Radiographic Changes of the Skull in Sickle Cell Anemia

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Skull radiographs of 194 patients from 4 months to 55 years old with sickle cell anemia revealed porous decreased bone density in 25%, widening of diploë associated with a relative decrease in the width of the outer table in 22%, and vertical "hair-on-end" striations in 5%. The youngest patient with vertical striations was 5 years old and the oldest was 39. Serial examinations in 60 patients revealed no decrease of the skull width nor disappearance of the striations with age.

Interest in skull and other bone lesions associated with severe anemia was stimulated in 1925 when Cooley and Lee [1] described striking radiographic abnormalities in the bones of children with the disease then known as "Mediterrranean anemia" and later identified as "Cooley's anemia" and "thalassemia major." The calvarial lesions described included widened diploë, thinning of external table, increased radiolucency, and vertical trabecular striations.

Cooley et al. [2, 3] later reported similar but less striking lesions in patients with sickle cell anemia. Since that time, there have been numerous reports of radiographic abnormalities and anatomic lesions in the skulls of patients with sickle cell hemoglobinopathies (table 1). Many of these are reports of a few interesting cases or small series of cases. They usually depict the more striking and unusual manifestations without furnishing information concerning the incidence of the various types of lesions, the age of the patient when the lesion was first manifest, or the changes that occur in the appearance of the lesions with age.

The most noteworthy coverage of the radiographic features of sickle cell anemia and related hemoglobinopathies is found in a monograph by Reynolds [4]. Other selected reports of radiographic abnormalities in bones are listed [5–11]. Anatomic lesions in the skull and other bones were reported by Diggs [12, 13].

Reported here are information about the skull afforded by a study of 194 patients with classical sickle cell anemia, the incidence of various abnormalities, and the evolution and progression of lesions with advancing age.

Subjects and Methods

Radiographic manifestations in bones and in other organs were studied as part of a long-term investigation of the natural history of sickle cell hemoglobinopathies. Patients seen at University of Tennessee Sickle Cell Center for any symptoms had a bone survey that was repeated at 5 year intervals, if possible. Before 1954, diagnosis of sickle cell anemia was established by classic clinical manifestations of a chronic, regenerative hemolytic anemia and recurrent painful crises together with sickle erythrocytes in air-exposed blood smears and in sealed moist preparations of blood. In later years, diagnosis of sickle cell anemia was confirmed by additional tests, including sodium metabisulfite moist preparation, tube solubility tests, electrophoretic mobility of hemoglobin, and concentrations of fetal hemoglobin, hemoglobin F, and hemoglobin A_2.

Hemoglobin SS patients studied totaled 194 (101 male and 93 female) and ranged from 4 months to 55 years old. Of the 194 patients, 134 had a single skull examination, 40 had two, 12 had three, and eight had four or more. The follow-up period of the 60 patients with more than one skull examination was 9 months to 13 years, (mean follow-up, 9.2 years). Routine skull examination included anteroposterior and lateral views.

Patients with the sickle cell trait (Hb AS), hemoglobin SC disease, sickle cell thalassemia, and other heterozygous S hemoglobinopathies were excluded from this study.

Results

Lateral views of the skull were evaluated for alterations in density and texture, expansion of the diploë, and the "hair-on-end" sign. The most frequent finding was a subtle change in texture of the frontal and parietal bones. Descriptively, it was a nonhomogenous, or "granular," decrease in bone density, and was present in 48 (25%) patients with sickle cell anemia. Because of the variable criteria for radiographically diagnosing osteoporosis, only the most severe changes of granularity were interpreted as positive for this study (fig. 1). The granular porous appearance of the skull was observed before expansion of the diploë occurred. Even with severe increased overall lucency, the inner table was distinct in all patients, the diploë revealed variable extents of granularity, and the outer table became progressively less distinct. Granularity was not observed in patients younger than 1 year.

Measurement of diploetic expansion was by the procedure used by Reynolds [4]. Total calvarial thickness, as well as the expansion of the diploë and the inner and outer tables, was measured on the lateral view of the skull with a caliper in the frontal and parietal bones at points of greatest diameter. The diploë was considered abnormally expanded when the diploetic width was at least 2.5 times greater than the combined measurement of the inner and outer tables. The width of the diploë in normal patients is considered less than 2.3 times the width of the bony tables [4]. Diploetic expansion was noted in 42 (22%) sickle cell disease patients. In 28 of 60

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TABLE 1
Literature Summary

Reference	No. Cases	Prominent Diploë Thickening of Calvarium		Radial Striations ("hair-on-end")	
		No.	%	No.	%
[4]	32	16	50	...	...
[7]	30	4	12	1	3.3
[8]	30	7	23.3	2	6.7
[9]	26	...	...	...	...
[10]	49	...	...	4	8.1
[11]	58	27	46.6	1	1.7
[15]	124	20	16.0	7	6
[19]	180	...	...	5	2.7
[20]	21	13	61.9	...	...

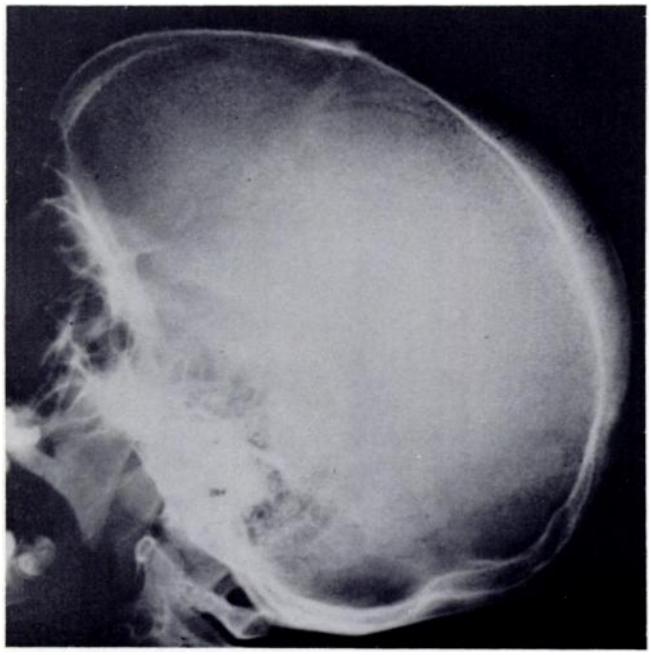

Fig. 1.—Coarsely granular appearance and diploeic widening of frontal and parietal bones in 10-year-old patient with sickle cell disease.

patients with multiple skull films, diploetic expansion occurred initially in the frontal area, followed later by expansion in the parietal area. Moreover, frontal expansion occurred first in all of the four patients who had more than one skull film before age 50. In the six patients 1 year old or less, frontal diploetic width was 7–12 mm compared to 5–9 mm for the greatest parietal diploetic width. In the 2–5 year age group, expansion of the parietal diploë became more prominent, and in the 6–12 year age group, parietal expansion surpassed the width of the diploë in the frontal bone (fig. 2). Parietal widening became progressively more prominent during the patients' second and third decades of life (fig. 3). In contrast to a previous report [14], the occipital diploë was not expanded in any of our 194 patients and no regression of the diploetic expansion was observed.

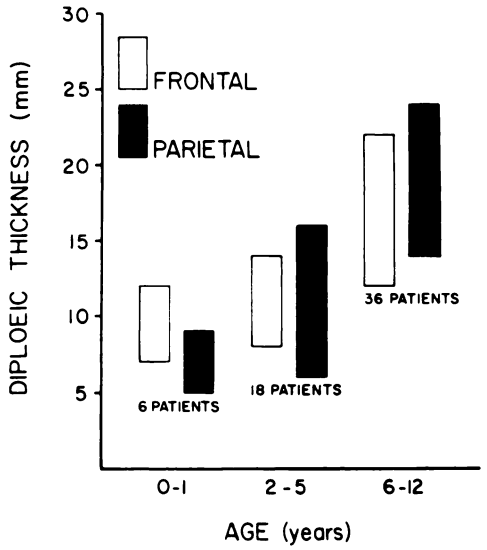

Fig. 2.—Progression of diploetic widening with age in frontal and parietal bones.

The classical "hair-on-end" sign was diagnosed only when definite long thin spicules were observed (fig. 4). It was present in 10 (5%) patients. Once present, this lesion persisted without regression in any patients observed from 2½ months to 22 years. There was no correlation between the prominence of this finding and the clinical course of the disease, nor was there a consistent relationship connecting onset, progression, and the severity of the anemia. Previously reported regression of calvarial changes with regression of sclerosis and widening were not observed in any patients in this study.

One patient with homozygous disease showed multiple discreet radiolucent lesions with distinct margins (fig. 5) resembling those seen in multiple myeloma. Repeated medical evaluations did not demonstrate any clinical or laboratory evidence of myeloma or metastatic disease. At autopsy, the multiple lytic areas proved to be islands of hyperplastic red marrow surrounded by fibrosis.

Discussion

Pathologic changes leading to abnormal radiographic appearance of bones in sickle cell anemia have been studied and are well described [4, 15–22]. Like the changes in axial and appendicular skeletons, skull abnormalities are produced by cellular hyperplasia, circulatory factors, or a combination of the two. The lesions, caused by red marrow hyperplasia, such as expansion of diploë, thinning of the outer table, progressive increase in the granular appearance of the skull, and vertical trabeculations ("hair-on-end"), are nonspecific and have been described by early investigators in thalassemia major, hereditary spherocytosis, and in iron deficiency anemia [23–26]. Circulatory factors, such as stasis and small vessel occlusions, result in patchy or diffuse opacity with gradual vault widening. The rare findings of distinct multiple radiolucent lesions amid diffusely scle-

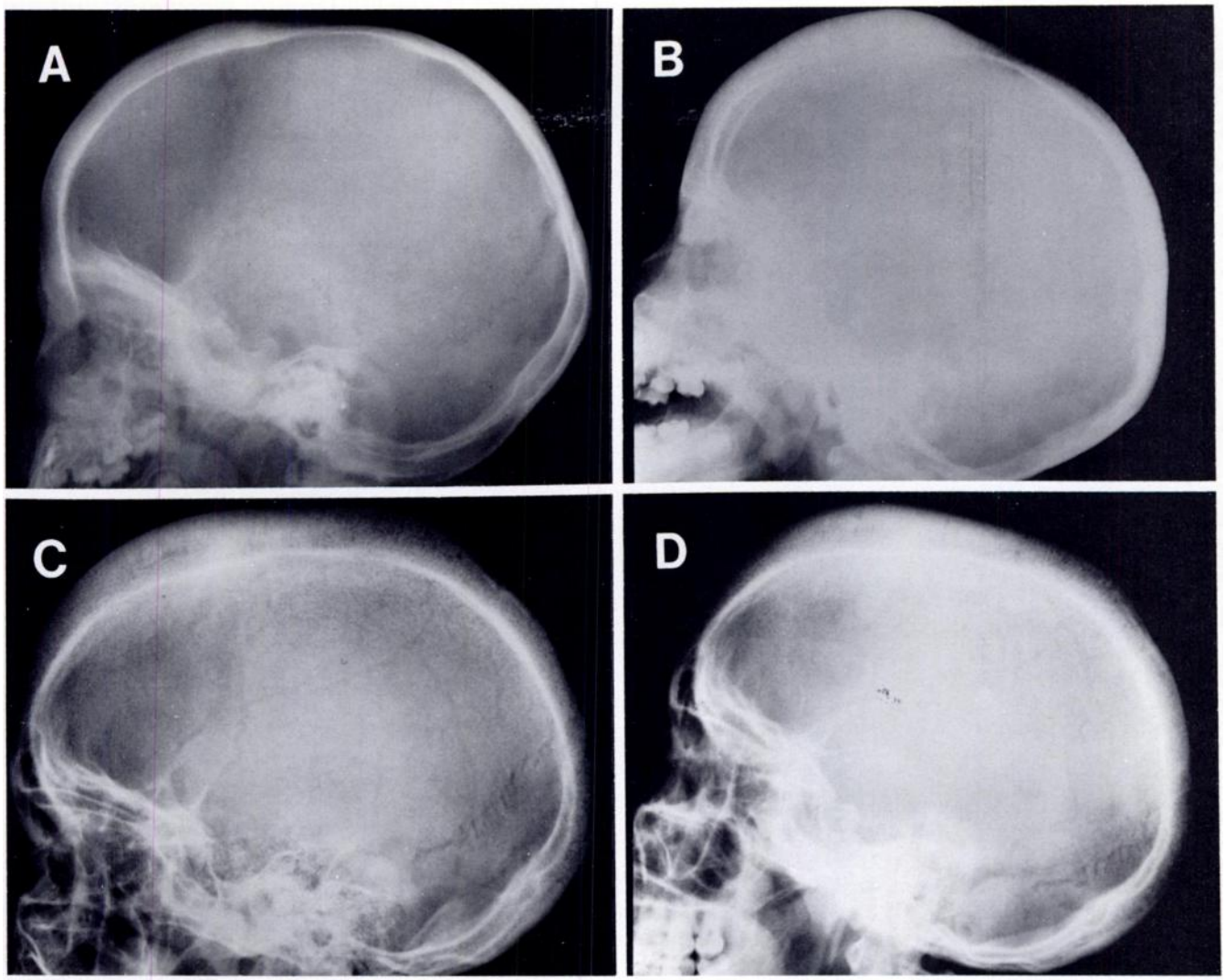

Fig. 3.—30 year progression of calvarial changes in male homozygous sickle cell anemia patient. **A**, At 1 year old, expansion of diploë begins in the posterior frontal area and is definitely identifiable. **B**, At age 2 expansion is prominent. At ages 23 (**C**) and 30 (**D**), false "hair-on-end" sign appears.

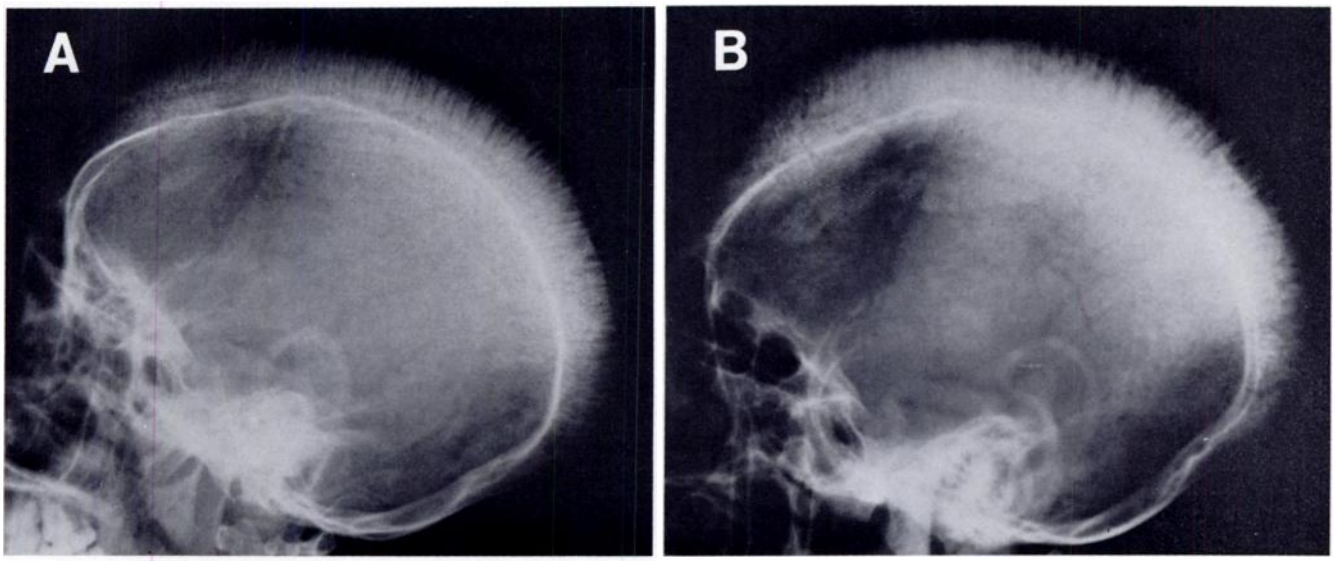

Fig. 4.—Classical "hair-on-end" effect. **A**, At age 15, long, thin vertical spicules. **B**, At age 31, they become wide, more sclerotic and distinct. Areas of sclerosis in frontal and anterior parietal areas have distinct lucent central component resembling "doughnut" lesions. Occipital bone is not expanded.

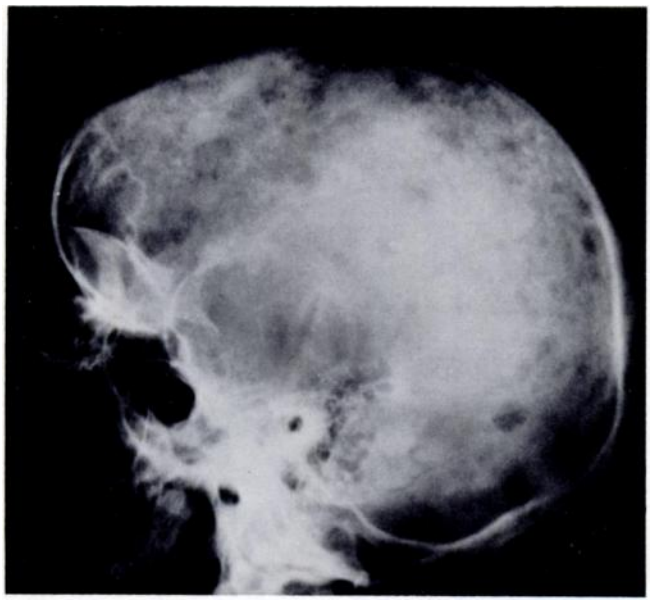

Fig. 5.—Multiple lytic lesions in 41-year-old sickle cell anemia patient with no clinical or laboratory evidence of myeloma.

rotic bone represent residual islands of hyperplastic red marrow rather than areas of calvarial infarction.

The granular appearance of the skull, which is usually misinterpreted as osteoporosis, results from increased red marrow volume, rather than removal of already present mineral. Granularity appears in the skull before widening of the diploë and vertical striations occur.

Our findings indicate that definite diploetic expansion can be seen before age 2 years. Four of the six patients having skull films at or before age 1 year showed definite expansion. Furthermore, in four of the six skulls, frontal rather than parietal expansion occurred first. Our findings do not support previous reports [6, 11, 27] indicating that expansion of the skull occurs most often after age 5 and usually involves the parietal region. In the 2–5-year-old group, seven of 18 skulls showed distinct calvarial expansion first in the frontal bone. Between ages 6 and 12, expansion of the diploë progressed posteriorly to involve the parietal areas but sparing the occipital bone.

The previously reported wide range incidences of diploetic expansion, 12% to 61.9%, result from the variable criteria used for evaluation. Objective measurement of calvarial thickness had not been carried out by most investigators. In our study, diploetic expansion was established only if the width of the diploë was greater than 2.5 times the combined thickness of the inner and outer tables.

The "hair-on-end" effect seen in 5% of our patients corresponds to the incidence in previous studies, reconfirming the rarity and nonspecificity of this finding. This has been exaggerated in the early literature on sickle cell disease, mostly because of its rather spectacular radiographic appearance. The true "hair-on-end" sign (figs. 3A and 3B) demonstrates thin long spicules extending through the entire width of the cranial vault, while in the false "hair-on-end" sign (figs. 2C and 2D), the vertical striations are not distinct and do not extend to the inner table.

While much has been written about long bone infarction, little is known about calvarial infarction [28]. No anatomic or pathologic studies concerning calvarial infarction are available in the literature. Areas of sclerosis, as well as marginated lucencies, are referred to as infarction.

Other reports of single [29] and multiple [30] calvarial lesions with a ringlike appearance have been referred to as "doughnut lesions." These lucent areas with a sclerotic rim were not associated with anemia or skeletal abnormalities, and were presumed to be areas of fibrosis. However, even on the basis of the histologic pattern of the biopsied lesion, no definite diagnosis of calvarial infarction could be made. In patients with sickle cell anemia, the areas of lucencies in the skull probably represent residual sites of active red marrow rather than infarction, as demonstrated by the autopsy findings in the last case described in this report.

REFERENCES

1. Cooley TB, Lee P: Series of cases of splenomegaly in children with anemia and peculiar bone changes. *Am Pediatr Soc Trans* 37:29–30, 1925
2. Cooley TB, Lee P: Observation on the sickle cell phenomenon. *Am Pediatr Soc Trans* 38:58–59, 1926
3. Cooley TB, Witwer ER, Lee P: Anemia in children with splenomegaly and peculiar changes in the bones. Report of cases. *Am J Dis Child* 34:347–363, 1927
4. Reynolds J: *The Roentgenological Features of Sickle Cell Disease and Related Hemoglobinopathies*. Springfield, Ill., Thomas, 1965
5. Grinnan A: Roentgenologic bone changes in sickle cell and erythroblastic anemia. *AJR* 34:297–309, 1935
6. Caffey J: The skeletal changes in the chronic hemolytic anemias (erythroblastic anemia, sickle cell anemia and chronic hemolytic icterus). *AJR* 37:293–324, 1937
7. Diggs LW, Pulliam HN, King JC: Bone changes in sickle cell anemia. *South Med J* 30:249–259, 1937
8. Macht SH, Roman PW: The radiologic changes in sickle cell anemia. *Radiology* 51:697–707, 1948
9. Legant O, Ball RP: Sickle cell anemia in adults, roentgenographic findings. *Radiology* 51:665–675, 1948
10. Carroll DS, Evans JW: Roentgen findings in sickle cell anemia. *Radiology* 53:834–845, 1949
11. Ehrenpreis B, Schwinger HN: Sickle cell anemia. *AJR* 68: 28–36, 1952
12. Diggs LW: Anatomic lesions in sickle cell disease, in *Sickle Cell Disease*, edited by Abramson H, Bertles JF, Wethers DL, St. Louis, Mosby, 1973, pp 189–229
13. Diggs LW: Bone and joint lesions in sickle cell disease. *Clin Orthop* 52:119–143, 1967
14. Tori G: Clinical radiological observations on 102 cases of sickle cell anemia. *Clin Radiol* 23:87–108, 1954
15. Carroll DS: Roentgen manifestations of sickle cell disease. *South Med J* 50:1486–1490, 1957
16. Middlemiss JH: Sickle cell anemia. *J Faculty Radiol* 9:16–24, 1958

17. Moseley JE: Patterns of bone change in the sickle cell states. *Mt Sinai J Med NY* 26:424–439, 1959
18. Golding JSR, MacIver JE, Went LN: The bone changes in sickle cell anemia and its genetic variants. *J Bone Joint Surg [Br]* 41:711–718, 1959
19. Cockshott WB: *Hemoglobin Diseases in Tropical Radiology*. London, Heinemen Medical Books, 1961, pp 79–97
20. Hewett BV, Nice CM: Radiographic manifestations of sickle cell anemia. *Radiol Clin North Am* 2:249–259, 1964
21. Middlemiss JH, Raper AB: Skeletal changes in hemoglobinopathies. *J Bone Joint Surg [Br]* 48:693–702, 1966
22. Argen RJ, Sullivan MA: Bone changes in sickle cell disease. *NY State J Med* 66:1238–1243, 1966
23. Eng LIL: Chronic iron deficiency with bone changes resembling Cooley's anemia. *Acta Haematol* (Basel) 19:263–268, 1958
24. Sax B: Roentgen manifestations of iron deficient anemia in the skull of infants and children simulating those seen in Cooley's and sickle cell hemolytic anemia. *J Germantown Hosp* 4:72–75, 1963
25. Moore S: The bone changes in sickle cell anemia with note on similar changes observed in skulls of ancient Mayan Indians. *J Missouri State Med Assoc* 26:561–564, 1929
26. Bohrer SP, Graham EC: Pathology in 700-year-old Nigerian bones. *Radiology* 98:581–584, 1971
27. Robinson IB, Sarnat BG: Roentgen studies of the maxillae and mandible in sickle cell anemia. *Radiology* 58:517–523, 1952
28. Bohrer SP: Bone infarcts in sickle cell anemia. *Tropenmed Parasitol* 22:299–312, 1971
29. Keats TE, Holt JF: The calvarial "doughnut lesion": a previously undescribed entity. *AJR* 105:314–318, 1969
30. Royen PM, Ozonoff MB: Multiple calvarial "doughnut lesions." A case report. *AJR* 121:121–123, 1974