DRUG-INDUCED ARTHROPATHY AND NECROSIS OF THE
FEMORAL HEAD

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Necrosis of the femoral head has long been known to occur after fractures and dislocations of the hip (Phemister 1934), in caisson disease (Kahlstrom, Burton and Phemister 1939), Gaucher's disease (Schein and Arkin 1942), sickle-cell disease (Carroll and Evans 1949; Moseley and Manly 1953) and after ionising radiation (Vaughan 1956). It has generally been assumed that some degree of vascular insufficiency is common to all of these conditions, and the term "avascular necrosis" has come to be applied to the femoral head lesion regardless of the circumstances in which it occurs.

Since 1960 similar changes have been observed in patients receiving corticosteroid therapy (Murray 1960; Sweetnam, Mason and Murray 1960; Sweetnam 1960; Heimann and Freiberger 1960; Isdale 1962; Boksenbaum and Mendelson 1963; Burrows 1965; Sutton 1968; Fisher and Bickel 1971) and in chronic alcoholics (Jones, Jameson and Engleman 1968). The existence of this entity of drug-induced arthropathy suggests that many previously unexplained examples of femoral head necrosis may fall into the same category. Thus, in the 125 cases of "idiopathic" necrosis reported by Merle d'Aubigné, Postel, Mazabraud, Massias and Gueguen (1965) alcoholism was "relatively common", while 36 per cent of their patients had received steroid therapy "counting only those cases in which cortisone was administered for another condition before the pain started". Likewise, in the cases described by Patterson, Bickel and Dahlin (1964) the incidence of alcoholism was 17 per cent, and 10 per cent of the patients had taken corticosteroids "in amounts larger than maintenance doses for prolonged periods". In a more recent report on forty-eight similar cases in a Swiss study, eight patients "presented with . . . symptoms of alcohol intoxication" and a like number had been treated with systemic corticosteroids (Zinn 1971). Finally, there can be little doubt that arthropathy after organ transplantation is attributable to immunosuppressive steroids (Jones, Engleman and Najarian 1965; Bravo, Herman and Smyth 1967; Cruess, Blennerhassett, MacDonald, MacLean and Dossetor 1968; Hall and Hume 1970; Harrington, Murray, Kountz and Belzer 1971).

The possibility that other drugs may be similarly implicated, especially the non-steroid anti-inflammatory and analgesic preparations, has also been considered (Murray 1966, Solomon 1968 and 1970, Arora 1968, Murray and Jacobson 1971). Few if any of the published reports on "idiopathic" necrosis contain details of all the drugs administered to these patients; yet it is often clear from the case histories that an underlying disorder such as osteoarthritis or gout must have been treated for some years with the usual range of popular remedies. Moreover, even those patients known to have had corticosteroids for conditions such as rheumatoid arthritis almost certainly had received other anti-inflammatory drugs as well; their possible role cannot be ignored.

The pathogenesis of the arthropathy induced by corticosteroids and alcohol is still a matter of considerable controversy. Current thought seems to have crystallised around two totally unrelated theories: that of subchondral osteoporosis and micro-fracture leading to bone collapse and localised aseptic necrosis (Murray 1966, Solomon 1968 and 1970, Storey 1968, Zinn 1971); and that of fat embolism, which postulates subchondral vascular occlusion by peripheral fat emboli (Jones, Engleman and Najarian 1965; Jones, Engleman, Steinbach, Murray and Rambo 1965; Bravo et al. 1967; Jones et al. 1968; Fisher, Bickel and Holley 1969).
The present study attempts to define more precisely the entity of drug-induced arthropathy, to elucidate the conditions under which it occurs and to offer a critical evaluation of the current theories of its pathogenesis.

**CLINICAL MATERIAL**

Seventy-two subjects with femoral head necrosis unassociated with previous trauma, blood dyscrasia or local infiltrative disease of bone were encountered between January 1965 and August 1971. Careful questioning elicited in every case a history of prolonged administration of some unusual substance, either as medication or by way of self-indulgence. Four groups were distinguished: 1) patients treated with corticosteroids (thirty-two cases); 2) white men who either admitted excessive alcohol intake or presented the familiar features of chronic alcoholism (ten cases); 3) South African negroes with the clinical features of iron-overload from drinking large quantities of home-brewed beer (sixteen cases); and 4) patients receiving large doses of non-steroid anti-inflammatory drugs for pre-existing arthritis of the hip (fourteen cases).

Apart from routine and radiographic examination each patient was fully investigated for blood dyscrasias. No case was admitted to the study unless Gaucher’s disease, sickle-cell disease, disorders of blood coagulability and caisson disease had been excluded.

The last thirty patients encountered in this series were investigated for abnormalities of lipid metabolism. They comprised twelve patients from Group 1, two from Group 2, ten from Group 3 and six from Group 4. In twelve of these, including some patients from each of the four groups, blood samples were repeatedly examined for fat globules by Gurd’s (1970) method. Liver biopsy was carried out in eight of these patients. For comparison, twenty-two ward patients of similar age and sex, suffering from a variety of orthopaedic disorders, but without subarticular bone collapse, were investigated in the same way.

**PATHOLOGICAL MATERIAL**

Forty-two femoral heads obtained from forty patients were available for study. Each specimen was divided in the coronal plane with a buther’s band-saw and the cut surface carefully examined for textural abnormalities. Slabs 2 to 3 millimetres thick were then cut from each half of the head and examined in direct and transmitted light. Each slab was radiographed and the trabecular pattern was studied for evidence of discontinuity or distortion. Thereafter the individual specimens were fixed and stored in 10 per cent neutral formalin. Selected slabs were further divided into blocks measuring 8 by 16 millimetres. After decalcification in 9 per cent nitric acid, one block from each specimen was embedded in gelatin and frozen in the laboratory cryostat. Sections were cut and stained for fat with oil red O by the method of Jones and Sakovich (1965). Similar blocks were used to prepare sections stained with haematoxylin and eosin.

In addition to this material, fourteen femoral heads removed for other reasons (fractures of the femoral neck, Gaucher’s disease, avascular necrosis after dislocation, arthritis without subchondral necrosis and collapse) were studied in the same way.

**DIAGNOSIS**

The provisional diagnosis of drug-induced arthropathy was based on the following criteria: 1) clinical evidence of progressive arthropathy manifested by pain, loss of movement and increasing instability of the joint; 2) the radiographic features of subchondral destruction associated with areas of increased density (Fig. 4), or unequivocal evidence, based on serial radiographs, of accelerated erosion or fragmentation of the bones on either side of the joint (Figs. 7 and 8); 3) a definite history of analgesic and anti-inflammatory drug therapy, or excessive intake of alcohol, preceding the onset of the arthropathy.
Many of the newer anti-inflammatory drugs, though they are possibly not analgesics in the strict pharmacological sense, bring about a marked relief of pain. Similarly alcohol, if taken in sufficient quantity, may so effectively abolish pain, and indeed all sensibility, as to amount to a mild anaesthetic.

Pre-existing arthritis did not invalidate the diagnosis provided the sudden joint collapse or femoral head necrosis presented as "a new event". In some cases this could be dated with reasonable certainty from the beginning of "effective" drug therapy. The rapid deterioration in the architecture of the joint contrasting with the patient's symptomatic improvement.

Osteoporosis of the affected area was common. Usually this was part of a generalised loss of bone density, as in hypercortisonism, chronic alcoholism and iron-overload osteoporosis. Sometimes, however, it was more apparent in the region of the affected joint, suggesting the presence of some long-standing local disorder like osteoarthritis.

**CLINICAL AND RADIOGRAPHIC FEATURES**

**Group 1: Corticosteroid arthropathy**—In thirty-two cases there was a history of prolonged administration of corticosteroids or a combination of these with non-steroid anti-inflammatory drugs. The age distribution was from twenty-four to seventy-one years and women outnumbered men by three to one. All but eight of these patients had rheumatoid arthritis; two had disseminated lupus erythematosus, one polyarteritis nodosa, one asthma, one pemphigus and one a "frozen shoulder" treated with systemic corticosteroids for six months. Only two cases following renal homotransplantation and immunosuppression with corticosteroids have been encountered so far.

The duration of treatment with corticosteroids before the onset of the arthropathy is shown in Figure 1. Only seven patients had received more than 10 milligrams prednisone equivalent a day: two had been maintained on 15 milligrams and one on 20 milligrams a day for at least six months, two had received 30 milligrams a day for short periods, and the two renal transplant patients had each received over 1,000 milligrams in the month after transplantation and were being maintained on 15 to 20 milligrams a day. Almost all the patients had some features of hypercortisonism, including the typical facies, muscle wasting, skin fragility and generalised osteoporosis.

Radiography of the hip joints showed varying degrees of destruction, in many instances no doubt reflecting the combined ravages of rheumatoid arthritis and steroid arthropathy. In
six cases, however, a pure steroid arthropathy occurred, and here the radiographic features could be traced unclouded by any pre-existing joint disease (Figs. 2 and 3). It is noteworthy that in two of these cases routine radiography failed to show any abnormality weeks after the onset of pain and stiffness. The earliest lesion discovered, after tomography in several planes, was a small area of demineralisation in the immediate subarticular zone of the weight-bearing part of the femoral head. At a slightly later stage this might be associated with a fine radiolucent fracture line running through the subarticular trabeculae (Fig. 2) or with simple flattening and distortion of the normally spherical outline of the femoral head. When the development of the lesion could be followed through all its stages it became clear that the increased radiographic density of the femoral head, long considered to be the most characteristic feature of avascular necrosis, was a late happening. In the untreated case the end-result was fragmentation and progressive destruction of the femoral head. In eighteen patients some degree of bone resorption occurred on the acetabular side of the joint; in the more advanced cases this led to protrusio. Seven patients in this group had similar changes in other bones, the weight-bearing joints being affected five times as often as the non-weight-bearing joints.

**Group 2: Arthropathy associated with chronic alcoholism**—Of the ten patients in this group, four were chronic alcoholics in special institutions and the other six admitted taking alcohol in excessive amounts. “Excessive drinking” is difficult to define precisely, yet there was little doubt about the existence of such a category. For instance, one patient, though not designated an alcoholic, consumed a bottle of brandy every day; another drank four or five cans of beer and a half-bottle of brandy every evening. Eight of these patients were men and two were women; their ages ranged from forty-eight to seventy-two years. The common symptom was pain in one or both hips and radiographs confirmed the presence of “avascular necrosis” or subchondral destruction of the femoral head in every case (Fig. 4).

**Group 3: Arthropathy associated with iron-overload**—Osteoporosis associated with scurvy and siderosis is a well recognised syndrome in certain African communities in which it is customary to drink large quantities of beer brewed in iron containers (Sefel, Malkin, Schmaman, Abrahams, Lynch, Charlton and Bothwell 1966). Most of the patients are middle-aged men and almost invariably the chief complaint is backache. Hepatomegaly is common and about half the patients have clinical evidence of scurvy. Radiographs show osteoporosis of the spine with compression fractures.
In these individuals “idiopathic necrosis” of the femoral head is quite often found (Fig. 5). The diagnosis is usually heralded by the sudden onset of pain in the hips; occasionally the condition is discovered as an incidental finding. All these patients give a history of drinking large quantities of the traditional Bantu beer. The amount varies from two to eight litres a week, but perhaps more significantly, most of it, together with more potent alcoholic concoctions, is consumed in one continuous bout of drinking over the weekend; on these occasions the revellers may pass through periods of relative insensibility.

At first it might seem that these cases fall into the same category as the chronic alcoholics. The resemblance, however, is superficial. The Africans’ drinking habits are part of social custom: the alcohol content of the beer, which is usually prepared from sorghum, is extremely low (about 3 per cent), and the concentration of protein and vitamins is sufficient to prevent the usual effects of alcoholic malnutrition. Specifically, there is no fatty degeneration of the liver, which is common in chronic alcoholism, and serum triglyceride levels are invariably normal or low.
Non-steroid analgesic arthropathy. Figure 7—The radiograph of a patient with bilateral osteoarthritis of the hips in 1965. Figure 8—A radiograph of the same case taken in 1967. Gross destruction of the femoral heads and acetabula has occurred over a period of two years.
The radiographic changes differed little from those of corticosteroid arthropathy. In two cases, however, a localised sequestration of the weight-bearing part of the femoral head could be demonstrated (Fig. 6).

**Group 4: Arthropathy associated with the administration of non-steroid anti-inflammatory drugs**—Fourteen patients with destructive arthropathy were known to have taken such drugs and analgesics in large doses for a year or longer. Two of these patients had rheumatoid disease, two had chronic gout and ten had osteoarthritis of the hip. No distinction could be made on the basis of the particular agent employed because all but one of these patients had taken a combination of drugs. Care was taken to exclude the possibility that the drug therapy had followed the onset of the arthropathy, and only those cases were included in which earlier radiographs showed no bone resorption or necrosis when treatment began.

All the patients in this group were between fifty-six and seventy-eight years of age. There were eleven women and three men, the unusual sex ratio reflecting not so much the distribution of the primary disorder (usually osteoarthritis of the hip) as the tenacity with which women often persevere for long periods on increasing doses of anti-inflammatory drugs.

The rate of articular destruction was slower in these cases than in steroid arthropathy. Nevertheless, some of the worst lesions in the series occurred in this group (Figs. 7 and 8).

**LIPID METABOLISM**

Serum lipids were estimated in thirty patients with femoral head necrosis and in twenty-two general ward patients who had no obvious joint pathology (Table 1). In only one patient—a man with corticosteroid arthropathy—was there a marked elevation of total lipids (1,800 milligrams per 100 millilitres) and of triglycerides (520 milligrams per 100 millilitres). However, slight increases above the "normal" range of triglyceride values were found in another five patients having corticosteroid therapy, in two patients with chronic alcoholism and in one patient receiving non-steroid anti-inflammatory drugs. Two patients in the "control group" had abnormally high serum triglyceride levels.

Liver biopsy was carried out in three patients with corticosteroid arthropathy, one with chronic alcoholism and four with iron overload osteoporosis. In two of those receiving corticosteroids fatty infiltration was demonstrated.

It has been stressed (Gurd 1970) that changes in serum triglyceride levels are less important in the diagnosis of fat embolism than the demonstration of fat globules greater than eight microns in diameter in the circulating blood. This feature was therefore sought in twelve patients with femoral head necrosis, including five receiving corticosteroid therapy. A significant fat globulinaemia was discovered in four of these patients. However, six of the twenty-two controls, who had no abnormality of the hips whatever, had circulating fat globules.

**Table 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>Number in group</th>
<th>Number studied</th>
<th>Hyperlipaemia (normal range: 400–1,000 milligrams/100 millilitres)</th>
<th>Hypertriglyceridaemia (normal range: 30–150 milligrams/100 millilitres)</th>
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</thead>
<tbody>
<tr>
<td>Corticosteroid arthropathy</td>
<td>32</td>
<td>12</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Alcohol arthropathy</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Iron-overload osteoporosis</td>
<td>16</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-steroid analgesic arthropathy</td>
<td>14</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Control group: general orthopaedic patients</td>
<td>22</td>
<td>22</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
from 12 to 35 microns in diameter. Taken together, these results showed that there was no consistent relationship between femoral head necrosis and either hypertriglyceridaemia or fat globulinaemia.

**MORBID ANATOMY**

Pathological material included several examples from each of the clinical groups described above. The changes in the femoral head were remarkably constant (Fig. 9), variations in the basic pattern being determined by 1) the presence or absence of any pre-existing disease, 2) the extent of the necrosis, 3) the rapidity with which it developed, and 4) the stage it had reached at the time of operation.

![Diagram](image)

**Fig. 9**


The articular cartilage (Zone A) is usually intact in the rapidly developing lesion such as one finds in the pure corticosteroid arthropathy, but may be fragmented or entirely absent in long-standing cases and in those complicated by an underlying arthritis. The necrotic area (Zone B) occurs immediately beneath the articular cartilage and invariably includes the weight-bearing area. It may extend no more than a few millimetres in depth or may involve more than half the head. It is usually bounded by vascular granulation tissue (Zone C) which appears as a congested demarcation line on the cut surface separating the necrotic area from viable bone. At about the same depth new bone formation is seen (Zone D) extending into the necrotic zone and replacing the acellular trabeculae; this produces the radiographic density generally associated with "avascular necrosis" and is best demonstrated on the slab radiographs of coronal sections. Beyond this the bone thins out to the normal trabeculae of the metaphysis (Zone E).

Details of one of the more rapidly developing lesions, that shown in Figure 2, are illustrated in Figures 10 to 12. Here the articular cartilage has been separated from the underlying bone by a fracture through the subarticular trabeculae. Zone B, the area of subchondral necrosis, is bounded on its deep aspect by the vascular bone of the granulation tissue zone (C). The congested area is best seen by transmitted light through thin slabs of
bone; when this pattern is compared with the contact radiographs of the same slabs it is clear that the zone of reactive bone formation (D) begins in the vascular region. Microscopically the several zones overlap each other to a considerable extent. In this particular case masses of degenerative cartilage and clumps of bone debris appear in the necrotic subchondral zone

![Figure 10](image10)

**Fig. 10**

The same case as Figure 2, showing the characteristic zones of subchondral necrosis, vascular congestion and reactive new bone. Figure 10—The cut surface. Figure 11—A slab radiograph. Figure 12—A transilluminated slab of the femoral head.

![Figure 11](image11)

![Figure 12](image12)

where many of the acellular trabeculae are already surrounded by advancing lamellae of new bone (Fig. 13). At a deeper level vascular granulation tissue and active new bone formation are seen side by side, osteogenesis occurring by endochondral ossification and appositional growth (Figs. 14 and 15).

Details of a more extensive though essentially similar lesion (that shown in Figure 4) are given in Figures 16 to 18. The necrotic zone occupies about half the femoral head and is demarcated by a clear-cut line of vascular bone and granulation tissue which overlaps the area of increased density in the corresponding slab radiograph.

Even in the advanced stage of destruction the characteristic patterns can usually be discerned. In the case illustrated in Figure 19 the weight-bearing area (Zone A) is fragmented and compressed into the underlying necrotic bone (Zone B). The usual granulation tissue zone (C) is replaced by a wide radiolucent band of fibrous tissue, suggesting the presence of a “pseudarthrosis” between the necrotic and the viable parts of the femoral head. Long-standing reactive bone formation has produced an unusually dense picture in the slab radiograph (Zone D).
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FIG. 13

FIG. 14
Photomicrographs of the same case as Figure 3. Figure 13—Showing cartilage and bone debris among the necrotic subchondral trabeculae. (Haematoxylin and eosin, ×80.) Figure 14—Showing reactive new-bone formation occurring by both endochondral and appositional ossification. (Haematoxylin and eosin, ×80.)
In many of the older lesions—and especially in those attributable to non-steroid anti-inflammatory drugs—there was microscopic fragmentation of the bony trabeculae, splinters of bone sometimes jamming the marrow spaces throughout the femoral head.

**Fat studies**—Fifty-six specimens were examined for intravascular fat in the subchondral region of the femoral head: forty-two were from cases of necrosis and fourteen from femoral heads removed for other reasons, including four normal heads removed after fracture of the femoral neck and seven removed for osteoarthritis unassociated with necrosis. As reported by Fisher et al. (1969), fat was commonly present in the Haversian canals in cases of drug-induced arthropathy (Fig. 20). That it was intravascular, however, could not be shown, and its presence in cases of rheumatoid arthritis, osteoarthritis and fracture of the femoral neck, all uncomplicated by bone necrosis, suggests that it is not specifically related to drug-induced arthropathy or bone necrosis.

**DISCUSSION**

Although the term “drug-induced arthropathy” has been used, it is conceded at once that no absolute proof of cause and effect has been presented in the cases described here. Nor is the author unaware of the dangers of grouping together conditions with features as disparate as those of iron-overload osteoporosis on the one hand and steroid-treated rheumatoid arthritis on the other. Yet there is sufficient in common to suggest a similarity in the pathogenesis of the arthropathy that characterises each condition.

There was always a history of prolonged administration of some anti-inflammatory or analgesic substance (including alcohol) followed by the appearance of a destructive arthropathy. While the pathological changes varied from a localised subchondral collapse to widespread destruction of the femoral head, and while some features were more common in one type of
The same case than another, all varieties of change were encountered in each clinical group. Some degree of osteoporosis, too, could be demonstrated either radiographically or histologically in all these cases. Furthermore, there was a strong suggestion that the distribution of the osteoporosis was related to that of the destructive arthropathy. Thus, in the patients taking corticosteroids, in whom osteoporosis was widespread and often severe, subchondral necrosis was encountered in most of the peripheral joints; in those with iron-overload osteoporosis, which is usually limited to the axial skeleton. bone collapse occurred only in the hips and spine: and in the non-steroid analgesic arthropathy subchondral necrosis was seen only in those joints with some long-standing underlying disorder.

The presence of osteoporosis in these patients has not always been conceded, nor its etiological significance fully appreciated, by other workers. Fisher and Bickel (1971), reviewing seventy-seven cases of corticosteroid-induced necrosis, state that "necrosis occurred without roentgenographic evidence of osteoporosis in nearly all cases . . ." Yet the very nature of the clinical disorders in their patients (systemic lupus erythematosus, rheumatoid arthritis, chronic alcoholism, endogenous hypercortisonism, chronic glomerulonephritis treated by dialysis and renal transplantation), coupled with the fact that in every case except one the dosage of corticosteroids was "in excess of physiological replacement", makes it likely that some degree of osteoporosis was present. The same authors point to the fact that femoral head necrosis
FIG. 19
The same case as Figure 5. A slab radiograph of the left femoral head. The articular surface has been driven into the underlying necrotic bone causing marked flattening of the femoral head. At a deeper level there is dense new-bone formation.

does not occur in other, more severe forms of osteoporosis; but this is to miss the very essence of the association postulated here—that of osteoporosis combined with a diminution of the normal inflammatory and protective pain responses.

Although the implicated drug usually contributes to the loss of bone density, this is not essential to our concept. What is important is that the analgesic and anti-inflammatory effects operate at the same time as the osteoporosis, regardless of the cause of the latter. It is in this context that the arthropathy associated with the non-steroid anti-inflammatory drugs can be understood. The latter relationship, though inherent in the findings presented in several publications, has been less readily recognised than that between corticosteroids and joint destruction. Thus, in the twenty-seven cases of femoral head destruction in rheumatoid arthritis and osteoarthritis described by Isdale (1962) "only ten patients had received steroids in any form". One might reasonably infer that the others were treated with non-steroid anti-inflammatory and analgesic drugs. So, too, the apparent connection between hyperuricaemia and "idiopathic" necrosis of the femoral head may hide a much more important relationship. Of sixty-five such cases described by McCollum, Clippinger, O'Neil and Mathews (1967), a "significant" elevation of serum uric acid was discovered in approximately one-third and 20 per cent of their patients later developed gouty arthritis. Equally important, however,
is the observation that 40 per cent were “either alcoholics or excessively heavy drinkers”. It is likely, too, that any patient with overt gout will have had repeated courses of anti-inflammatory drugs and analgesics. This is all too clearly illustrated in the case reported by Hunder, Worthington and Bickel (1968); their patient, who is described as “overweight”, consumed twelve aspirin tablets and two to four cans of beer each day.

Whether the anti-inflammatory and analgesic effects operate directly to permit fragmentation of the thinned subarticular trabeculae, or whether some intermediate step is interposed, remains uncertain. There is evidence that microfractures of subchondral bone occur in osteoporosis (McFarland and Frost 1961, Frost 1963, Lagier 1971, Zinn 1971) and in osteoarthritis of the hip (Trueta 1968). This would appear to be even more likely in states of diminished sensibility, especially if combined with increased exposure to trauma, as may be the case in those who take alcohol to excess. In the cases described here trabecular fragmentation was not uncommon, and in two instances comminuted intracapital fractures had occurred without the patient’s knowledge. The disproportionately high incidence of subchondral necrosis in weight-bearing as compared with non-weight-bearing joints—and specifically in the stress areas—also favours the proposed mechanism.

The alternative theory, that subchondral necrosis is due to fat embolism in bone (Jones, Engleman and Najarian 1965; Jones, Engleman, Steinbach, Murray and Rambo 1965) is based on the observation that both hypercortisonism and chronic alcoholism may be associated with fatty infiltration of the liver, hyperlipaemia and systemic fat embolism (Durlacher, Meier, Fisher and Lovitt 1954; Lynch, Raphael and Dixon 1959; Hill 1961). The demonstration of subchondral intravascular fat in steroid-induced femoral head necrosis (Fisher et al. 1969) has lent considerable weight to the original suggestion, though it offers no proof of the proposed sequence of events. Indeed, fat in the Haversian canals could as well be the result as the cause of subchondral necrosis.

In the specimens examined here no constant relationship could be found between the presence of intravascular fat and femoral head necrosis. Fat in the Haversian canals appeared to be no less common in a number of disorders unassociated with osteonecrosis and even in the normal femoral head, while some cases of corticosteroid arthropathy showed no intravascular fat at all. Nor was the presence of either Haversian canal fat or subchondral necrosis positively related to a disturbance of lipid metabolism. The fatty liver, which is held to be the source of the circulating fat globules in hypercortisonism and chronic alcoholism, does not occur in African patients with iron-overload osteoporosis and femoral head necrosis.

Though the pathogenesis remains uncertain, the form of the pathological lesion has been clarified. The initial change is demineralisation and fragmentation of the subchondral trabeculae, which produces little alteration in the routine radiograph. Unfortunately, increased radiographic density of the femoral head is still regarded as the cardinal sign of necrosis, whereas it signifies the stage of repair and is due to bone replacement along the acellular trabeculae. The importance of this observation is that the criteria for diagnosing aseptic necrosis of bone should be revised so that treatment may be directed towards protecting the vulnerable weight-bearing area long before the signs of bone replacement make their appearance. In the wider context, the association of femoral head necrosis with the use of corticosteroids and other anti-inflammatory and analgesic drugs calls for a reappraisal of their role in the treatment of many common disorders.

**SUMMARY**

1. It is well known that the administration of corticosteroids may result in necrosis and progressive destruction of the femoral head. Identical changes have been found in chronic alcoholics, in South African negroes suffering from iron-overload osteoporosis and in patients with arthritis of the hip treated with non-steroid anti-inflammatory and analgesic preparations. The term “drug-induced arthropathy” is used to describe the common pathological lesion.
2. Seventy-two patients with this complication have been investigated and forty-two femoral heads were available for detailed study. The characteristic change is subchondral fragmentation and osteonecrosis, followed later by reactive bone formation and the typical increased radiographic density.

3. The frequent occurrence of fat occupying the Haversian canals in the affected femoral heads has not been adequately explained and its relationship to the destructive arthropathy remains obscure. The findings presented here do not support the theory that fat emboli are responsible for the subchondral bone changes.

4. More credence is given to the theory of subchondral microfracture in osteoporotic bone. The destructive arthropathy invariably follows the administration of some anti-inflammatory or analgesic preparation. It is postulated that a state of diminished sensibility predisposes to microtrauma in osteoporotic bone resulting in subarticular collapse of the femoral head.

REFERENCES


