yet become well developed [16,17,21].

Clinically, lesions of acute infarction present with acute localized pain, swelling, and fever. Children younger than age eight to ten years often develop acute dia- metaphyseal infarcts associated with marked pain and swelling. A more gradual and often asymptomatic marrow ischemia and necrosis occurs in older age groups. In a review of 198 diaphyseal infarcts in 81 Nigerian patients, Bohrer reported that 91 percent of the lesions occurred before age nine. The tibia was the most common site of involvement, and bilateral infarcts were noted in 23 percent of the cases [16,22]. Malignant transformation of the infarcts to, most typically, malignant fibrohistiocytoma, is possible but only rarely reported in sickle-cell disease.
Painful Crisis

Painful crisis is one of the most characteristic manifestations of sickle-cell disease and consists of pain in the extremities, back, chest, or abdomen. It is usually associated with a febrile episode, making distinction from acute infection difficult. Acute bony infarction is usually seen in the meta-diaphyseal region, and multiple sites are commonly involved. Juxta-articular areas are especially vulnerable and accompanied by joint effusion. The pain is usually bilateral and sometimes migratory when extremities are involved [11,16,22].

Painful crises usually start at five years of age and progress in various unpredictable patterns until after age thirty. Precipitating factors include: infection, cold temperature, acidosis, pregnancy, hypoxia, and dehydration [23]. Necrotic marrow material, such as fat globules and even spicules of bone, may embolize to small vessels in the brain, lungs, or kidneys [24]. The increased marrow pressure from marrow hyperplasia and the acute-phase reaction to infarction may predispose that site to subsequent hematogenous infection.

Hand-Foot Syndrome

A well-known clinical entity seen in sickle-cell disease patients is dactylitis, also known as hand-foot syndrome. This syndrome was originally described by Danford and subsequently characterized by Smith [25]. In an earlier review by Watson et al. (1963), 66 percent of the cases reported in the series of 52 patients were younger than two years of age [26]. Estimates of the prevalence of this condition have varied from 11 percent to as high as 80 percent in the African population. Stevens in a recent study
from Jamaica reported an incidence of 8 percent by the age of six months, 24 percent by one year, and 45 percent by two years [27]. This early age of involvement implies that dactylitis may often be the presenting symptom of patients with sickle-cell disease.

The pathophysiology again reflects ischemic infarction. As previously mentioned, active marrow is present in the small bones of the hands and feet in young children. Clinically, the child presents with acute non-pitting edema of one or more extremities that is usually painful and associated with fever. Pain and swelling usually resolve in one week; however, recurrences are frequent. Radiographs are initially normal, but consistent with infarction and periosteal new bone formation becomes apparent by the second week. The differential diagnosis in a child presenting with dactylitis must include osteomyelitis, leukemia, and other forms of inflammatory and infectious disorders.

**Osteonecrosis of the Femoral Head**

Ischemic necrosis of the proximal femur in sickle-cell disease has been diagnosed as early as six years of age. Its reported incidence ranges from 15 percent to 30 percent, and some report a higher prevalence in patients with hemoglobin SC disease than hemoglobin SS disease. Sebes, in 1983, reported a similar incidence for both patient populations [28,29].

The vascular anatomy of the femoral head is complex and changes with age, as well characterized by Trueta. After the age of three or four years, the growth plate acts as a barrier to the metaphyseal vessels. Sufficient perfusion is initiated through the ligamentum teres by the age of eight to ten [30]. Following fusion of the physis, circulation through the metaphyseal system is re-established. Most of the patients with sickle-cell disease present with changes of osteonecrosis after the age of twelve. This condition corresponds to a stage of multiple sources of blood supply to the femoral head, in contrast to patients with Legg-Calve-Perthes disease.

Clinical features are no different from avascular necrosis secondary to other causes. Pain on weight bearing is the primary presenting symptom. Sebes, however, reported nearly 50 percent of his patients with this disorder were asymptomatic [29]. Outcome is dependent upon the age of involvement. Necrosis of the immature epiphysis leading to a flattening of the femoral head with corresponding remodeling of the acetabulum can often result in maintenance of near normal range of motion and a relatively asymptomatic course for long duration. This concept of a congruous incongruity has been well described in association with Legg-Calve-Perthes disease. Involvement of the mature femoral head often leads to segmental collapse, resulting in persistent pain and progressive degeneration of the hip joint [31].

Early diagnosis of avascular changes can be achieved with comparative marrow technetium sulfur colloid scan and technetium pyrophosphate bone scan. Both techniques demonstrate low activity following acute infarction. Later, however, the marrow scan will remain cold while the bone scan will have increased activity secondary to the reparative phase. These changes are usually evident on scan before plain radiographic findings become apparent. Magnetic resonance imaging techniques are currently the most sensitive and recommended diagnostic modality for this disorder [32,33].

Surgical treatment for this condition ranges from myotomy of the adductors, osteotomy of both the femur and acetabulum, arthrodesis, to various forms of arthroplasties [28] (Figs. 3, 4). Most of these approaches have met with poor success. Arthrodesis is especially inappropriate due to the high incidence of bilateral involve-
ment. Cup arthroplasty has also been disappointing. Gunderson, in 1977, reported the results of 11 total hip replacements in seven patients who had hemoglobin SS disease [34]. Complication included two femoral fractures and one infection. Epps and Castro, in 1978, reported complications in 24 of 41 hip arthroplasties performed in 30 patients with hemoglobinopathies [35]. Sebes and Kraus, in 1983, reported uniform failure in patients who underwent a hemiarthroplasty [29]. Most recently, Hanker et al. and Bishop et al. reported poor results in their respective series. Hanker and Amstutz reported a projected revision rate of 50 percent within 5.4 years from a primary arthroplasty using the Kaplan-Meir survivorship analysis method [36]. This result is in dramatic contrast to the reported revision rate of 10–15 percent for age-matched patients with idiopathic avascular necrosis of the femoral head. In Bishop’s series, four out of 11 had an infection, while four required a revision and three required a resection arthroplasty [37]. Both articles also emphasized the presence of multiple technical difficulties due to the underlying medical problems and poor quality of bone stock.

Avascular necrosis can affect other bones as well. Humeral head involvement has been reported to have an incidence of 2–17 percent and is often seen with avascular
changes in the hip joint [38] (Fig. 5). Tarsal bones, ribs, skull, and mandible have all been described in sites of involvement.

**Osteomyelitis**

Hodges and Holt, in 1951, first recognized an association between sickle-cell disease and salmonella osteomyelitis [39]. Since then salmonella infections have become a major subject of study for those interested in sickle-cell disease [40–51].

Salmonella is an uncommon cause of osteomyelitis in the general population. Hughes and Carrol, in 1957, reported four cases in over 100 reviewed [47]; they were all in sicklers. Hook estimated that diagnosis of hemoglobin SS disease occurred 70 times more frequently than expected in patients with salmonella infections [46]. Barrett-Connor had calculated a 25-fold increase in the risk of developing salmonella infection in sickle-cell disease [42]. Engh et al. reported a 29 percent incidence of hemoglobinopathies among 142 cases reviewed in the orthopaedic literature [45]. In a comprehensive review of osteomyelitis in New York City, in 1978, Ortiz-Neu et al. identified 37 cases of salmonella osteomyelitis. Fourteen of these patients had hemoglobinopathy [49]. In a recent report from Nigeria of 63 cases of salmonella osteomyelitis, 57 patients had sickle-cell disease [40]. Ebong described four cases of bilateral massive pelvic osteomyelitis [43]. Two of these patients had salmonella as the causative agent, and both had sickle-cell disease. More recently, Mallough reviewed 12 cases of bony infections in sickle-cell patients in Saudi Arabia and found that 83 percent of these were caused by salmonella [48].

Despite the above-mentioned experience, staphylococcal infections are still the most common bony infections seen in sickle-cell patients. The major organism recovered in 21 consecutive patients with sickle-cell disease over a 24-month period was staphylococcus [50].

**FIG. 5.** Osteonecrosis of the humeral head and ischemic infarction of the humeral shaft.
The prompt and accurate diagnosis of osteomyelitis in patients with sickle-cell disease is essential. The signs of bone pain, fever, and local swelling may very well represent either bone infarction or osteomyelitis. Laboratory parameters and plain radiographs are often nonspecific and cannot reliably differentiate the two [41,52–56]. Though bone infarction is much more frequent than osteomyelitis in sickle-cell disease, a high level of suspicion and judicious use of clinical parameters assisted by scintigraphic evidence are crucial to establish an early diagnosis of deep infection in these patients.

The mechanism of the noted susceptibility to salmonella is unclear. It is postulated that this organism enters the circulation through microinfarcts in the intestinal mucosa. Immunological studies in sicklers have demonstrated near normal cell-mediated responses and immunoglobulin levels; however, complement-mediated opsonization is decreased in these individuals. The previously infarcted and now necrotic bony segments are probably more susceptible to a septic episode [42,51,57].

In the past, treatment has been centered on identification of the subtype of salmonella, and administering an appropriate combined intravenous antibiotic regimen for six weeks. The usual therapeutic approach consists of ampicillin and a cephalosporin. There is some early evidence that ciprofloxacin may be the drug of choice in eradicating even the carrier state in these patients.

*Septic Arthritis*

Septic arthritis in patients with hemoglobin SS disease is uncommon. Barrett-Connor described 250 infections in 166 sickle-cell patients and found only two cases of septic arthritis [42]. Nelson reported only four cases of joint infection among 289 cases of arthritis over a 19-year period [58]. Ebong described nine patients with septic arthritis; they all had concurrent osteomyelitis. The septic joint, however, did not necessarily occur next to the site of active bony infection. Salmonella arthropathy is very rare, as was pointed out by David and Black in a comprehensive review of 84 cases of salmonella joint infections over 64 years, only one of which was seen in a sickle-cell patient [59].

The prognosis for sickle-cell disease patients with septic arthritis is guarded at best. In the small number of cases discussed by Ebong, only 30 percent of the joints involved resolved in less than three months [44]. Early aggressive drainage, debridement, and splintage as with joint infections in other patients are crucial. A two-week course of intravenous antibiotic therapy in joint infection without concomitant osteomyelitis is usually sufficient. In addition to orthopedic management, it is essential to maximize the patient's general medical condition with hydration, oxygenation, and nutrition in order to minimize other complications.

Other joint manifestations of sickle-cell disease include a sterile arthritis occurring during painful crisis [60]. These events may be attributed to adjacent infarcts in the patella or in the synovium. A migratory polyarthritis along with a cardiac murmur is sometimes present during painful crisis and has been mistaken for rheumatic fever. The increased purine turnover of accelerated erythropoiesis results in a greater production of uric acid [61]. In younger patients with sickle-cell disease, plasma levels of uric acid are balanced by increased renal clearance. With aging and renal damage, urate levels may rise significantly, but frank gouty arthritis is uncommon in sickle-cell disease. One should, however, be aware of this potential complication.
Risk in Anesthesia and Surgery

Sickle-cell trait is associated with a very low complication rate with general anesthesia. Sickle-cell disease, on the other hand, does constitute a significantly increased risk for anesthesia and surgical procedures.

Goals in management of anesthesia include avoidance of acidosis due to hypoventilation, prevention of circulatory stasis due to improper positioning or hypovolemia, and maintenance of temperature regulation. The role of exchange transfusion to decrease the percentage of sickled erythrocytes has long been debated. For major procedures such as total hip arthroplasty, however, it should be a routine pre-operative measure.

Tourniquets create a static reservoir of blood which must inevitably undergo sickling and removal of the tourniquet would release a bolus of the sickled cells into the circulation. Stein and Urbaniak, however, reviewed two groups of patients over a period of 15 years; 21 cases of sickle-cell patients were compared to 50 controls; they concluded there was no increased rate of complications with the use of a tourniquet during the surgical procedure [62].

Radiographic contrast medium used in studies such as arteriography or pyelograms can change the serum viscosity, and this change may lead to a sickling crisis. It is important for the treating physician to appreciate these special situations and their potential complications. Appropriate measures must be undertaken in order to minimize morbidity posed to these patients, such as those approaches described above for anesthetic management.

Bony Changes in Sickle-Cell Variants

Patients with sickle-hemoglobin C disease have the same radiographic changes and similar clinical risks for infarcts and infections as patients with homozygous SS disease. Some authors have reported a higher incidence of osteonecrosis in patients with SC disease than in SS disease [12]. Sebes and Kraus, however, did not find any increase in avascular necrosis affecting the femoral head in their review [29]. Patients with sickle-thalassemia also develop the same characteristic changes as those observed in individuals with hemoglobin SS disease. The severity and frequency of these findings, however, are generally less in sickle-thalassemia due to the higher levels of normal hemoglobin molecules in these patients. Patients with heterozygous sickle-cell trait usually have sufficient amounts of hemoglobin A to preclude hypoxic episodes under physiologic conditions. They can develop the characteristic changes seen in SC and SS disease patients when subjected to hypoxemia. In a recent report on total hip arthroplasties for end-stage osteonecrosis in patients with sickle-cell disease, 20 percent had sickle-cell trait [63].

CONCLUSION

In summary, sickle-cell disease is a multi-system disorder. Musculoskeletal involvement accounts for much of the morbidity suffered by these patients. The principal radiographic changes seen in bone are secondary to marrow hyperplasia and ischemic osteonecrosis as well as the complications of both these processes. It remains difficult to differentiate vaso-occlusive crises of sickling from acute infections of the musculoskeletal system, but the use of isotope scans and magnetic resonance imaging are useful adjuncts to obtaining an accurate diagnosis. Joint infections are extremely uncommon in sickle-cell disease. If there is concomitant osteomyelitis, however, a high degree of
suspicion for acute septic arthritis is appropriate. Aggressive management of painful crisis and maintenance of a stress-free environment must be undertaken to minimize morbidity to these patients. Reconstructive surgical procedures for bone and joint destruction offer, at best, a fair prognosis for patients affected with sickle-cell disease.

REFERENCES

1. Herrick JB: Peculiar elongated and sickle-shaped red corpuscles in a case of severe anemia. Arch Int Med 6:517–521, 1910
2. Washburn RE: Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. Virginia Med Sem Monthly 15:490, 1911
3. Danford EA, Marr R, Elsey EC: Sickle cell anemia with unusual bone changes. Am J Roentgenol 45:223–226, 1941
4. Pauling L, Itano HA, Singer SJ, Wells IC: Sickle cell anemia. A molecular disease. Science 110:543–548, 1949
5. Ingram VM: Gene mutations in human hemoglobin, the chemical difference between normal and sickle cell hemoglobin. Nature 180:326–328, 1957
6. Dean J, Schechter AN: Sickle cell anemia: Molecular and cellular bases of therapeutic approaches. N Engl J Med 299:752–763, 1978
7. Dykes G, Crepean RH, Edelstein SJ: Three dimensional reconstruction of the fibers of sickle cell hemoglobin. Nature 272:506–512, 1978
8. Bertles JF, Milner PFA: Irreversibly sickle erythrocytes: A consequence of the heterogenous distribution of hemoglobin types in sickle cell anemia. J Clin Invest 47:1731–1735, 1968
9. Eaton JW, Jacob HS, White JG: Membrane abnormalities of irreversibly sickled cells. Semin Hematology 16:52–58, 1979
10. Kan YW, Dozy AM: Evolution of the hemoglobin S and C genes in world population. Science 209:388–391, 1980
11. Vinchinsky EP, Lubin BH: Sickle cell anemia and related hemoglobinopathies. Ped Clin N Am 27:429–447, 1980
12. Diggs LW: Bone and joint lesions in sickle cell disease. Clin Orthop 52:120–143, 1967
13. Golding JSR, Maclver JE, Went LN: The bone changes in sickle cell anemia. J Bone Joint Surg 41B:711–718, 1959
14. Middlemiss JH, Raper AB: Skeletal changes in the haemoglobinopathies. J Bone Joint Surg 48B:693–702, 1966
15. Resnick D, Niwayama G: Diagnosis of Bone and Joint Disorders. 2nd Edition. Philadelphia, WB Saunders, 1988, p 2338
16. Bohrer SR: Acute long bone diaphyseal infarction in sickle cell disease. Br J Radiol 43:685–697, 1970
17. Bohrer SP: Bone Ischemia and Infarction in Sickle Cell Disease. St. Louis, Warren H Greene, Inc, 1981
18. Diggs LW: Anatomic lesions in sickle cell disease. In Sickle Cell Disease: Diagnosis, Management, Education, and Research. Edited by H Abranson, JF Gertles, DL Wethers. St. Louis, CV Mosby, 1973, pp 189–229
19. Rhinelander FW: Circulation of bone. In Biochemistry and Physiology of Bone, 2nd Edition. Edited by GH Bourn. New York, Academic Press, 1972, p 2
20. Trueta J, Cavadias AK: A study of the blood supply of the long bones. Surg Gynecol Obstet 118:485–496, 1964
21. Keeley K, Buchanan GR: Acute infarction of long bones in children with sickle cell anemia. J Pediatrics 101:170–175, 1982
22. Sennara H, Gorry F: Orthopedic aspects of sickle cell anemia and allied hemoglobinopathies. Clin Orthop 130:154–157, 1978
23. Serjeant GR: Sickle Cell Disease. Oxford, Oxford University Press, 1985, p 191
24. Vance BM, Fischer RC: Sickle cell disease: Two cases presenting fat embolism as fatal complication. Arch Pathol 32:378, 1941
25. Smith CH: Blood Disease of Infancy and Childhood. St. Louis, Mosby, 1960, p 256
26. Watson RJ, Burko H, Megas H, Robinson M: The hand-foot syndrome in sickle cell disease in young children. Pediatrics 31:975, 1963
27. Stevens MCG, Padwick M, Serjeant GR: Observations on the natural history of dactylitis in homozygous sickle cell disease. Clin Pediat 20:311–314, 1981
28. Chung MKS, Alavi A, Russell MD: Management of osteonecrosis in sickle cell anemia and its variants. Clin Orthop 130:158–174, 1978

29. Sebes JI, Kraus AP: Avascular necrosis of the hip in the sickle cell hemoglobinopathies. J de L'association Canadienne des Radiol 34:136–139, 1983

30. Trueta J: The normal vascular anatomy of the human femoral head during growth. J Bone Joint Surg 39B:358–394, 1957

31. Washington ER, Root L: Conservative treatment of sickle cell avascular necrosis of the femoral head. J Pedi Orthop 5:192–194, 1985

32. Hauzeur JP, Pastels JL, Schoutens A: The diagnostic value of magnetic resonance imaging in non-traumatic osteonecrosis of the femoral head. J Bone Joint Surg 71A:641–649, 1989

33. Robinson HJ, Hartleben PD, Lund G, Schreiman J: Evaluation of magnetic resonance imaging in the diagnosis of osteonecrosis of the femoral head. Accuracy compared with radiographs, core biopsy, and intra-osseous pressure measurements. J Bone Joint Surg 71A:650–663, 1989

34. Gunderson C, D'Ambrosia RD, Shoji H: Total hip replacement in patients with sickle cell disease. J Bone Joint Surg 59A:760–762, 1977

35. Epps CH, Castro O: Complications of total hip replacements in sickle cell disease. Orthop Trans 2:236, 1978

36. Hanker GJ, Amstutz HC: Osteonecrosis of the hip in the sickle cell diseases. J Bone Joint Surg 70A:499–506, 1988

37. Bishop AR, Roberson JR, Eckman JR, Fleming LL: Total hip arthroplasty in patients who have sickle cell hemoglobinopathy. J Bone Joint Surg 70A:853–855, 1988

38. Chung MKS, Ralston EL: Necrosis of the humeral head associated with sickle cell anemia and its genetic variants. Clin Orthop 80:105–117, 1971

39. Hodges FJ, Holt JF: Year Book of Radiology. Chicago, Year Book Publishers, 1951, p 89

40. Adeyokunnu AA, Hendrickse RG: Salmonella osteomyelitis in childhood. Arch Dis Child 55:175–184, 1980

41. Armas RR, Goldsmith SJ: Gallium scintigraphy in bone infarction correlation with bone imaging. Clin Nuc Med 4:1–13, 1984

42. Barrett-Connor E: Bacterial infection and sickle cell anemia. Medicine 50:97–108, 1971

43. Ebong WW: Bilateral osteomyelitis in children with sickle cell anemia. J Bone Joint Surg 64A:945–946, 1982

44. Ebong WW: The treatment of severely ill patients with sickle cell anemia and associated septic arthritis. Clin Orthop 149:145–152, 1980

45. Engh CA, Hughes JL, Abrams RC, Bowerman JW: Osteomyelitis in the patient with sickle cell disease. J Bone Joint Surg 53A:1–14, 1971

46. Hook EW, Campbell CG, Weens HS, Cooper GR: Salmonella osteomyelitis in patients with sickle cell anemia. N Engl J Med 257:403–407, 1957

47. Hughes JG, Carrol DS: Salmonella osteomyelitis complicating sickle-cell disease. Pediatrics 19:184–191, 1957

48. Mallough A, Talab Y: Bone and joint infection in patients with sickle cell disease. J Pedi Orthop 5:158–162, 1985

49. Ortiz-Neu C, Marr JS, Cherbin CE, Neu HC: Bone and joint infections due to salmonella. J Inf Dis 138:820–829, 1978

50. Sudat-Ali, Sankarau-Kutty, Kutty K: Recent observations on osteomyelitis in sickle cell disease. Int Orthop 9:97–99, 1985

51. Specht EE: Hemoglobinopathic Salmonella osteomyelitis. Clin Orthop 79:110–117, 1971

52. Amundsen TR, Siegel MD, Siegel BA: Osteomyelitis and infarction in sickle cell hemoglobinopathies: Differentiation by combined technetium and gallium scintigraphy. Radiology 153:807–812, 1984

53. Koren A, Garty I, Katzuni E: Bone infarction in children with sickle cell disease: Early diagnosis and differentiation from osteomyelitis. Eur J Pediatr 142:93, 1984

54. Lisbona R, Rosenthal L: Observations on the sequential use of 99m Tc phosphate and complex and 67 Ga imaging in osteomyelitis, cellulitis, and septic arthritis. Nuc Med 123:123–129, 1976

55. Rao S, Solomon N, Miller S, Dunn E: Scintigraphic differentiation of bone infarction from osteomyelitis in children with sickle cell disease. J Pediat 107:685–688, 1985

56. Wethers D, Grover R: Pitfalls in diagnosis of osteomyelitis in children with sickle cell disease. Clin Pediat 22:614–618, 1983

57. Givner LB, Luddy RE, Schwartz AD: Etiology of osteomyelitis in patients with major sickle hemoglobinopathies. J Pediat 99:411–413, 1981
58. Nelson JD: Sickle cell disease and bacterial bone and joint infections. N Engl J Med 292:534–536, 1975
59. David JR, Black RL: Salmonella arthritis. Medicine 39:385–390, 1960
60. Espinoza LR, Spilberg I, Osterland CK: Joint manifestations of sickle cell disease. Medicine 53:295–305, 1974
61. Rothchild BM, Sienknecht CW, Kaplan SB, Spindler JS: Sickle cell disease associated with uric acid deposition disease. Ann Rheum Dis 39:392–395, 1980
62. Stein RE, Urbanik J: Use of the tourniquet during surgery in patients with sickle cell hemoglobinopathies. Clin Orthop 151:231–233, 1980
63. Acuino MT, Friedman RJ: Total hip replacement in patients with sickle cell hemoglobinopathies. Presented at the annual meeting of the American Academy of Orthopaedic Surgeons, New Orleans, February 1990