OSTEONECROSIS ASSOCIATED WITH METABOLIC DISEASE AND CORTICOSTEROID THERAPY

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Mechanisms responsible for osseous ischemia may involve such changes in functional requirements as anemia, hypoxia, vasospasm, and hypotension; or a sudden increase in the tissue's metabolic demands; or, more probably, mechanical disturbances (*e.g.*, sudden and complete interruption or occlusion of vessels by traumatic severance, compression, endarteritis, thrombosis, or embolism). Various physiological and metabolic abnormalities have been considered by the author, and a hypothesis was formulated to determine whether a common etiology exists in nontraumatic fat embolism of bone in adults as a possible initiating event in the pathogenesis of nontraumatic avascular necrosis (Jones, 1971).

Fat embolism has been observed in the decompression-sickness syndrome, during crises in sickle-cell hemoglobinopathies, and in hypercortisonism, alcoholism, and pancreatitis, each of which may be complicated by avascular necrosis (Jones and Engelman, 1966). It is known that under certain circumstances the liver may be a major fat depot. In patients with acute fatty metamorphosis, the liver may be composed principally of neutral fat and may weigh more than 5000 gm, which is about 20 times the amount of fat that can be extracted from the adult human femur and tibia combined (Peltier, 1956). Lynch *et al.* (1959) demonstrated that 1 ml of liquid fat could result in 10 million fat emboli 40 μ in diameter.

Both clinical studies (MacMahon and Weiss, 1929; Hill, 1961) and experimental ones (Hartcroft and Ridout, 1951; Owens and Northington, 1962) indicate that the fatty liver is capable of spontaneously releasing large numbers of embolic-sized fat globules into hepatic venous channels after rupture of fatty cysts into adjacent sinusoids and central veins.

The liver is more heavily perfused by circulating blood volume than any extremity, which facilitates extensive drainage of fat globules through hepatic venous outflow tracks. Moreover, pancreatic enzymes, upon entering portal venous radicals in patients with pancreatitis, could conceivably cause further release of intravascular fat from fat-laden hepatic cells.

After penetrating the pulmonary vascular bed, fat emboli enter vessels supplying the brain, kidneys, and all other bodily organs and tissues, including those parts of the skeleton that are the most vulnerable to avascular necrosis. In general, these areas derive their nourishment from only a few primary vessels, principally terminal arteries with relatively poor circulation.

Only those metabolic disturbances known to be commonly associated with nontraumatic osteonecrosis in a working population between the ages of 20 and 60 years will be reviewed, since individuals with these conditions should be comprehensively evaluated on preemployment examinations before exposure to dysbaric phenomena. Dysbaric osteonecrosis, Gaucher's disease, Legg-Calvé-Perthes syndrome, radiation exposure, pregnancy, and other rarely associated entities will not be discussed.

CLINICAL OBSERVATIONS

Alcoholism

The commonest source of continuous, low-grade, and relatively asymptomatic showers of systemic fat emboli is probably the alcohol-induced fatty liver (Lynch *et al.*, 1959; Kimble, 1961). Osseous avascular necrosis may be specifically associated with alcoholism. Thirty patients with idiopathic osteonecrosis, all with a history of prolonged, excessive alcohol consumption, were studied in various hospitals in the San Francisco–Oakland Bay area. Osteonecrosis was diagnosed by roentgenograms in all 30 and confirmed histologically in 19. Of the patients 18 were Caucasian, 11 black, and 1 Chinese; 24 were male and 6 female; and their mean age was 47 years. Of the 30 patients, 27 had significant hepatomegaly, and 22 of 24 patients had abnormal bromsulphalein retention. Six of a sample

of 8 had hypertriglyceridemia, and fatty metamorphosis was demonstrated histologically in 7 of 9 livers examined. Evidence of systemic fat embolism was found in 9 of 19 patients. Lipuria was detected in 8 cases, probable intravascular fat globules in resected femoral heads were seen in 2 instances, and emboli were found at autopsy in 1 case.

In the sampling of 30 patients, there were 77 lesions (Fig. 1); bilateral symmetry was marked. Of the necrotic lesions 56% were in femoral heads, as seen in Fig. 2, and 11% in humeral heads. Metadiaphyseal infarctions within the distal femur and proximal tibia accounted for nearly one-third of the lesions.

Although Axhausen (1928) was probably the first to report osteonecrosis in an alcoholic patient, Vignon *et al.* (1960) reported that 5 of their 9 patients with idiopathic necrosis had a significant history of alcoholism; Mankin and Brower (1962) reported a similar history in 3 of 5 patients with osteonecrosis. Serre and Simon (1962) and Patterson *et al.* (1964) found that, respectively, 19% and 17% of their patients with avascular necrosis had a significant history of alcoholism. Malka (1966) noted that 3 of his 6 patients with femoral-head necrosis were alcoholics.

The majority of the 27 patients in Thibodeau's review (1968) of 41 hips with avascular necrosis were alcoholics. Of 50 patients with idiopathic ischemic necrosis of the femoral head reported in the Swiss Multi-Center Study, at least 6 were alcoholic with chronic liver disease (Zinn, 1971). Hartmann (1971) noted that 7 of 38 patients in the Swiss study had hyperlipidemia. In our experience the hyperlipidemias associated with alcoholism have been predominantly Type IV (Fredrickson and Lees, 1965), comprising chylomicrons and pre-beta lipoproteins.

Schreiber (1972) documented a 23-year-old heroin addict with bilateral idiopathic avascular

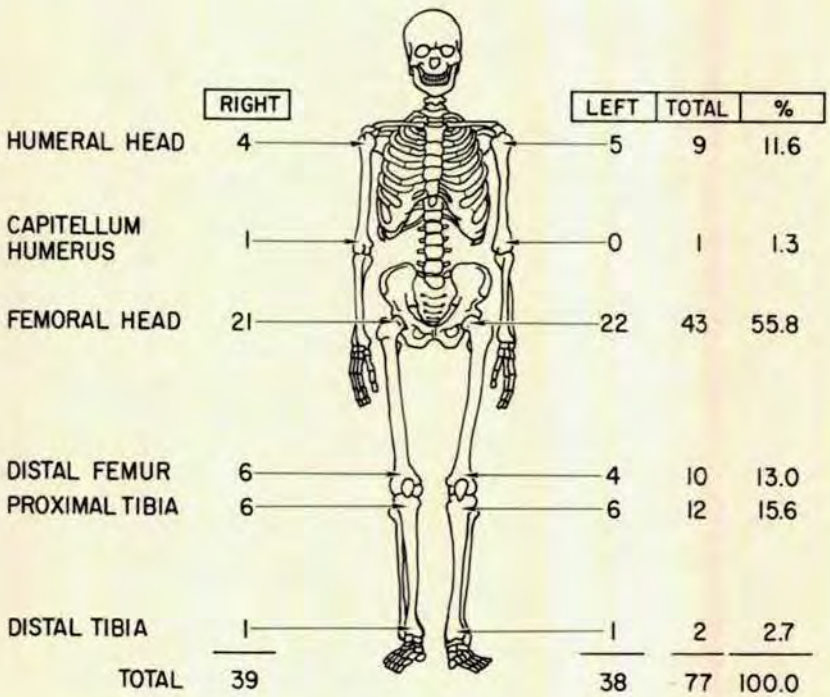

FIG. 1. Skeletal distribution of 77 osteonecrosis lesions, diagnosed roentgenographically, in 30 alcoholic patients. (Jones, 1971. Illustration courtesy of publisher.)

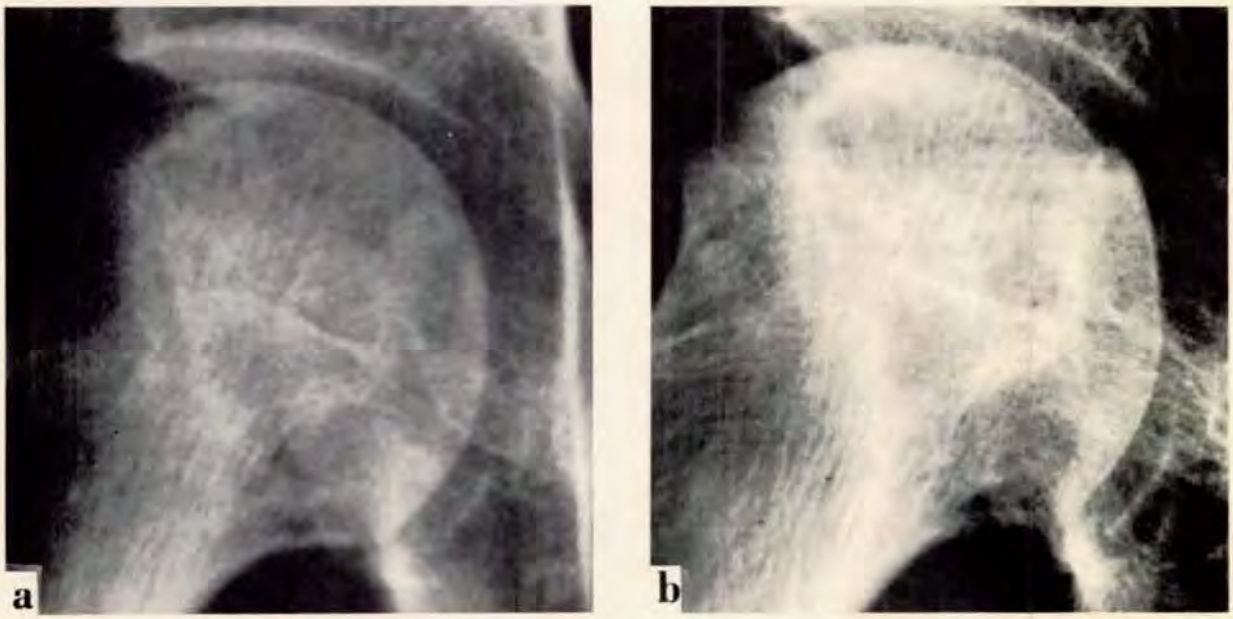

FIG. 2. A-P projections of R femoral head of male alcoholic. (*a*) Visible are scattered radiolucencies with minimal sclerosis and no gross evidence of architectural distortion. (*b*) Vascular necrosis and segmental collapse of irregular articular surface have occurred 13 months later.

necrosis of the femoral head. The association of acute and chronic liver disease with heroin dependency is well known. Laboratory evidence of hepatic dysfunction has been reported in up to 75% of parenteral heroin addicts (Norris and Potter, 1965). Stimmel *et al.* (1972) studied hepatic dysfunction in 46 heroin addicts and found that 89% had past or present liver disease. Liver biopsies were performed on 12 patients; hepatic injury attributed to alcohol was present in 10, all of whom had significant fatty changes.

Gout and Hyperuricemia

Of 68 patients with idiopathic aseptic necrosis, McCollum *et al.* (1971) reported that 34% had bilateral disease; 85% were male, and the average age of onset was 39.7 years. Of the 68 patients, 26 were alcoholics, 17 had gouty arthritis, and 10 had hyperuricemia. Mauvoisin *et al.* (1955) originally reported the occurrence of aseptic necrosis of the femoral head in a patient with gout. Wissinger (1963) first demonstrated uric-acid crystals in the synovium of the hip of a patient with aseptic necrosis, which was subsequently confirmed by Hunder *et al.* (1968). Rondier *et al.* (1970) investigated blood lipids in 50 patients with gout and found considerably higher levels of mean blood triglycerides, principally Type IV hyperlipoproteinemias.

Boettcher *et al.* (1970) reported excessive alcohol consumption in 37 of 50 patients with nontraumatic femoral-head necrosis. Abnormal bromsulphalein retention was found in 12 of 21 patients with liver disease; gout or hyperuricemia existed in 16 of them. Of 33 patients studied, 10 had significant hyperuricemia.

Pancreatitis

Avascular necrosis has not been reported in acute pancreatitis. However, Immelman *et al.* (1964) reported 3 patients with acute pancreatitis and lytic lesions involving the long bones. They considered these abnormalities secondary to fat necrosis resulting from increased circulating lipase. Blauvelt (1946) believed that these lesions were caused by pancreatic acinar emboli.

Ponfick (1872) first described intramedullary necrosis in a patient with pancreatitis. Gerle *et al.* (1965) reported 6 cases of chronic pancreatitis with avascular femoral-head necrosis. No histological evidence was reported, and all 6 were in patients with chronic alcoholism. Irregular serpentine metadiaphyseal lesions are most likely calcified areas of intramedullary fat ne-

crosis, possibly resulting from the lipolytic action of circulating lipase or the local liberation of pancreatic enzymes from minute pancreatic cell emboli.

Two patients with chronic pancreatitis and probable femoral-head osteonecrosis have been evaluated; both are also chronic alcoholics, and one has hyperuricemia. One can only speculate about the relationship between avascular necrosis and hyperuricemia, gout, pancreatitis, and drug addiction. A direct relationship cannot be proved, because alcoholism with fatty liver and hyperlipemia (Havel, 1969) is often associated with these conditions as well.

Hypercortisonism

Osteonecrosis associated with corticosteroid therapy was first described in 1957 by Pietrogrande and Mastromarino. Jones *et al.* (1965) reported osteonecrosis as a complication in renal transplantation, following which massive corticosteroid dosage is used for a prolonged period. Since then additional cases have been reported (see Table I).

Of those kidney-transplant recipients surviving longer than three months, approximately 6% have developed avascular necrosis affecting one or more bones. The first human lung transplant was performed in 1963 and the first human heart transplant in 1967; no lung or heart recipient has developed osseous avascular necrosis. However, repeat kidney transplantation for graft failure has been a recent development, and the risk of developing necrosis is significantly greater in those patients receiving two or more grafts.

Since 1963, a series of 32 patients who were treated with corticosteroids for various diseases have developed osteonecrosis (Jones, 1971); 13 patients were male and 19 female. The average age when necrosis was diagnosed was 21 years for the transplant group and 43 years for the non-transplant group.

In these 32 patients, 71 lesions were found (Fig. 3). Approximately 25% of the lesions were in non-weight-bearing bones, and about 80% affected the proximal epiphyseal regions of bones (Fig. 4). Less commonly affected sites included the body of the talus, the proximal portion of the carpal scaphoid, and the condyles of the femur (Fig. 5).

Efforts were made to obtain presumptive evidence of systemic fat embolism in 11 of these patients. Such evidence was detected in 6 of them. Fat globules were consistently found in the urine of 5 patients; in 2 of them renal glomerular fat was demonstrated by biopsy. Two patients appeared to have intravascular fat globules in their necrotic femoral heads (Jones, 1971).

Sutton *et al.* (1963) reported 8 cases of corticosteroid-induced osteonecrosis and reviewed 62 others. Sutton (1968) again reviewed the subject and considered aseptic necrosis of bone to be a definite complication of corticosteroid therapy. More than 175 cases had been reported in the world literature by 1971. Fisher and Bickel (1971) noted that all cases have had certain common features: *1*) None was associated with significant trauma; *2*) none was associated with conditions usually considered to cause nontraumatic avascular necrosis; *3*) corticosteroids had been given systemically in excess of physiological requirements for prolonged periods, either reg-

Table I. ANALYSIS OF OSTEONECROSIS AS A COMPLICATION IN RENAL TRANSPLANTATION

Series	Number of kidney transplant recipients	Number of recipients with osteonecrosis	% osteonecrosis
Harrington *et al.* (1971)	204	18	8.8
Cruess *et al.* (1968)	27	10	37.0
Najarian, J. D. (personal communication)	290	8	2.8
Evarts and Phalen (1971)	203	15	7.5
Fisher and Bickel (1971)	70	1	1.4
Irby and Hume (1968)	140	6	4.3
Bravo *et al.* (1967)	60	5	8.3
Totals	994	63	6.3

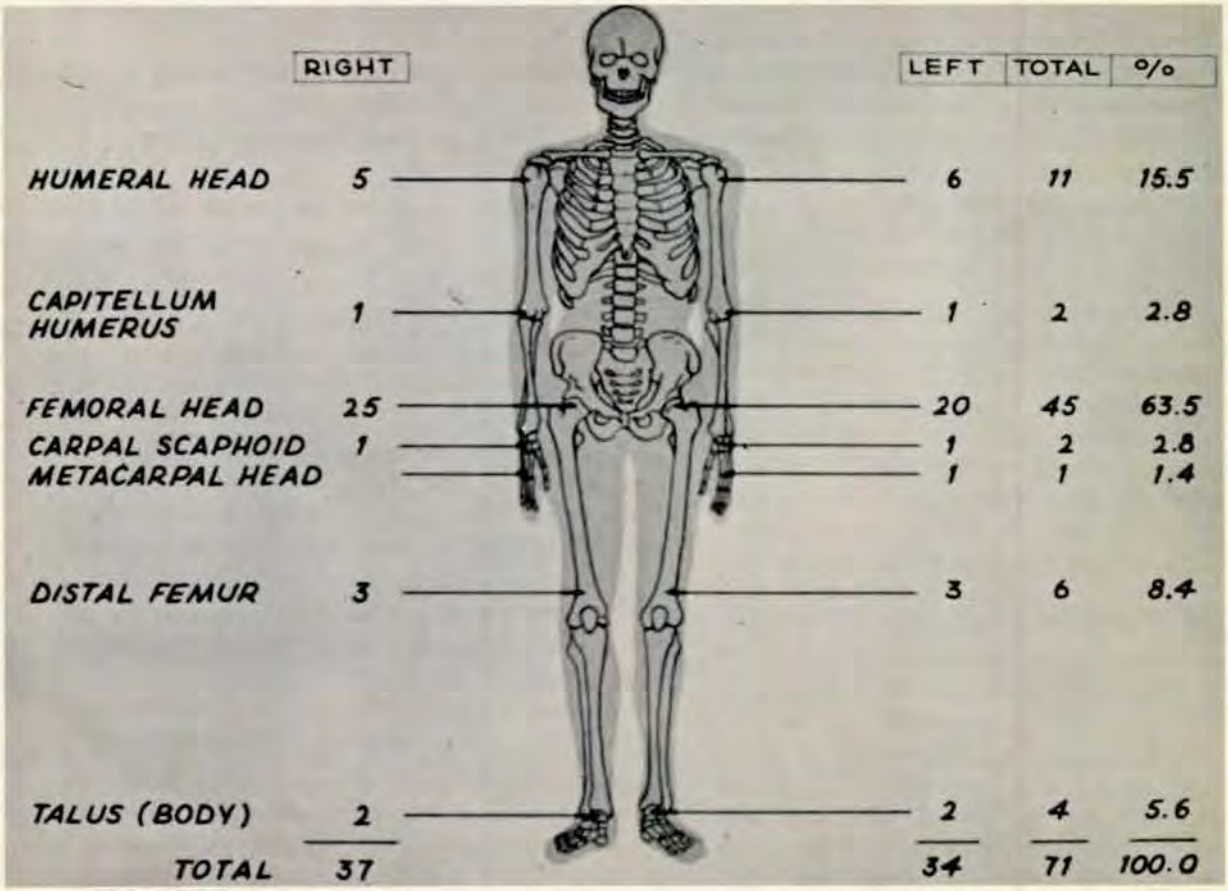

FIG. 3. Skeletal distribution of 71 osteonecrosis lesions, diagnosed roentgenographically, in 32 patients with hypercortisonism. (Jones, 1971. Illustration courtesy of publisher.)

ularly or intermittently; *4*) the diseases for which the therapy had been used were unrelated to the development of avascular necrosis.

Fisher and Bickel (1971) confirmed previous observations (Jones, 1971) by reporting intravascular fat emboli in 12 of the 25 femoral heads removed from 20 of 77 corticosteroid-treated patients with avascular necrosis seen at the Mayo Clinic from 1950 to 1968. Vasculitis had been proposed as the mechanism for vessel obstruction and subsequent ischemia. But no patient in this series had a clinical diagnosis of vasculitis, either prior to or after corticosteroid therapy. No consistent coagulation defects were noted in 16 patients studied in this series. Bromsulphalein retention was abnormal in 15 of 26 patients tested; however, 25 of the 77 patients receiving corticosteroids were also alcoholics.

Hemoglobinopathies

Diggs *et al.* (1937) first recognized femoral-head abnormalities in patients with sickle-cell disease. Diggs and Anderson (1971), as well as Chung and Ralston (1969), have reviewed aseptic necrosis of the femoral head in sickle-cell anemia and its genetic variants. Chung and Ralston (1971) have also recently reviewed necrosis involving the humeral head associated with sickle-cell anemia (SS hemoglobin) and the sickle-cell variants (SC disease and S-thalassemia). Kimmelstiel (1948) suggested that a decrease in oxygen tension sufficient to cause sickling of the red blood cells—*i.e.*, Po_2 below 60 mm Hg in sickle-cell anemia, or O_2 tension of 15 mm Hg or below in sickle-cell trait (AS hemoglobin) — would lead to circulatory stasis productive of thrombosis and occlusion of the epiphyseal blood supply.

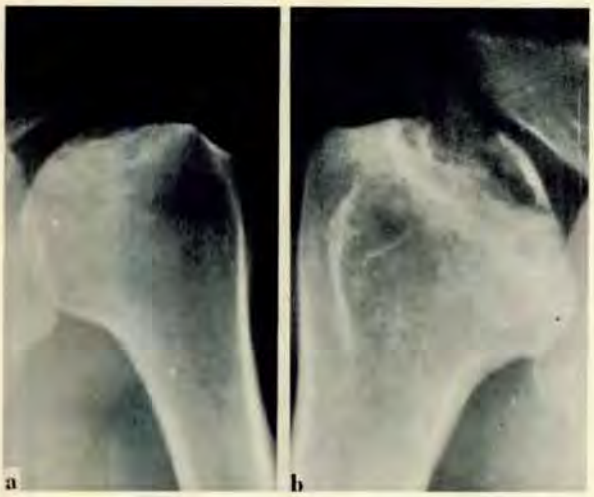

FIG. 4. Shoulders of patient receiving corticosteroids for immunosuppression following renal transplantation: (*a*) subchondral radiolucent crescent line with minimal structural collapse and subjacent sclerosis affecting L humeral head; (*b*) obvious structural collapse with articular incongruity in R humeral head.

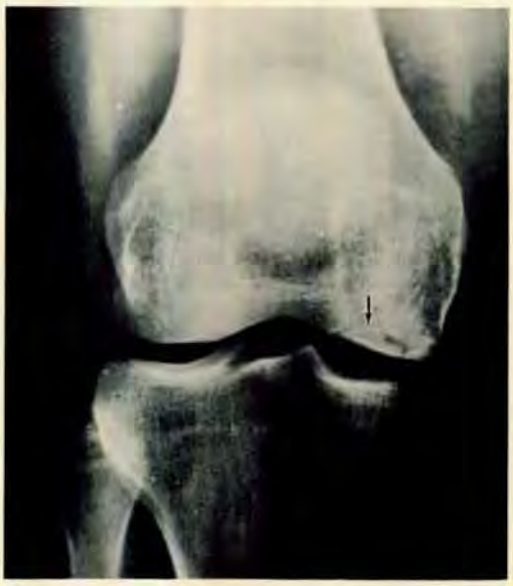

FIG. 5. A-P projection of R knee of patient receiving high-dosage corticosteroids for immunosuppression following renal transplantation. Subchondral osteochondritic lesion (arrow) affects central third of R medial femoral condyle with minimal gross distortion of joint space.

The frequency of femoral-head involvement observed as SS disease has varied from 0% in the 120 cases studied by Cockshott (1963) in West Africa to 12% in the 51 cases studied by Tanaka and co-workers (1956) in the United States. On the other hand, hip involvement in SC disease has been found to vary from 20% to 68% by Barton and Cockshott (1962) and Smith and Conley (1954). Of the 13 patients with sickle-cell hemoglobinopathies and femoral-head necrosis reported by Chung and Ralston (1969), 7 had SS disease, 2 had SC disease, 2 had S-thalassemia, and 2 had sickle-cell trait. Osteonecrosis had been reported earlier by Ratcliff and Wolf (1962) in 2 cases of sickle-cell trait and by Blau and Hamerman (1967) in 1 patient.

Reich and Rosenberg (1953) first reported avascular necrosis of bone in Caucasians with chronic hemolytic anemia due to combined sickling and thalassemia traits, and in blacks with S-Thal disease by Golding and co-workers (1959). In addition, osteonecrosis has been found in the hereditary persistence of fetal hemoglobin associated with the sickle-cell gene (SF) by Conley *et al.* (1963) and by Jacob and Raper (1958). Moseley and Manly (1953) concluded that there was no direct correlation between the severity of the hemoglobinopathy and the occurrence of bone necrosis in their 5 cases.

Roentgenograms of the shoulders and hips were performed by Jones and Johnston (1972) on 38 patients with various hemoglobinopathies, 7 of whom (18%) had evidence of avascular necrosis. Two of 21 patients with SS hemoglobin had involvement of the femoral head (Fig. 6 and 7), whereas 3 of 13 patients with SC disease had osteonecrosis. In 2 of 4 patients with S-Thal disease, roentgenographic evidence of avascular necrosis was found.

It is generally considered that the pathogenesis of necrosis in the sickle-cell hemoglobinopathies is as follows: In the presence of lowered O_2 tension the sickle hemoglobin causes increased blood viscosity, stasis, capillary thrombosis, and, finally, infarction. It is conceivable that small intraosseous vessels are thrombosed many times throughout life. But collateral blood supply and regenerative capacity, especially in the young

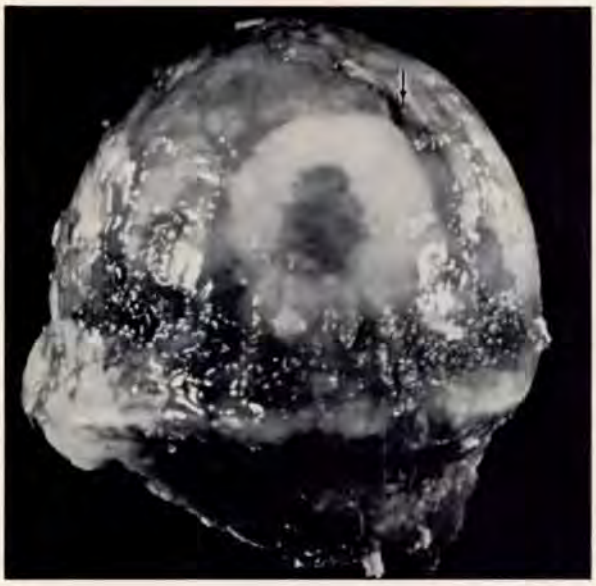

FIG. 6. Gross appearance of anterior-superior quadrant of L femoral head of 28-year-old black female with sickle-cell hemoglobinopathy. Small cleft (arrow) extends through cartilage medial to the light ring-shaped area with dark central discoloration, affecting cartilage and subchondral bone of necrotic zone.

individual, may prevent manifestations of bone necrosis, whereas frequent thromboses probably result in clinically obvious osteonecrosis.

Unfortunately, few femoral- or humeral-head specimens from patients with the sickle-cell hemoglobinopathies have been available for histological examination. Sherman (1959) studied 3 specimens from SS patients and suggested that hip-joint destruction depends on several mechanisms, all secondary to local damage to extremely small vessels. However, no investigator has actually found sickled erythrocytes within vessels adjacent to the necrotic area, although Tanaka *et al.* (1956) found blood vessels thrombosed within the necrotic area, which they assumed were caused by the sickling phenomenon. Chung and Ralston (1969) examined bone specimens from 2 patients, which had histological evidence of avascular necrosis but were without sickle-cell thromboses.

Reynolds (1965) suggested that, following sickle-cell crises, intravascular sickling occurs, resulting in increased blood viscosity and vascular stasis with progression to tissue ischemia and infarction. In the absence of bone-marrow and/or fat emboli, however, on tissue examination he noted no overt thromboses in the classic pathological sense.

Charache and Page (1967) studied the frequency of demonstrable marrow necrosis in SS patients, and noted that bone-marrow infarction is not necessarily an irreversible event in patients with sickle-cell disorders. Bone-marrow aspirations revealed that infarction is probably a relatively common event in the painful crises of sickle-cell disorders, occurring 1 to 3 days after the onset of pain. Inflammatory reaction was present 3 to 7 days after the onset of pain, followed by a phase of hypocellularity lasting 1 to 2 weeks after the crisis began. Within 1 month following a crisis, the bone-marrow cavity was repopulated by normal hematopoietic tissue.

Myerson (1959) established that the incidence of SS disease was approximately three times greater than that of SC disease in the American black population — *i.e.*, 1:1000 and 1:3000, respectively. Nevertheless, the incidence of avascular necrosis is higher in SC disease, but the crises are fewer and milder with no acceleration of erythrocyte destruction. In addition, osteonecrosis involving the femoral and humeral heads is uncommon in children with hemoglobinopathies who are under age 15.

Between 1953 and 1965 Charache and Page (1967) autopsied 6 SC and 12 SS patients. Bone-marrow necrosis and pulmonary-marrow and pulmonary-fat embolism were found in 3 of the SC patients and 2 of the SS patients. It is thought that fat embolism is less common in SS than in the genetic variants because the marrow in sickle-cell anemia is red and cellular (erythroid hyperplasia), containing little fat, whereas in sickle-cell trait (or in combination diseases) it is predominately fatty.

There are at least 17 reports of fat embolism complicating the sickle-cell hemoglobinopathies, particularly SC disease. The most recent include Graber (1961), Rywlin *et al.* (1963), and Diggs (1967), who suggest that the sequence of events productive of bone-marrow and fat emboli is as follows: There is massive sickling of erythrocytes in bone-marrow capillaries and sinusoids, cessation of blood flow in focal areas, hypoxia, endothelial injury with edema, hemorrhage, and the exudation of leukocytes with liberation of proteolytic enzymes, cellular degeneration and disintegration, and probable fibrinolysis. The increase in intramedullary pressure drives fat globules in the semiliquid marrow into intraosseous

FIG. 7. Gross sagittal sections of L femoral head of patient with SS hemoglobin, at level of *fovea centralis*, revealing irregular subchondral lesions in superior region of head and fracture cleft (arrow) extending into cartilage. Note marked erythroid hyperplasia of bone marrow.

veins, which are maintained patent by their attachment to the rigid trabecular and cortical bone. Jones and Johnston (1972) are studying an alternative hypothesis, which attributes the increased incidence of avascular necrosis affecting epiphyseal regions (particularly in SC disease) to possible blockade of terminal intraosseous vessels by intermittent systemic fat emboli arising from fatty bone marrow.

There is insufficient evidence to implicate sickle-cell trait (AS) as a predisposing condition for the development of osteonecrosis. AS is present in 8% to 10% of American blacks (Myerson, 1959). The coexistence of any two relatively common but unrelated entities in five reported patients with AS and avascular necrosis may therefore be purely coincidental.

Antecedent Unrelated Injuries

Individuals who experience multiple major, apparently unrelated injuries may incur a higher risk than normal of developing idiopathic ischemic necrosis of the femoral head. Two patients who had sustained multiple fractures and subsequently experienced idiopathic bone infarctions were observed by Kahlstrom *et al.* (1939). Jones (1971) and G. E. Sims (personal communication) each reported on a patient who had experienced idiopathic osteonecrosis of the right femoral head following multiple unrelated trauma. It is conceivable that in these instances multiple episodes of unrecognized traumatic fat embolism may have been the pathogenic mechanism.

Neither of these cases had clinical or roentgenographic evidence of prior hip fractures or dislocations, but it is possible that a nondisplaced femoral-neck fracture was missed at a time when attention was directed toward treatment of other injuries. Although fatigue (stress) fracture of the femoral neck was first reported by Blecher (1905), this entity is relatively uncommon. Prior to 1966 only 124 femoral-neck fatigue fractures had been reported in the literature. Devas (1965) and Blickenstaff and Morris (1966) recently reviewed the world literature; the latter reported 41 such fatigue fractures in 36 patients. They recognized that posttraumatic femoral-head avascular necrosis is extremely unlikely in incomplete or nondisplaced fatigue fractures, which

usually heal with progressive sclerosis (endosteal and/or periosteal callus).

Occlusive Vascular Disease

Although relatively few divers or compressed-air workers have severe occlusive vascular disease, advanced arteriosclerosis should be checked on in preemployment examinations. The reason is that osteonecrosis has been reported following the Leriche syndrome (Hughes *et al.*, 1971), thrombotic occlusion and intimal thickening (Hirsch, 1938), and vascular occlusion resulting from athero-emboli from distant atheromatous plaques (Bucky, 1959; Siller and Matthews, 1963; Bullough *et al.*, 1965). A review of many patients without evidence of osteonecrosis but with severe arteriosclerosis affecting the aorto-iliac portion of the vascular system leads to the conclusion that the association is probably relatively rare, in view of the number of individuals suffering from severe arteriosclerosis.

SUMMARY

Persons employed in deep-diving activities, hyperbaric-chamber operations, or compressed-air work are subject to dysbaric osteonecrosis. But there are certain other systemic and metabolic abnormalities associated with nontraumatic osseous avascular necrosis that likewise cause disabling juxta-epiphyseal lesions and asymptomatic metadiaphyseal lesions that are virtually indistinguishable from those of dysbaric osteonecrosis. However, once an individual has been exposed to dysbaric phenomena, any lesion that subsequently develops will unfortunately be attributed to the occupational exposure.

Therefore, applicants who have conditions associated with nontraumatic osteonecrosis, as well as previous dysbaric exposure, should be thoroughly evaluated during the preemployment examination. Many of these disturbances have been reviewed — alcoholism, gout, hyperuricemia, pancreatitis, hyperlipemia, hypercortisonism, hemoglobinopathies, earlier injuries, and occlusive vascular disease — all of which can be found in an otherwise healthy population of working men.

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