Ischaemia of bone

MARY CATTO

From the Department of Orthopaedic Pathology, University of Glasgow at the Western Infirmary, Glasgow

In recent years bone necrosis has become of increasing significance and has stimulated much interest amongst clinicians, radiologists and pathologists. It is now an important cause of disability because it commonly complicates intracapsular femoral neck fracture which is frequent in aging populations (Barnes *et al*, 1976; Graham and Wood, 1976). It is a hazard not only to tunnellers working in compressed air (MRC Decompression Sickness Panel Report, 1971) but also to divers whose numbers and activities are ever expanding with the exploitation of North Sea oil (Lancet, 1974; Davidson, 1976). It gives rise to articular symptoms in some patients receiving therapeutic steroids (Fisher and Bickel, 1971; Park, 1976) and particularly in those on the high dosages and prolonged administration associated with immunosuppression following organ transplant. In addition to necrosis associated with these and other well accepted causes, so-called idiopathic or spontaneous necrosis may occur, especially in the femoral head (table I). The predisposing causes of such 'idiopathic' necrosis are currently the subject of intensive investigation (Zinn, 1971a and b) (table II).

Unfortunately the clinical diagnosis of bone necrosis is not easy. There are usually no signs to indicate an ischaemic episode until many months have elapsed and necrotic bone shows no radiological change unless the part is immobilized, then the dead bone may appear denser than the adjacent viable, porotic bone. A true increase in radiological density may result from laying down of new bone during repair, from compaction of trabeculae or from calcification within living or dead tissue (Johnson, 1964). Diagnosis may thus be difficult and caution is required in inferring underlying tissue changes even from well recognized radiological patterns.

The widespread use of prosthetic replacement of bone and joints has provided the pathologist with the opportunity of studying more rewarding material than the small biopsy or the end-stage necropsy specimen, and there is now fairly general agreement on the pattern of morphological changes following necrosis (Catto, 1976): the sequence of events which brought these changes about is, however, open to more than one interpretation. In many conditions the

pathogenesis of necrosis is controversial and is not always accepted as being primarily vascular (table I). Many questions remain unanswered, including one of major clinical importance; why is revascularization so often arrested and incomplete?

The purpose of this paper is to indicate how bone necrosis may be recognized, to describe in a general way the main morphological features, and to point out areas of difficulty and controversy. Many topics, and particularly the osteochondritides of childhood, are omitted since it is rare for the pathologist to obtain material from them.

Recognition of dead bone

Experimental evidence suggests that ischaemia of more than a few hours (Woodhouse, 1962; Henard and Calandruccio, 1970), perhaps up to 48 hours (Kenzora *et al*, 1969), results in death of bone. It is generally accepted that if bone is fresh, rapidly fixed and the sections of good quality, bone death is recognized histologically by loss of osteocytes from lacunae. However, artefactual loss by physical displacement of osteocytes from lacunae during sectioning or their failure to stain because of slow fixation or overdecalcification must be taken into account. Conversely, dead sequestra or stored allografts occasionally retain pyknotic nuclei. Unfortunately, loss of osteocytes in conventionally prepared histological sections may not become apparent for a few days nor be complete for a few weeks after the onset of ischaemia (fig 2) (Bonfiglio, 1964; Catto, 1965a). While special techniques such as the Feulgen reaction have been used in experimental animals to demonstrate early changes in osteocyte nuclei following ischaemia, their assessment requires control material for comparison (Rösingh and James, 1969). Ischaemic changes in haemopoietic marrow, such as the formation of large fat-filled spaces and loss of nuclear staining, may be recognizable within a few days (fig 1), but death of fatty marrow is more difficult to recognize because of its relatively low cellularity. The practical implication of these observations is that the pathologist can seldom answer the orthopaedic surgeon who, following a recent femoral neck fracture,

	<i>Favoured Sites</i>	<i>Clinical</i>	<i>Postulated Mechanisms</i>
Trauma	Femoral head, carpal scaphoid, talus, lunate	Intracapsular fracture of femoral neck in old porotic women → some degree of necrosis in more than 66%. Of the 75% which unite about 25% later develop collapse of femoral head	Local pattern of blood supply
Radiation	Femoral head, shoulder girdle, ribs	Follows both external and internal radiation. Actual necrosis only in severe osteodysplasia. May develop fracture especially of femoral neck? cause and unassociated collapse of femoral head	Direct effect on osteocytes. Secondary effect from vascular narrowing. Alteration in matrix strength → trabecular fracture and secondary necrosis
Dysbarism	Shafts of femur, humerus, tibia Humeral head, femoral head	Tunnellers: probably 20% develop bone necrosis. Divers: 50% in poorly supervised Japanese; only 5% in Royal Navy. May be bilateral. Likelihood of developing lesions increases with number of decompressions, length of exposure, higher pressure levels and number of attacks of decompression sickness	Profuse expanding nitrogen bubbles. Platelet aggregation Fat emboli etc.
Haemoglobinopathies	Acute 'dactylitis'. Shafts of humerus, femur, tibia, any long bone. Femoral head, humeral head. ?End plates of vertebral bodies (not proven by histology)	Always investigate for sickling when → bone necrosis in Africans. Young children may → severe pain and swelling of fingers due to acute infarction. Older patients most disabled by collapse of femoral or humeral head. May have associated marrow hyperplasia due to haemolytic anaemia. Salmonella osteomyelitis may complicate	Red cell sickling + sluggish circulation → vascular occlusion → endothelial damage → infarction
Pancreatic disease and occasionally polycythaemia	Long bone shafts, rarely femoral or humeral heads	Necrosis occurs occasionally from acute or chronic pancreatitis and very rarely in lipase-producing pancreatic carcinomas	Lipase release to peritoneal fluid → lymphatics → bloodstream → necrosis of fatty marrow and sometimes of bone. Systemic fat emboli.
Gaucher's disease	Femoral head, humeral head. Shafts of long bones	Deficiency of glucocerebrosidase leads to accumulation of kersin in macrophages. Familial—Jewish predilection. Often bilateral involvement of bones	Packing of marrow by Gaucher cells → compression of sinusoids. Perhaps blocking of lumina of sinusoids with Gaucher cells as in liver. Necrosis of cells followed by dense fibrosis of marrow
Steroid therapy	Femoral head, humeral head, femoral condyle, upper tibia, talus, scaphoid, capitulum of humerus, capitate, shaft, of femur	May develop pain in joints within 6 months radiological evidence usually later—often multiple bones and symmetrical involvement. Lowering of dosage of steroids by use of antilymphocytic serum reduced incidence of bone necrosis in some series of renal transplant patients	Systemic fat emboli Trabecular microfracture with secondary necrosis
'Idiopathic' or 'spontaneous'	Femoral head Medial femoral condyle	M4: F1, age 30-60. Pain may be sudden or insidious. Second hip involved later in up to 70% and may at first be asymptomatic—Compared with Europe and USA appears relatively uncommon in UK. Mostly elderly women—seldom bilateral, sudden onset of pain—often followed by loose body formation and osteoarthritis	Numerous associations (see table II). In some, eg, alcoholics, systemic fat emboli are postulated; in others trabecular microfractures
	Other sites are rare		

Table I Summary of ischaemia of bone

Alcoholism
Gout and hyperuricaemia
Diabetes and hyperglycaemia
Minor congenital anomalies of the hip
Disorders of fat metabolism
Obesity
Systemic lupus erythematosus
(Steroids have now been separated from this group)

Table II Some of the factors reported to be associated with idiopathic necrosis

wishes to know whether a core biopsy from the femoral head is live or dead. Not only is there a problem in sampling, since ischaemia may affect only part of the femoral head, but the tissue biopsied soon after fracture may misleadingly fail to show the changes of necrosis.

If the bone marrow is revascularized by the in-growth of blood vessels from adjacent living tissue there is then both osteoclastic resorption of dead

Fig 1

Fig 2

Fig 3

Fig 1* Five days after femoral neck fracture haemopoietic marrow from the femoral head shows loss of nuclear staining and formation of fat-filled spaces. Osteocytes are still recognizable in the bone trabecula ($\times 100$).

Fig 2* Seventeen weeks after fracture all of the osteocyte lacunae of the bone trabeculae are empty and the marrow is 'ghosted' ($\times 100$).

Fig 3* The marrow is revascularized. Osteoclasts are resorbing dead bone and some new bone has been laid down by osteoblasts (arrowed) ($\times 125$).

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Fig 4 Eighteen months after intracapsular fracture of the femoral neck the femoral head was removed because of collapse of the weight-bearing area. Dead trabeculae from the depths of the head (arrowed) are seen covered by living bone. The marrow blood vessels are slightly congested ($\times 65$).

Fig 5† There are scattered empty lacunae in this subchondral bone trabecula from a 75-year-old woman. The fatty marrow is not necrotic ($\times 140$).

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bone and the laying down of new living bone on the surface of dead trabeculae (fig 3), a process traditionally described as 'creeping substitution'. Often nowadays, perhaps because of early mobilization of

the patient, the amount of resorption is relatively small and the dead trabeculae become encased in living bone, so that 'creeping apposition' is a better description (Bohr and Larsen, 1965; Kenzora *et al*, 1969). The dead central cores may persist for months or even years and remain as a histological marker of previous bone necrosis (Catto, 1965b) (fig 4).

Osteocyte loss in aging and in occlusive vascular disease

Focal osteocyte loss is a well recognized feature of aging bone. The parts of the bone furthest away from blood vessels, such as the interstitial lamellae between the cortical osteons (Haversian systems), tend to be affected first and even in childhood occasional empty lacunae may be seen here (Jaffe and Pomeranz, 1934; Frost, 1960a). With advancing age, and presumably a deteriorating blood supply, the number of empty lacunae increases. The outer rings of cortical osteons and the subchondral bone plate are chiefly involved, but less marked focal loss may be seen in medullary trabeculae (Frost, 1960a). Sometimes the usual slit-like lacunae are enlarged and filled with mineral (Jowsey, 1960; Frost, 1960b). Usually the patchy distribution of osteocyte loss and the normal-appearing marrow help to distinguish microscopically this slow 'physiological' loss (fig 5) from more acute and severe ischaemic episodes with marrow damage and complete loss of osteocytes (fig 2). However, some caution is needed in interpreting empty lacunae in small central bony cores in the aged, the group especially likely to suffer intracapsular fractures of the femoral neck.

Similar but more severe osteocyte loss may be seen in the tibia of legs amputated for peripheral gangrene, much of the cortex being necrotic (Jaffe and Pomeranz, 1934; Sherman and Selakovich, 1957). These extensive pathological changes are usually symptomless and radiologically unsuspected. Localized medullary infarcts are occasionally reported in association with peripheral gangrene. However, the importance of occlusive vascular disease in the production of medullary infarcts in elderly patients without peripheral gangrene is not known; certainly similar infarcts are occasionally found incidentally in younger patients (Kahlstrom *et al*, 1939; Bullough *et al*, 1965).

Patterns of bone necrosis

Bone necrosis is conveniently divided for practical purposes into two groups, symptomless medullary lesions and juxtaarticular lesions, which are potentially disabling since collapse of the joint surface may

occur and is followed by secondary degenerative changes in the joint.

MEDULLARY LESIONS

Medullary lesions are found, especially in association with dysbarism and the haemoglobinopathies (Middlemiss, 1976), and occasionally in steroid-treated patients or 'spontaneously'. The shaft of the lower femur, the tibia and the humerus are most often affected, sometimes bilaterally. The extent of necrosis varies from small foci to large areas involving much of the width of the medullary cavity and sometimes also areas in the deeper cortex. It is important to realize that extensive bone necrosis may be present without any detectable radiological abnormality even in radiographs of thin slices of the bone. These unrecognized infarcts, which have been seen especially in steroid-treated patients (Bullough *et al*, 1965; Catto, 1976) appear as sharply demarcated zones of opaque, yellowish marrow with an irregular margin outlined by congestion and haemorrhage (fig 6).

In more mature lesions fairly well defined zones may also be distinguishable (fig 7). In the central area dead trabeculae are surrounded by necrotic marrow which may retain its cellular outlines or become liquefied, cystic or spottily calcified. This zone of dead tissue is often surrounded by a greyish serpiginous collagenous capsule in which dead trabeculae may be unaltered or show apposition of new viable bone on the surface. Outwith this, in the living marrow, acellular trabeculae, often continuous with those in the dead central zone, may be covered by viable bone. Perhaps the most likely explanation of these morphological appearances is that there has been partial revascularization of the dead bone with incomplete, arrested repair (Phemister, 1940; Bullough *et al*, 1965).

JUXTAARTICULAR LESIONS

Juxtaarticular lesions are found most often in the femoral or humeral heads and less commonly in the femoral condyles, talus, scaphoid, capitate or capitulum of the humerus (table I). In the femoral head the site most frequently affected is the load-bearing supero-lateral part and in the humeral head the central dome. As in the medullary lesions, well defined zones are usually apparent; immediately beneath the articular cartilage there is a variable depth of yellowish, opaque marrow and dead bone, separated by a band of vascular granulation or dense collagen from adjacent viable marrow and from bone trabeculae which may be widened and sclerotic due to the presence of new bone on the surface of dead (fig 8). The trabeculae tend to be thickest where they abut on dense fibrous tissue and gradually give place to trabeculae of normal thickness containing their

Fig 6† This 21-year-old girl received two renal transplants, the first two years, and the second 18 months, before her death. A skeletal survey showed no abnormality but at necropsy there was an extensive area of medullary necrosis in the lower end of the left femur and juxtaarticular lesions in both femoral heads. The area of necrosis was outlined by congested marrow but there was no surrounding bony reaction and no abnormality in the slab radiograph.

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full complement of osteocytes. In most conditions the widely accepted interpretation of these morphological findings is that bone necrosis has been followed by revascularization and repair which has stopped short of completion, the dense collagen representing the furthest extent of the process. At this stage, there are no clinical symptoms and either no radiological abnormality is apparent or if, after some months, the trabeculae become sufficiently broadened, linear or more diffuse radiological sclerosis may outline the necrotic subchondral tissue.

After necrosis has been present for months, or sometimes for years, trabecular fracture may occur within the dead bone resulting in partial separation

Fig 7a

Fig 7 The patient was a 50-year-old male who died a few weeks after a renal transplant. He suffered from the nephrotic syndrome for 10 years and was at first treated with steroids. A year before his death he developed uraemia and hypertension necessitating dialysis. A skeletal survey at this time revealed thickening and irregularity of the cortex of both femoral shafts along with patchy medullary calcification (a). There was also increased density in both femoral heads without structural failure. On section (b) irregular areas of opaque yellowish marrow were surrounded by white fibrous tissue. This fibrous tissue was partially calcified as can be seen in the slab radiograph (c). There were also small foci of calcification within the dead tissue. The dead zone involved the deep part of cortex as well as the medulla (d). The dead fatty marrow on the left has, in places, retained its cellular outlines. At the margin collagen is seen and the dead trabecula on the right shows some appositional live bone on its surface ($\times 50$).

Fig 7b

Fig 7c

Fig 7d

of an articular sequestrum. Frequently fracture occurs just beneath the subchondral plate, giving rise to a narrow crescentic line of radiolucency running parallel to the joint surface (Norman and Bullough, 1963) (fig 9). The contour of the bone end may at first appear unchanged but pressure on the articular surface shows that it is easily indented and unduly resilient. Cracks and fissures are seen at the margin of the sequestrum (fig 10), synovial fluid may pene-

trate through these fissures and bone detritus, resulting from grating together of the dead surfaces, may escape into the joint spaces. Sometimes fibrocartilage, which can form without a blood supply, covers the undersurface of the sequestrum. Trabecular fracture may occur deeper below the articular surface, occasionally at the junction of the zone of fibrosis, thus separating a thicker sequestrum. Various explanations of the trabecular fractures have

Fig 8a

Fig 8b

Fig 8c

Fig 8* The patient was a 33-year-old tunnel worker who had been intermittently employed in compressed air for 14 years. He died within 12 hours of an attack of acute decompression sickness. The humeral head appeared normal externally but on section (a) showed a shallow juxtaarticular zone of necrosis bordered by collagen and by thick trabeculae which consisted (c) of dead trabeculae ensheathed by living bone ($\times 75$). On the slab radiograph (b) these gave rise to a sclerotic line which outlined the extent of the remaining dead bone.

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Fig 9a

Fig 9b

Fig 9* This 72-year-old woman suffered a displaced intracapsular fracture. A nailplate was inserted and after a year bony union appeared complete but five months later the patient began to complain of pain and slight flattening with collapse of the femoral head was observed. Twenty-one months after fracture a prosthesis was inserted. Fracture had occurred through the remaining dead trabeculae immediately beneath the subchondral plate in the load-bearing segment. The resulting crescentic line of translucency is well seen in the slab radiograph. Fibrosis between the dead and living tissue was not dense and here there was only moderate thickening of dead trabeculae by living bone producing a slightly sclerotic border outside the dead tissue. The nail track and the healed fracture site are also marked by broad trabeculae.

Fig 10a

Fig 10b

Fig 10 This 31-year-old man complained of pain in the right hip for three months. He had not been exposed to compressed air. He weighed 24 stones and attributed his obesity to heavy drinking. Excision of the femoral head (a) revealed a relatively normal joint contour but the articular surface was unusually resilient and could be sprung like a pingpong ball. Cracks were visible at the margin of the partially detached sequestrum (arrows). Section showed a fracture through dead bone close to the joint surface (b). The dead bone trabeculae beneath this subchondral fracture formed a continuous meshwork with broad trabeculae consisting of living bone covering the surface of dead trabeculae. One year after arthroplasty there is no evidence of involvement of the left hip.

Fig 11a

Fig 11b

Fig 11c

Fig 11d

Fig 11† This 32-year-old man worked in compressed air for six months and suffered one attack of acute decompression sickness. Arthroplasty was performed four years later, two-and-a-half years after the onset of pain in the hip. (a) The load-bearing surface of the femoral head has sunk down leaving a surrounding bony ridge. The margin of the head is distorted by osteophytes and hyperplastic synovium. (b) A large wedge of pale dead bone remains. There is fracture of dead trabeculae running laterally from the upper foveal margin. Fibrous tissue marks the junction between dead and living bone. (c) In the inferomedial part of the head the bony meshwork is continuous between dead and living tissue but laterally dead bone has been replaced by collagen. Broad trabeculae are seen in the radiograph (d) forming a sclerotic margin outlining the dead tissue. The articular cartilage covering dead bone is well preserved but osteophytes have formed at the living inferior margin.

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been put forward; eg, that they result from 'fatigue' fracture of the dead bone trabeculae (Brown and Abrami, 1964) or are secondary to osteoclastic resorption of dead bone at its junction with living tissue, either at the deep surface (Sherman and Phemister, 1947) or at the margin of the subchondral plate. Whatever the cause and whatever the site of the fracture through dead bone, it is followed by sinking down of the load-bearing part of the joint surface (fig 11). The uncollapsed margin of the bone end may produce a ring-like ridge around the sunken dome. In the femoral head the breaks in the smooth articular contour may be recognized radiologically; they tend to occur beneath the acetabular lip and at the superior margin of the fovea. The flattening and collapse of the joint surface leads to incongruity and secondary degenerative changes in the cartilage covering living bone while, at the joint margin, osteophytes form. Joint pain is usually insidious in

onset, but occasionally and especially when the humerus is involved, may be sudden and presumably associated with sudden collapse of the surface of the head.

Joint collapse and osteoarthritis

The articular cartilage covering dead bone and even that of a partially detached articular sequestrum (figs 9, 10, 11) usually is not thinned or fibrillated. Apart from some loss of lustre it may look relatively normal and if, in longstanding cases, there is loss of chondrocytes this is almost always confined to the deeper layers furthest from the nutrient synovial fluid. This relatively good preservation is in contrast to the severe degenerative changes which often occur in the cartilage covering living or revascularized bone in patients with collapse of the joint surface (Catto, 1965b). Then the cartilage becomes thin and fibril-

lated, its vascularization is associated with remodeling of the joint surface and the formation of marginal osteophytes (fig 11). These degenerative changes may be distinguished, at least at first, from those of primary osteoarthritis by the good preservation of the joint space, due to the normal thickness of the cartilage covering dead bone, and the relative sparing of the other articular surface forming the joint. Occasionally, the articular cartilage and the underlying dead bone may later become fragmented and ground away so that little or no evidence remains that bone necrosis was the underlying cause of the osteoarthritis (fig 12). Similarly, difficulties arise in attempting to confirm or refute the radiological impression that necrosis may be the cause of unusually rapid disintegration of an already osteoarthritic femoral head in some patients taking indomethacin, phenylbutazone and similar analgesics (Park, 1976). By the time the femoral head is removed it is often

Fig 12a

Fig 12b

Fig 12c

Fig 12† This 33-year-old man worked in compressed air at pressures up to 34 psi but had never required recompression for acute decompression sickness. After 11 months he began to complain of pain in both hips and transferred to work in free air. Three years later lateral radiographs of both hips showed partial separation and fragmentation of an articular sequestrum in the weight-bearing-zone (a). Nine years after starting work there was severe bilateral osteoarthritis (b) and arthroplasty was performed. The sequestrum had presumably been ground away, the exposed bone trabeculae were sclerotic and both subchondral 'cysts' and marginal osteophytes had formed (d). Only the early radiograph (a) and the unusually sharply defined cartilage loss in the gross specimen (c) revealed that the osteoarthritis was secondary to previous necrosis.

Fig 12d

Fig 13a

Fig 13b

Fig 13† This 58-year-old woman developed a fracture of the femoral neck two years after radiotherapy for a carcinoma of cervix. Two years later there was fracture of subchondral trabeculae with slight flattening of the load-bearing segment of the femoral head. Only the fringe of subchondral bone trabeculae in the partially separated articular sequestrum was necrotic. The underlying bone was viable but porotic, part of the varied picture of radiation osteitis seen throughout the bone. The radiological picture of femoral head collapse in this patient appeared to result from fracture of porotic live trabeculae and not to have been preceded by bone necrosis. Another irradiated patient with a typical radiograph (c) showed a similar histological picture in the collapsed femoral head.

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Fig 13c

reduced to a stump and histological examination at this end stage may be unhelpful. Certainly it is unwise to assume that collapse of a joint surface is always due to underlying bone necrosis (fig 13).

Variations in patterns of necrosis

Regardless of the cause, the general pattern of juxta-articular necrosis and collapse of the joint surface with secondary degenerative changes is similar, apart from minor variations. In post-traumatic necrosis of the femoral head the necrotic bone tends

to form a single compact subarticular mass. In some cases of dysbaric osteonecrosis, however, there may be an impression that areas of necrosis result from the confluence of smaller foci (deSèze *et al*, 1963), while dead bone may remain in the medial part of the femoral head rather than in the load-bearing area (Catto, 1976). These more complex appearances suggest that in contrast to post-traumatic necrosis, major vascular territories are not always involved.

The morbid anatomical changes in 'idiopathic' necrosis of the femoral head conform in general to the pattern already described (Patterson *et al*, 1964;

Fig 14a† This 36-year-old male developed pain and collapse of the right talus four months after renal transplantation. The clinical radiograph shows collapse of the load-bearing surface of the femoral head, formation of an osteophyte at the lateral margin and loss of joint space. Increased bone density is not a striking feature. When the femoral head was removed a year later the synovial fluid contained gritty material and the femoral head was reduced to a stump.

Fig 14b A wedge of remaining dead bone can be seen where it is faintly outlined by a rather broad band of vascular loose fibrous tissue. Foci of marrow damage with lipophages were seen distal to this. Adjacent living bone trabeculae form a continuous meshwork with dead trabeculae. Little new bone has been laid down.

Fig 14c Dead marrow is seen on the right and adjacent to it vascular fibrous tissue abuts on a dead trabecula ($\times 120$). The appearances here suggested an extending necrosis rather than revascularization and healing.

Fig 15a

Fig 15b

Fig 15c

Fig 15d

Fig 15 This specimen is from the same patient as the medullary infarct in fig 7 (a, c). Juxtaarticular necrosis is seen in the femoral head, outlined by congested vessels and (b) not associated with evident subchondral trabecular porosis or fracture. (d) The margin of the necrotic area marked by congested vessels and fibrinous exudate. Dead bone without reactive new bone on its surface continued a little beyond this margin and there was also focal damage to fatty marrow ($\times 160$).

Merle d'Aubigné *et al*, 1965; Welfling, 1971) as do many examples of necrosis associated with steroid therapy (Cruess *et al*, 1968; Fisher *et al*, 1969; Cruess, 1976). However, some specimens from steroid-treated patients or those with 'idiopathic' necrosis show changes suggesting that the necrosis is extending rather than that it has undergone even incomplete revascularization and healing. In these cases, which include collapsed, juxtaarticular lesions (fig 14), the necrotic zone is surrounded by a wide reactive margin with congested vessels, loose fibrous tissue, macrophages and sometimes fibrinous exudate (fig 15) while beyond this foci of damage are seen in the fatty marrow (Johnson, 1964). Dead trabeculae may extend a little way beyond the main zone of necrosis and new bone formation on their surfaces is often minimal. The compact zone of bone and mar-

row necrosis is then not outlined histologically or radiologically by sclerosis due to broadened trabeculae (figs 14 and 15).

Some unsolved problems

The cause of bone necrosis, especially in the 'idiopathic' and steroid-treated groups, is controversial. Some authors regard localized subchondral osteoporosis, followed by trabecular fracture as the initial lesion, any necrosis being secondary to this structural failure (Solomon, 1973). While this sequence of events may explain some lesions, in others necrosis appears to precede localized trabecular porosis or fracture (fig 15) (Catto, 1976). Another suggestion is that systemic fat emboli, perhaps derived from a fatty liver, cause the bone infarction (Fisher *et al*, 1969).

Jones, 1971). Unfortunately the precise location of fatty globules demonstrated in frozen sections of bone is not always easy. The pathogenesis remains uncertain and needs further investigation.

The biggest unsolved puzzle, and certainly the most important clinically, is why revascularization is so often incomplete, even in the non-traumatic cases where healing of a fracture does not delay the spread of revascularization. In some cases of juxtaarticular necrosis with collapse, fracture through dead trabeculae may occur at the junction between dead and living bone. This secondary fracture may then effectively prevent further extension of revascularization. In many specimens, however, the fracture through dead trabeculae occurs at some distance from the furthest extent of revascularization (fig 11) while incomplete and apparently halted revascularization is seen also in medullary lesions (fig 7) and juxtaarticular ones without trabecular fracture (fig 8). The interruption of repair is not so difficult to understand in the steroid-treated patients who, whatever the precise cause of the necrosis, are continuously exposed to the hormone. Recently it has been suggested that the failure of revascularization of the femoral head in children with Perthes' disease might be due to more than one ischaemic episode (McKibbin, 1975; Inoue *et al.*, 1976; Jensen and Lauritzen, 1976). While there is rather similar suggestive evidence in some specimens from patients with dysbaric osteonecrosis (Catto, 1976) failure of revascularization is seen in the occasional patient with a single exposure to compressed air. Multiple ischaemic episodes seem unlikely therefore to be the whole explanation. It has been suggested that there may be a critical size beyond which a bone infarct fails to revascularize completely (Boyd, 1957).

Many important questions thus remain to be answered by the pathologist. From a practical point of view it is worth examining any available material from groups of patients at risk, whether or not they have radiological evidence of necrosis. It is from the earlier and unsuspected examples that one may obtain some clue to the pathogenesis. Equally it is important to examine bones with radiological abnormalities because the nature of the underlying tissue changes still remains speculative and controversial, especially in the less common conditions.

I am much indebted to Dr J. D. Briggs of the Renal Unit and to many orthopaedic colleagues at the Western Infirmary, Glasgow, for their help and for clinical information about their patients. The MRC Decompression Sickness Panel has been generous in making available to me specimens for study. My thanks are due to Mr Peter Kerrigan and Mr

Alasdair Smith, of the Pathology Department Photographic Unit, for preparing the illustrations.

References

- Barnes, R., Brown, J. T., Garden, R. S., and Nicoll, E. A. (1976). Subcapital fractures of the femur. *Journal of Bone and Joint Surgery*, **58B**, 2-24.
- Bohr, H., and Larsen, E. H. (1965). On necrosis of the femoral head after fracture of the neck of the femur. *Journal of Bone and Joint Surgery*, **47B**, 330-338.
- Bonfiglio, M. (1964). Aseptic necrosis of the femoral head. Intact blood supply is of prognostic significance. In *Proceedings of the Conference on Aseptic Necrosis of the Femoral Head*, pp. 155-162. National Institutes of Health, St. Louis.
- Boyd, H. B. (1957). Avascular necrosis of the head of the femur. *Instructional Course Lectures, American Academy of Orthopedic Surgeons*, **14**, 196-204.
- Brown, J. T., and Abrami, G. (1964). Transcervical femoral fracture. A review of 195 patients treated by sliding nail-plate fixation. *Journal of Bone and Joint Surgery*, **46B**, 648-663.
- Bullough, P. G., Kambolis, C. P., Marcove, R. C., and Jaffe, H. L. (1965). Bone infarctions not associated with caisson disease. *Journal of Bone and Joint Surgery*, **47A**, 477-491.
- Catto, M. (1965a). A histological study of avascular necrosis of the femoral head after transcervical fracture. *Journal of Bone and Joint Surgery*, **47B**, 749-776.
- Catto, M. (1965b). The histological appearances of late segmental collapse of the femoral head after transcervical fracture. *Journal of Bone and Joint Surgery*, **47B**, 777-791.
- Catto, M. (1976). Pathology of aseptic bone necrosis. In *Aseptic Necrosis of Bone*, edited by J. K. Davidson, pp. 3-100. Excerpta Medica, Amsterdam.
- Cruess, R. L. (1976). Steroid-induced avascular necrosis of the head of the humerus. *Journal of Bone and Joint Surgery*, **58B**, 313-317.
- Cruess, R. L., Blennerhassett, J., MacDonald, F. R., MacLean, L. D., and Dossetor, J. (1968). Aseptic necrosis following renal transplantation. *Journal of Bone and Joint Surgery*, **50A**, 1577-1589.
- Davidson, J. K. (1976). Dysbaric osteonecrosis. In *Aseptic Necrosis of Bone*, edited by J. K. Davidson, pp. 147-212. Excerpta Medica, Amsterdam.
- de Sèze, S., Jaffres, R., Merer, P., Mitrovic, D., and Mazabraud, A. (1963). Aspects histologiques de l'ostéonécrose aseptique barotraumatique. *Semaine des Hôpitaux de Paris*, **39**, 869-878.
- Fisher, D. E., and Bickel, W. H. (1971). Corticosteroid-induced avascular necrosis: a clinical study of seventy-seven patients. *Journal of Bone and Joint Surgery*, **53A**, 859-873.
- Fisher, D. E., Bickel, W. H., and Holley, K. E. (1969). Histologic demonstration of fat emboli in aseptic necrosis associated with hypercortisonism. *Mayo Clinic Proceedings*, **44**, 252-259.
- Frost, H. M. (1960a). *In vivo* osteocyte death. *Journal of Bone and Joint Surgery*, **42A**, 138-143.
- Frost, H. M. (1960b). Micropetrosis. *Journal of Bone and Joint Surgery*, **42A**, 144-150.
- Graham, J., and Wood, S. K. (1976). Aseptic necrosis of bone following trauma. In *Aseptic Necrosis of Bone*, edited by J. K. Davidson, pp. 101-146. Excerpta Medica, Amsterdam.
- Henard, D. C., and Calandruccio, R. A. (1970). Experimental production of roentgenographic and histological changes in the capital femoral epiphysis following abduction, extension and internal rotation of the hip. (Abstract). *Journal of Bone and Joint Surgery*, **52A**, 601.

- Inoue, A., Freeman, M. A. R., Vernon-Roberts, B., and Mizuno, S. (1976). The pathogenesis of Perthes' disease. *Journal of Bone and Joint Surgery*, **58B**, 453-461.
- Jaffe, H. L., and Pomeranz, M. M. (1934). Changes in the bones of extremities amputated because of arteriovascular disease. *Archives of Surgery*, **29**, 566-588.
- Jensen, O. M., and Lauritzen, J. (1976). Legg-Calvé-Perthes' disease. *Journal of Bone and Joint Surgery*, **58B**, 332-338.
- Johnson, L. C. (1964). Histogenesis of avascular necrosis. In *Proceedings of the Conference on Aseptic Necrosis of the Femoral Head*, pp. 55-77. National Institutes of Health, St. Louis.
- Jones, J. P. (1971). Alcoholism, hypercortisoidism, fat embolism and osseous avascular necrosis. In *Idiopathic Ischemic Necrosis of the Femoral Head in Adults*, edited by W. M. Zinn, pp. 112-132. Thieme, Stuttgart. University Park Press, Baltimore.
- Jowsey, J. (1960). Age changes in human bone. *Clinical Orthopaedics*, **17**, 210-218.
- Kahlstrom, S. C., Burton, C. C., and Phemister, D. B. (1939). Aseptic necrosis of bone. II. Infarction of bone of undetermined etiology resulting in encapsulated and calcified areas in diaphyses and in arthritis deformans. *Surgery, Gynecology, and Obstetrics*, **68**, 631-641.
- Kenzora, J. E., Steele, R. E., Yosipovitch, Z., Boyd, R., and Glimcher, M. J. (1969). Tissue biology following experimental infarction of femoral heads. I. Bone studies. (Abstract). *Journal of Bone and Joint Surgery*, **51A**, 1021.
- Lancet (1974). Bone necrosis in divers. (Editorial). *Lancet*, **2**, 263-264.
- McKibbin, B., Ed. (1975). Recent developments in Perthes' disease. In *Recent Advances in Orthopaedics*, No. 2, pp. 173-195, edited by B. McKibbin. Churchill Livingstone, Edinburgh.
- Medical Research Council Decompression Sickness Panel Report (1971). Decompression sickness and aseptic necrosis of bone. *British Journal of Industrial Medicine*, **28**, 1-21.
- Merle d'Aubigné, R., Postel, M., Mazabraud, A., Massias, P., and Gueguen, J. (1965). Idiopathic necrosis of the femoral head in adults. *Journal of Bone and Joint Surgery*, **47B**, 612-633.
- Middlemiss, H. (1976). Aseptic necrosis and other changes occurring in bone in the haemoglobinopathies. In *Aseptic Necrosis of Bone*, edited by J. K. Davidson, pp. 271-300. Excerpta Medica, Amsterdam.
- Norman A., and Bullough, P. (1963). The radiolucent crescent line: an early diagnostic sign of avascular necrosis of the femoral head. *Bulletin of the Hospital for Joint Diseases*, **24**, 99-104.
- Park, W. M. (1976). Spontaneous and drug-induced aseptic necrosis. In *Aseptic Necrosis of Bone*, edited by J. K. Davidson, pp. 213-269. Excerpta Medica, Amsterdam.
- Patterson, R. J., Bickel, W. H., and Dahlin, D. C. (1964). Idiopathic avascular necrosis of the head of the femur. A study of fifty-two cases. *Journal of Bone and Joint Surgery*, **46A**, 267-282.
- Phemister, D. B. (1940). Changes in bones and joints resulting from interruption of the circulation. II. Nontraumatic lesions in adults with bone infarction, arthritis deformans. *Archives of Surgery*, **41**, 1455-1482.
- Röising, G. E., and James, J. (1969). Early phases of avascular necrosis of the femoral head in rabbits. *Journal of Bone and Joint Surgery*, **51B**, 165-174.
- Sherman, M. S., and Phemister, D. B. (1947). The pathology of ununited fractures of the neck of the femur. *Journal of Bone and Joint Surgery*, **29**, 19-40.
- Sherman, M. S., and Selakovich, W. G. (1957). Bone changes in chronic circulatory insufficiency. *Journal of Bone and Joint Surgery*, **39A**, 892-901.
- Solomon, L. (1973). Drug-induced arthropathy and necrosis of the femoral head. *Journal of Bone and Joint Surgery*, **55B**, 246-261.
- Welfling, J. (1971). Primary necrosis of the femoral head. Current state of the subject in French medical opinion. In *Idiopathic Ischemic Necrosis of the Femoral Head in Adults*, edited by W. M. Zinn, pp. 100-102. Thieme, Stuttgart. University Park Press, Baltimore.
- Woodhouse, C. F. (1962). Anoxia of the femoral head. *Surgery*, **52**, 55-63.
- Zinn, W. M. (1971a). Idiopathic ischaemic necrosis of the femoral head in adults. In *Modern Trends in Rheumatology*, 2nd edn, edited by A. G. S. Hill, pp. 348-365. Butterworths, London.
- Zinn, W. M. Ed. (1971b). Introduction; II. Clinical picture and laboratory findings; XV. Conclusions. In *Idiopathic Ischemic Necrosis of the Femoral Head in Adults*, pp. 1-7, 9-33, 213-14. Thieme, Stuttgart. University Park Press, Baltimore.

Further reading

Trauma

- Hulth, A. (1961). Necrosis of the head of the femur. A roentgenological, microradiographic and histological study. *Acta Chirurgica Scandinavica*, **122**, 75-84.
- Jaffe, H. L. (1969). Ischemic necrosis of bone. *Medical Radiography and Photography*, **45**, 58-86.
- Jaffe, H. L. (1972). *Metabolic, Degenerative and Inflammatory Diseases of Bones and Joints*. Lea and Febiger, Philadelphia.
- Sevitt, S. (1964). Avascular necrosis and revascularisation of the femoral head after intracapsular fractures. *Journal of Bone and Joint Surgery*, **46B**, 270-296.

Radiation

- Goodman, A. H., and Sherman, M. S. (1963). Post-irradiation fractures of the femoral neck. *Journal of Bone and Joint Surgery*, **45A**, 723-730.
- Jaffe, H. L. (1958). *Tumors and Tumorous Conditions of the Bones and Joints*. Lea and Febiger, Philadelphia. Henry Kimpton, London.
- MacDougall, J. T., Gibson, A., and Williams, T. H. (1950). Irradiation necrosis of the head of the femur. *Archives of Surgery*, **61**, 325-345.

Dysbarism

- de Sèze, S., Durieu, J., de Brux, J., Guéguen, Y., and Welfling, J. (1951). A propos d'un cas de "maladie des caissons". *Revue du Rhumatisme*, **18**, 469-475.
- Jaffe, H. L. (1972). *Metabolic, Degenerative and Inflammatory Diseases of Bones and Joints*. Lea and Febiger, Philadelphia.
- Kahlstrom, S. C., Burton, C. C., and Phemister, D. B. (1939). Aseptic necrosis of bone. I. Infarction of bones in caisson disease resulting in encapsulated and calcified areas in diaphyses and arthritis deformans. *Surgery, Gynecology, and Obstetrics*, **68**, 129-146.
- Laufer, A. (1957). Aseptic necrosis of the femoral head. *Journal of the Mount Sinai Hospital*, **24**, 957-967.
- McCallum, R. I., Stanger, J. K., Walder, D. N., and Paton, W. D. M. (1954). Avascular necrosis of the femoral heads in a compressed air worker. *Journal of Bone and Joint Surgery*, **36B**, 606-611.
- McCallum, R. I., Walder, D. N., Barnes, R., Catto, M. E., Davidson, J. K., Fryer, D. I., Golding, F. C., and Paton, W. D. M. (1966). Bone lesions in compressed air workers. *Journal of Bone and Joint Surgery*, **48B**, 207-235.

Swain, V. A. J. (1942). Caisson disease (compressed-air illness) of bone with a report of a case. *British Journal of Surgery*, **29**, 365-370.

Welfling, J. (1971). Hip lesions in decompression disease. In *Idiopathic Ischemic Necrosis of the Femoral Head in Adults*, edited by W. M. Zinn, pp. 103-106. Thieme, Stuttgart. University Park Press, Baltimore.

Haemoglobinopathies

Diggs, L. W. (1967). Bone and joint lesions in sickle-cell disease. *Clinical Orthopaedics*, **52**, 119-143.

Diggs, L. W., and Anderson, L. D. (1971). Aseptic necrosis of the head of the femur in sickle cell disease. In *Idiopathic Ischemic Necrosis of the Femoral Head in Adults*, edited by W. M. Zinn, pp. 107-111. Thieme, Stuttgart. University Park Press, Baltimore.

Graham, G. S. (1924). A case of sickle cell anemia with necropsy. *Archives of Internal Medicine*, **34**, 778-800.

Jaffe, H. L. (1972). *Metabolic, Degenerative and Inflammatory Diseases of Bones and Joints*. Lea and Febiger, Philadelphia.

Sherman, M. (1959). Pathogenesis of disintegration of the hip in sickle cell anemia. *Southern Medical Journal*, **52**, 632-637.

Weinberg, A. G., and Currarino, G. (1972). Sickle cell dactylitis: Histopathologic observations. *American Journal of Clinical Pathology*, **58**, 518-523.

Pancreatic disease

Gerle, R. D., Walker, L. A., Achord, J. L., and Weens, H. S. (1965). Osseous changes in chronic pancreatitis. *Radiology*, **85**, 330-337.

Immelman, E. J., Banks, S., Krige, H., and Marks, I. N. (1964). Roentgenologic and clinical features of intramedullary fat necrosis in bones in acute and chronic pancreatitis. *American Journal of Medicine*, **36**, 96-105.

Lucas, P. F., and Owen, T. K. (1962). Subcutaneous fat necrosis, "polyarthritides" and pancreatic disease. *Gut*, **3**, 146-148.

Gaucher's disease

Jaffe, H. L. (1972). *Metabolic, Degenerative and Inflammatory Diseases of Bones and Joints*. Lea and Febiger, Philadelphia.

Laufer, A. (1957). Aseptic necrosis of the femoral head. *Journal of the Mount Sinai Hospital*, **24**, 957-967.

Steroid therapy

Aichroth, P., Branfoot, A. C., Huskisson, E. C., and Loughridge, L. W. (1971). Destructive joint changes following kidney transplantation. *Journal of Bone and Joint Surgery*, **53B**, 488-494.

Evarts, C. M., and Phalen, G. S. (1971). Osseous avascular necrosis associated with renal transplantation. *Clinical Orthopaedics*, **78**, 330-335.

Hall, M. C., and Hume, D. M. (1970). Separation of massive avascular osteocartilaginous fragment of femoral condyle following renal transplantation. *Journal of Bone and Joint Surgery*, **52A**, 550-555.

Harrington, K. D., Murray, W. R., Kountz, S. L., and Belzer, F. O. (1971). Avascular necrosis of bone after renal transplantation. *Journal of Bone and Joint Surgery*, **53A**, 203-215.

Pierides, A. M., Simpson, W., Stainsby, D., Alvarez-Ude, F., and Uldall, P. R. (1975). Avascular necrosis of bone following renal transplantation. *Quarterly Journal of Medicine*, **44**, 459-480.

Uehlinger, E. (1964). Aseptische Knochennekrosen (Infarkte) nach Prednisonbehandlung. *Schweizerische medizinische Wochenschrift*, **94**, 1527-1530.

'Idiopathic' (earlier papers include steroid-treated cases)

Hastings, D. E., and MacNab, I. (1965). Spontaneous avascular necrosis of the femoral head. A clinical and pathological review. *Canadian Journal of Surgery*, **8**, 68-83.

Jacqueline, F., and Rutishauser, E. (1971). Idiopathic necrosis of the femoral head (anatomopathological study). In *Idiopathic Ischemic Necrosis of the Femoral Head in Adults*, edited by W. M. Zinn, pp. 34-48. Thieme, Stuttgart. University Park Press, Baltimore.

Jaffe, H. L. (1972). *Metabolic, Degenerative and Inflammatory Diseases of Bones and Joints*. Lea and Febiger, Philadelphia.

Springfield, D. S., and Enneking, W. F. (1976). Idiopathic aseptic necrosis. In *Bones and Joints*, edited by L. V. Ackerman, H. J. Spjut, and M. R. Abell, pp. 61-87. Williams and Wilkins, Baltimore.

Zinn, W. M. Ed. (1971). *Idiopathic Ischemic Necrosis of the Femoral Head in Adults*. Thieme, Stuttgart. University Park Press, Baltimore.