Periprosthetic Bone Loss in Total Hip Arthroplasty

Polyethylene Wear Debris and the Concept of the Effective Joint Space*

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ABSTRACT: Thirty-four hips in which there had been prosthetic replacement were selected for study because of the presence of linear (diffuse) or lytic (localized) areas of periprosthetic bone loss. In all hips, there was careful documentation of the anatomical location of the material that had been obtained for histological analysis, and the specific purpose of the removal of the tissue was for examination to determine the cause of the resorption of bone. Specimens from twenty-three hips were retrieved during an operation and from eleven hips, at autopsy. The area of bone loss was linear only in sixteen hips, lytic only in thirteen, and both linear and lytic in five.

In all thirty-four hips, intracellular particulate debris was found in the macrophages that were present in the area of bone resorption. All thirty-four had intracellular particles of polyethylene, many of which were less than one micrometer in size. Thirty-one hips had extracellular particles of polyethylene as well. Twenty-two of the thirty-four hips had intracellular metallic debris; in ten, metallic debris was found extracellularly as well. Ten of the sixteen cemented specimens had intracellular and extracellular polymethylmethacrylate debris.

In the mechanically stable prostheses — cemented and uncemented — polyethylene wear debris was identified in areas of bone resorption far from the articular surfaces. The number of macrophages in a microscopic field was directly related to the amount of particulate polyethylene debris that was visible by light microscopy.

Although the gross radiographic appearances of linear bone loss and lytic bone loss were different, the histological appearance of the regions in which there was active bone resorption was similar. Regardless of the radiographic appearance and anatomical origin of the specimen, bone resorption was found to occur in association with macrophages that were laden with polyethylene debris. In general, the number of macrophages present had a direct relationship to the degree of bone resorption that was seen.

We believe that these findings indicate that joint fluid penetrates far more extensively than previously thought, even in a well fixed component, along the interface between the prosthesis and bone and in the periprosthetic tissues; it is often more extensive than is shown by arthrography.

We therefore suggest the concept of the effective joint space to include all periprosthetic regions that are accessible to joint fluid and thus accessible to particulate debris. We also suggest that the difference between lytic (localized) bone loss and linear (diffuse) bone loss may be related to the local concentration or distribution of particulate wear debris; this may in turn depend on patterns of the flow of joint fluid (preferential flow) within the effective joint space.

Before total hip arthroplasty became common, localized bone destruction was almost always secondary to tumor, infection, or metabolic disease and was rarely seen with endoprostheses[40]. When periprosthetic bone loss appears localized or scalloped, it has been called osteolysis or lysis[11], to distinguish it from bone loss that is linear or more evenly distributed around the implant.

Osteolysis was observed by Charnley early in the development of low-friction arthroplasty, but because of the frequent occurrence of infection early in his series, he attributed the osteolysis to the infection[8]. The discovery of particulate polymethylmethacrylate in specimens from focal areas of lysis around both stable and loose prostheses, as well as from areas of more linear and uniform bone resorption, gave rise to the concept of so-called cement disease[25,27]. One of the proposed advantages of fixation without cement is avoidance of this complication. However, lysis has been reported in association with both stable and loose uncemented femoral components, indicating that the problem is broader in scope and is far from solved[21,29].

The observation of particulate metallic debris in histological sections from localized regions of aggressive lysis around uncemented implants has generated additional controversy about the best alloy for joint replace-

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TABLE I

DATA ON THE THIRTY-FIVE HIPS*

Case†	Sex, Age (Yrs.)	Diagnosis	Type of Fixation, Prosthesis‡	Duration *in Situ* (Mos.)	Symptoms	Source	Location	Bone Loss	Mechanical Stability
1	M, 68	Post-traumat. arthritis	Uncemented, H-G	20	Pain in thigh	Operation	Femur	Linear	Loose
2	M, 65	Osteoarth.	Uncemented, H-G	17	Pain in thigh	Operation	Femur	Linear	Loose
3	M, 56	Osteoarth.	Uncemented, H-G	36	Pain in thigh	Operation	Femur	Linear	Well fixed
4	M, 59	Osteoarth.	Uncemented, H-G	27	Pain	Operation	Femur	Linear	Loose
5	M, 57	Osteoarth.	Uncemented, H-G	21	Pain	Operation	Femur	Linear	Loose
6	M, 61	Osteoarth.	Uncemented, H-G	36	Pain in thigh	Operation	Femur	Lytic	Loose
7	M, 40	Slipped cap. femoral epiphysis	Uncemented, H-G	35	Pain in thigh	Operation	Femur	Linear/lytic	Well fixed
8	F, 59	Avascular necrosis	Uncemented, H-G	44	Pain in thigh	Operation	Femur	Lytic	Loose
	F, 59	Avascular necrosis	Uncemented, H-G	44	Pain in thigh	Operation	Acetab.	Linear	Well fixed
9	M, 41	Post-traumat. arthritis	Uncemented, H-G	50	Pain in thigh	Operation	Femur	Lytic	Loose
10	M, 68	Osteoarth.	Uncemented, H-G	72	Pain	Operation	Femur	Linear/lytic	Loose
	M, 68	Osteoarth.	Uncemented, H-G	72	Pain	Operation	Acetab.	Lytic	Well fixed
11	F, 55	Post-traumat. arthritis	Uncemented, AML	16	Pain	Operation	Femur	Linear	Loose
12	M, 57	Osteoarth.	Uncemented, PCA	36	Pain in thigh	Operation	Acetab.	Linear	Loose
13	M, 39	Slipped cap. femoral epiphysis	Uncemented, H-G	57	Pain in thigh	Operation	Femur	Linear	Loose
14	F, 62	Fracture	Uncemented, H-G	6	Pain in groin	Operation	Femur	None	Well fixed
15	M, 56	Osteoarth.	Uncemented, PSR	52	Asymptomatic	Operation	Femur	Lytic	Well fixed
16	M, 53	Osteoarth.	Uncemented, PSR	30	Asymptomatic	Operation	Femur	Lytic	Well fixed
17	F, 57	Osteoarth.	Uncemented, PSR	39	Asymptomatic	Operation	Femur	Lytic	Well fixed
18	M, 62	Osteoarth.	Cemented, Mueller	38	Pain	Operation	Femur	Lytic	Loose
19	M, 63	Osteoarth.	Cemented, Mueller	60	Pain	Operation	Femur	Lytic	Loose
20	F, 62	Congen. disloc. of hip	Cemented, Harris	72	Pain	Operation	Femur	Lytic	Well fixed
21	F, 58	Congen. disloc. of hip	Cemented, Harris	93	Pain in groin	Operation	Femur	Lytic	Well fixed
22	F, 60	Osteoarth.	Cemented, T-28	86	Asymptomatic	Operation	Femur	Lytic	Well fixed
23	F, 42	Post-traumat. arthritis	Cemented, Harris	156	Pain in groin	Operation	Femur	Lytic	Well fixed
24	M, 66	Osteoarth.	Uncemented, AML	60	Asymptomatic	Autopsy	Femur	Lytic	Well fixed
25	M, 70	Osteoarth.	Cemented, Mueller	156	Asymptomatic	Autopsy	Acetab.	Linear	Well fixed
26	M, 73	Osteoarth.	Cemented, HD-2	114	Asymptomatic	Autopsy	Acetab.	Linear	Well fixed
27	F, 94	Osteoarth.	Cemented, HD-2	NA	Asymptomatic	Autopsy	Acetab.	Linear	Well fixed
28	F, 97	Osteoarth.	Cemented, A-T	118	Asymptomatic	Autopsy	Acetab.	Linear	Well fixed
29	F, 93	Osteoarth.	Cemented, Mueller	209	Asymptomatic	Autopsy	Acetab.	Linear	Loose
30	F, 91	Osteoarth.	Cemented, HD-2	129	Asymptomatic	Autopsy	Acetab.	Linear	Loose
31	F, 79	Osteoarth.	Cemented, Mueller	180	Asymptomatic	Autopsy	Femur	Linear	Well fixed
32	F, 73	Osteoarth.	Cemented, A-T	102	Asymptomatic	Autopsy	Femur	Linear	Well fixed
33	M, 82	Osteoarth.	Cemented, Mueller	82	Pain	Autopsy	Femur	Linear/lytic	Loose
34	F, 82	Osteoarth.	Cemented, HD-2	137	Asymptomatic	Autopsy	Femur	Linear/lytic	Well fixed
35	M, 52	Osteoarth.	Uncemented, H-G	82	Pain	Operation	Greater troch.	Lytic	Well fixed
	M, 52	Osteoarth.	Uncemented, H-G	82	Pain	Operation	Acetab.	Lytic	Well fixed

*One hip (Case 14) that had no bone loss was included for comparison.

†Cases 7, 18 and 19, 20 and 21, 22 and 23, 25 through 30, and 31 and 32 have been reported on previously[11,22,28-30,43].

‡H-G = Harris-Galante prosthesis, AML = Engh prosthesis, PCA = porous-coated anatomic prosthesis, PSR = porous-surface replacement, HD-2 = Harris Design 2 prosthesis, T-28 = Trapezoidal-28 prosthesis, and A-T = Aufranc-Turner prosthesis.

ment. Both particulate cobalt-chromium and particulate titanium alloy have been observed in association with loosening and with loss of bone stock in total hip arthroplasty without cement[2,6,16,29,35].

Immunohistological comparison of tissue from areas of aggressive localized bone resorption (osteolysis) with tissue from areas of linear bone loss led Santavirta and associates to propose that the aggressive localized lesions are a distinct pathological entity[38-40,43,44].

We undertook the present study in an attempt to define further the mechanisms of periprosthetic bone resorption.

Materials and Methods

Twenty-three carefully documented operative cases and eleven autopsy cases were included; for each, the exact anatomical origin of the specimen of tissue was known, and every specimen had been obtained specifically to study the pathology of bone loss. The collection included examples of both diffuse (linear) and lytic (localized) bone loss around well fixed and loose implants, cemented and uncemented, from the femur and acetabulum (Table I).

Bone loss was strictly linear in sixteen hips, lytic in thirteen, and both linear and lytic in five. The prosthesis had been cemented in sixteen hips (in eight of these the bone resorption was lytic), and no cement had been used in nineteen (ten had lysis). The area of bone loss that was studied was in the femur in twenty-four cases, in the acetabulum in seven, and in both the femur and acetabulum in three.

We included two hips that had been analyzed in our original report on osteolysis after total hip replacement[11], two from our study of osteolysis in mechanically stable cemented total hip replacements[22], two from the follow-up report on bone lysis in well fixed cemented femoral components[28], and one from the study of osteolysis in association with stable uncemented femoral components[29]. Two femoral specimens retrieved at autopsy[30] and six acetabular components retrieved at autopsy also had been reported on previously[43]. All specimens that had been reported on previously were re-examined.

In three of the hips from our present study, the prostheses were porous-surface replacement implants with a femoral bearing surface of titanium alloy. These have been shown to have a high rate of wear and are associated with rapidly progressive destruction of bone in the femoral neck and head, leading to early clinical failure[35].

In addition to the thirty-four hips in which there was periprosthetic bone resorption, one hip (Case 14) was included for comparison. This hip was mechanically stable, had uncemented implants, and had no bone loss as demonstrated on radiographs. Revision had been done at six months because the patient had substantial limb-length inequality and pain in the groin secondary to an incorrectly sized biarticular component.

TABLE II

LOOSENING, AS DEMONSTRATED ON PLAIN RADIOGRAPHS AND ON ARTHROGRAMS

	Plain Radiographs		Arthrograms	
Case	Femoral Component	Acetabular Component	Femoral Component	Acetabular Component
1	Loose	Well fixed	Not done	Not done
2	Loose	Loose	Negative	Negative
3	Well fixed	Well fixed	Negative	Negative
4	Loose	Well fixed	Positive	Negative
5	Well fixed	Well fixed	Positive	Negative
6	Loose	Well fixed	Positive	Negative
7	Loose	Well fixed	Positive	Negative
8	Loose	Well fixed	Positive	Negative
9	Loose	Well fixed	Positive	Negative
10	Loose	Well fixed	Not done	Not done
11	Loose	Bipolar	Negative	Bipolar
12	Well fixed	Loose	Negative	Negative
13	Loose	Well fixed	Not done	Not done
14*	Well fixed	Bipolar	Positive	Bipolar
15	Well fixed	Well fixed	Not done	Not done
16	Well fixed	Well fixed	Not done	Not done
17	Well fixed	Well fixed	Not done	Not done
18	Loose	Loose	Not done	Not done
19	Loose	Loose	Not done	Not done
20	Well fixed	Well fixed	Not done	Not done
21	Well fixed	Loose	Negative	Positive
22	Well fixed	Well fixed	Negative	Negative
23	Well fixed	Loose	Negative	Positive
24	Well fixed	Well fixed	Not done	Not done
25	Not applic.	Well fixed	Not done	Not done
26	Not applic.	Well fixed	Not done	Not done
27	Not applic.	Well fixed	Not done	Not done
28	Not applic.	Well fixed	Not done	Not done
29	Not applic.	Well fixed	Not done	Not done
30	Not applic.	Well fixed	Not done	Not done
31	Well fixed	Not applic.	Not done	Not done
32	Well fixed	Not applic.	Not done	Not done
33	Loose	Not applic.	Not done	Not done
34	Well fixed	Not applic.	Not done	Not done
35	Well fixed	Well fixed	Negative	Negative

*No bone loss was seen on radiographs.

The radiographs were assessed for the stability of the components as well as for the type and the location of the bone loss. The radiographic criteria for loosening of the femoral component were subsidence or any other change in the position of the component or development of a radiolucency at the interface between the metal and the cement[32]. The radiographic criteria for a loose acetabular component were migration of the component, fracture of the cement, or a complete radiolucency of any width about the entire cement-bone interface on any radiograph[14,32,43]. Arthrography was done before the operation in fifteen hips (Table II). The arthrographic criteria for loosening of either the femoral or the acetabular component have been published[36].

All implants were tested mechanically for stability with the exception of Case 22, in which there were no symptoms or radiographic signs of loosening; only a biopsy and grafting of the lytic lesion in the lateral portion of the mid-femur were performed.

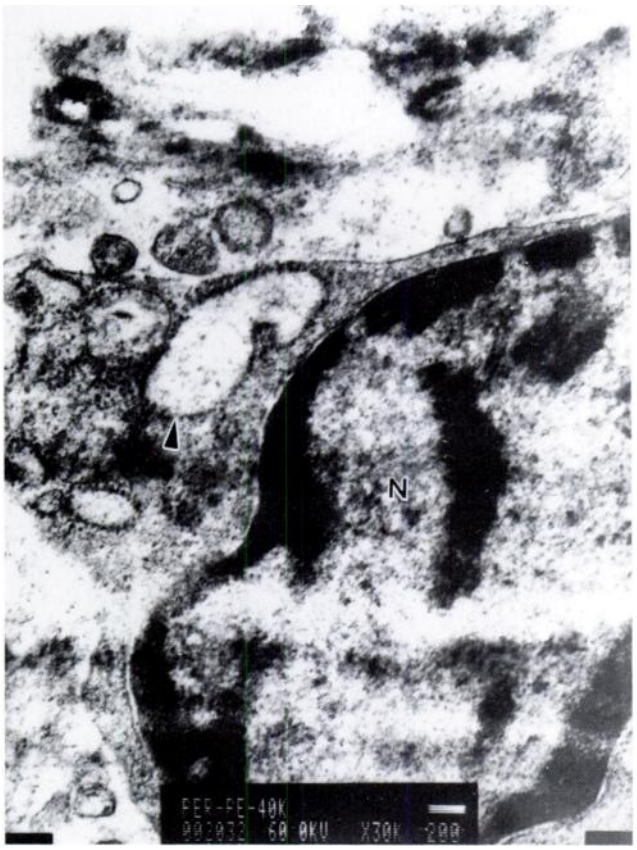

FIG. 1

Case 17. Transmission electron micrograph (× 30,000) showing tissue taken from an area of aggressive bone resorption in the proximal part of the femur after an uncemented surface replacement arthroplasty. The macrophage contains intracytoplasmic, oval, granular, electron-lucent, membrane-bound structures that are considered to be phagocytized polyethylene particles. In this field, the large particle (arrowhead) measures approximately 1.2 by 0.4 micrometers and the small particle (below the arrowhead) measures approximately 0.2 by 0.1 micrometer. N = nucleus.

For the specimens that were retrieved at an operation, conventional (stemmed) femoral components were tested intraoperatively by application of a 22.6-newton-meter torque load in retroversion and measurement of the amount of displacement relative to bone[7]. Surface-replacement components were only loaded manually and assessed qualitatively. Acetabular components were evaluated at the operation by the surgeon, who applied a load manually to the rim of the component in both tension and compression and watched for motion and for evidence of blood or other fluid arising from the interface. Visible motion or any fluid expressed from the interface indicated lack of rigid fixation of the acetabular component to bone[14].

For specimens that were retrieved at autopsy, stability of the femoral component was also assessed by application of a torque load in retroversion. Additionally, axial and transverse motions of the stem were measured under conditions of simulated stance and stair-climbing with methods that have been described[7,30]. Acetabular components that were retrieved at autopsy were evaluated for mechanical stability in simulated stance with the use of a method described previously[10]. In another loading test, torque was applied parallel to the mouth of the unloaded socket, and the displacement of the polyethylene component relative to the bone was recorded for torques of as much as 11.3 newton-meters[43].

Specimens obtained for histological analysis were fixed in formalin, decalcified in EDTA, embedded in paraffin, cut into five-micrometer sections, stained with hematoxylin and eosin, and examined under both plain and polarized light. Due to the small size of some prosthetic particulate debris, cells in all sections were examined meticulously with a magnification factor of as much as 2000 and with the use of oil immersion and very high-quality optics. All sections were studied blindly and were graded in a semiquantitative fashion for cellular constituents and particulate debris (Table III) by two of us (T. P. S. and M. J.). Grade 0 indicated that the particles in question were not seen in that section; Grade 1, that the particles were present in a limited amount or distribution and were not readily apparent; Grade 2, that the particles were a general feature of the section; and Grade 3, that the amount of particles was striking and dominated the histological picture. A qualitative estimation of the ratio of macrophages to fibroblasts in a histological section was also recorded. In regions of active bone resorption, the cellular constituents and predominant species of particle in the immediate vicinity of the bone resorption were specifically recorded in an attempt to define the pathogenesis of the bone resorption more clearly.

Particulate metal was identified as oval particles that did not transmit light or take up stain and therefore appeared dark or black with plain-light illumination. Particles of metal were also identified by light diffraction around their edges, which was enhanced with polarized light.

Because particulate polyethylene transmits light and is not stained by hematoxylin and eosin, it is usually not visible with plain-light illumination, an important criterion for the correct identification of polyethylene. When viewed under polarized light, however, polyethylene is birefringent and appears as needles or filaments within the area that appears unoccupied when plain-light examination is used. Particulate polymethylmethacrylate may be difficult to identify with certainty on standard sections that have been stained with hematoxylin and eosin. The processing of specimens in xylene (used for all specimens in this study) dissolves out lipids and most, if not all, of the particulate polymethylmethacrylate; sites previously occupied by these particles then appear as empty spaces. These spaces may be within a macrophage or may be extracellular and surrounded by inflammatory cells. They may contain granules of barium sulfate if it was added to the polymethylmethacrylate for radiographic contrast.

Further confirmation of the presence of very small

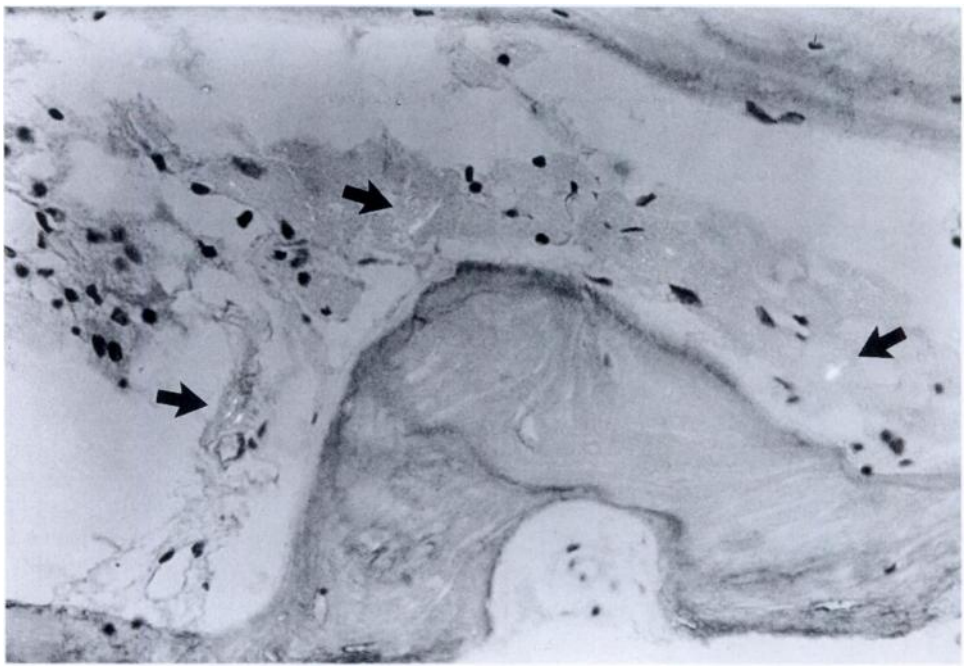

FIG. 2

Case 22. Photomicrograph (hematoxylin and eosin, × 250) showing tissue obtained from the area of bone resorption, containing numerous foamy macrophages. The cytoplasm of these macrophages is filled with particulate polyethylene. The larger particles appear as bright needles (arrows) under polarized light.

particulate polyethylene debris was obtained by examination of several representative sections with transmission electron microscopy. These specimens were fixed in glutaraldehyde and were processed with standard techniques. The specimens chosen for transmission electron microscopy had shown a predominance of macrophages on light microscopy; when examined with polarized light, these macrophages were full of birefringent polyethylene particles of various sizes.

Results

Both linear and lytic bone loss were found in associ-

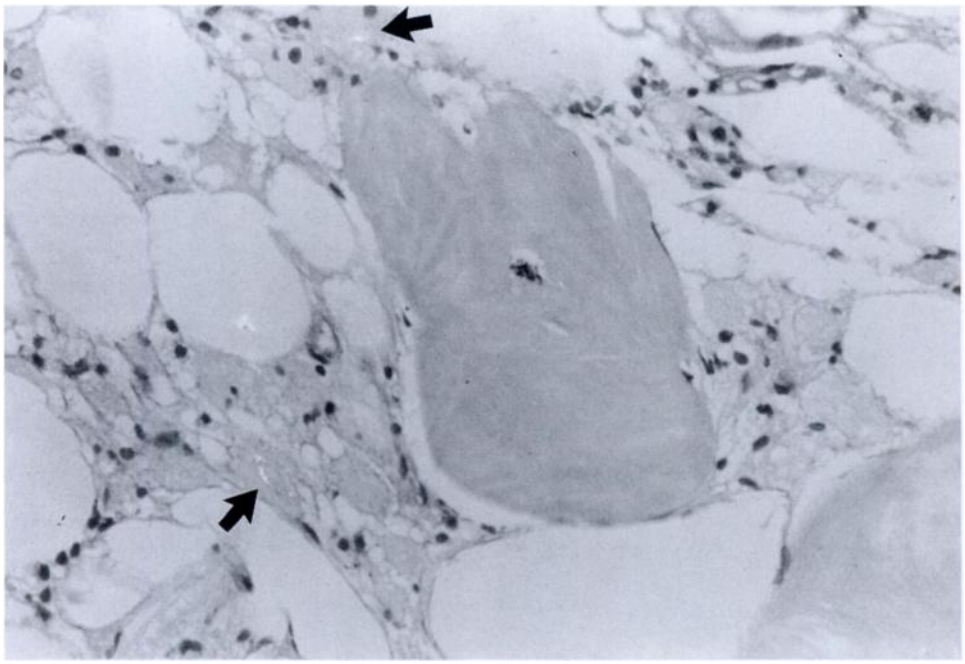

FIG. 3

Case 21. Tissue obtained from the area of osteolysis reveals numerous foamy macrophages that infiltrate the marrow (hematoxylin and eosin, × 250). The cytoplasm of these macrophages is filled with particulate polyethylene. Under polarized light, the larger particles appear as bright needles (arrows).

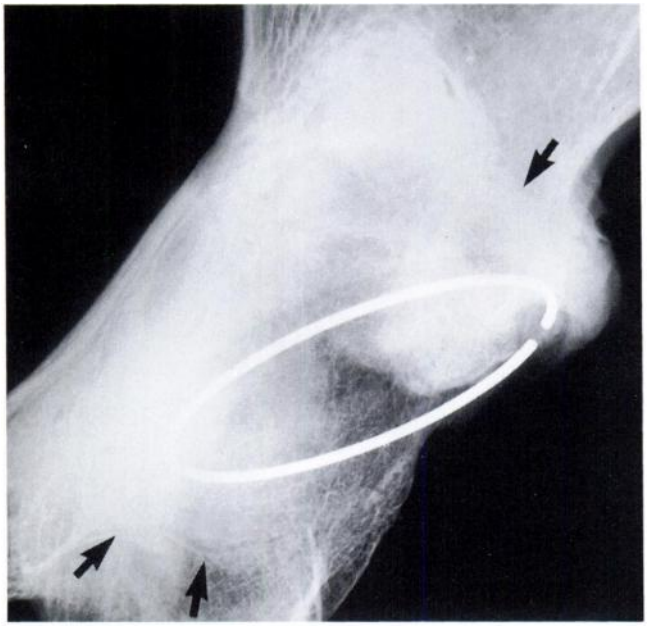

FIG. 4-A

Figs. 4-A through 4-D: Case 28. Linear (diffuse) bone loss.

Fig. 4-A: Anteroposterior radiograph of an acetabular specimen that was retrieved at autopsy, displaying diffuse narrow, linear radiolucencies (arrows). The acetabular component was shown to be well fixed by mechanical testing.

ation with cemented and uncemented implants, whether or not the prosthesis was stable (Table I).

Particles of polyethylene were found in macrophages in all thirty-four hips, and extracellular particles of polyethylene were found in thirty-one. Many of the particles of polyethylene were less than one micrometer in length. Giant cells were also identified, but they were relatively rare; larger particles were seen in giant cells more often than in macrophages. The lengths of the polyethylene particles ranged from less than one micrometer to more than 100 micrometers; most of the particles were intracellular and were less than ten micrometers long.

Particulate polyethylene was found at great distances from the articular surfaces in association with both linear and lytic bone loss and in both stable and unstable implants. In hips with or without cement, particulate polyethylene was found in areas of bone resorption that were distal to the tip of the femoral component.

A finding that was common to all specimens, with and without cement, was a very fine diffuse birefringence in the cytoplasm of the macrophages and giant cells under polarized light. This diffuse birefringence was not seen in any other cells and was similar to the birefringence characteristic of needle-like or filamentous polyethylene particles that are several micrometers long. Such diffuse birefringence was seen in phagocytic cells, both with or without intracellular particles that were several micrometers long, which were easily identified as polyethylene on the basis of their characteristic morphology and birefringence. Analysis of selected sections by transmission electron microscopy confirmed the presence of particles that were less than one micrometer in length within the macrophages. The appearance of these small particles on electron microscopy supported the proposal that these particles were composed of polyethylene (Fig. 1).

Twenty-two of the thirty-four hips had intracellu-

FIG. 4-B

A portion of the cement-bone interface from the area of linear radiolucency shown in Figure 4-A. Polymethylmethacrylate was dissolved out of the section during processing, but it had occupied the space at the top of the section (hematoxylin and eosin, × 100). A layer of predominantly fibrous tissue is interposed between the cement and the bone (small arrows); it contains only scattered macrophages. This region corresponds to the linear radiolucent line. Deep to the layer of fibrous tissue, however, there is a focal excavation into the bone (large arrow).

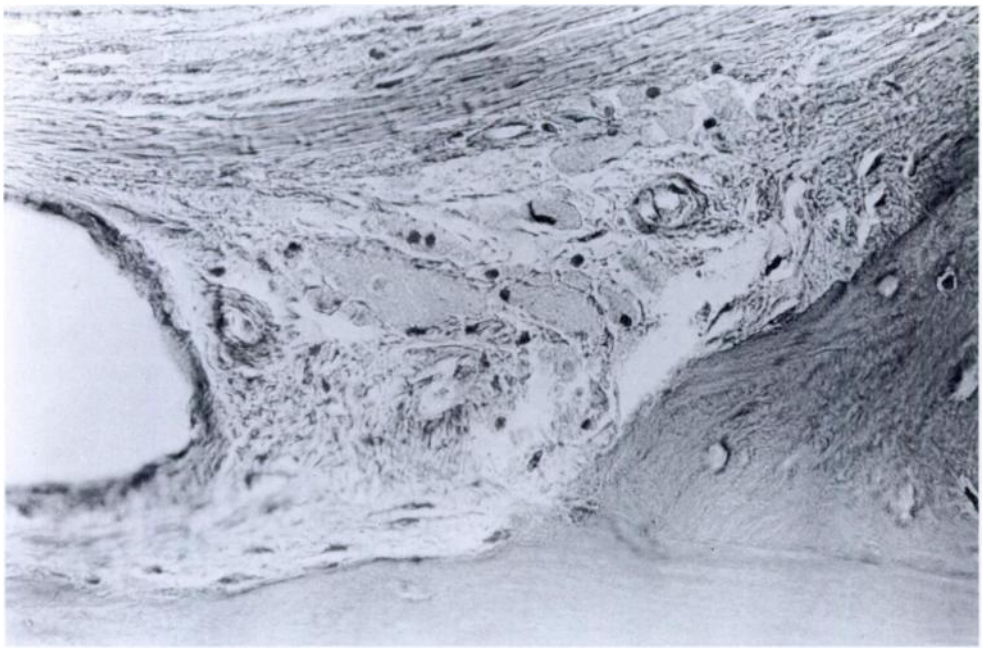

FIG. 4-C

The tissue eroding the bone is distinctly different in composition, containing a small collection of macrophages (hematoxylin and eosin, × 250).

lar metallic debris, and extracellular metallic debris was found in ten hips. The range in the size of particulate metal that was detectable within the spectrum of visible light was quite narrow (from less than one to five micrometers).

Both particulate polyethylene and metal were identified in specimens from all hips with no cement. Metallic debris was predominant and impressive in some (such as Cases 1, 2, and 3). However, particulate polyethylene always was present when particulate metal was found. In general, the particulate polyethylene was dispersed more widely throughout the specimens; particulate metal often was limited to the side of the specimen that faced the implant.

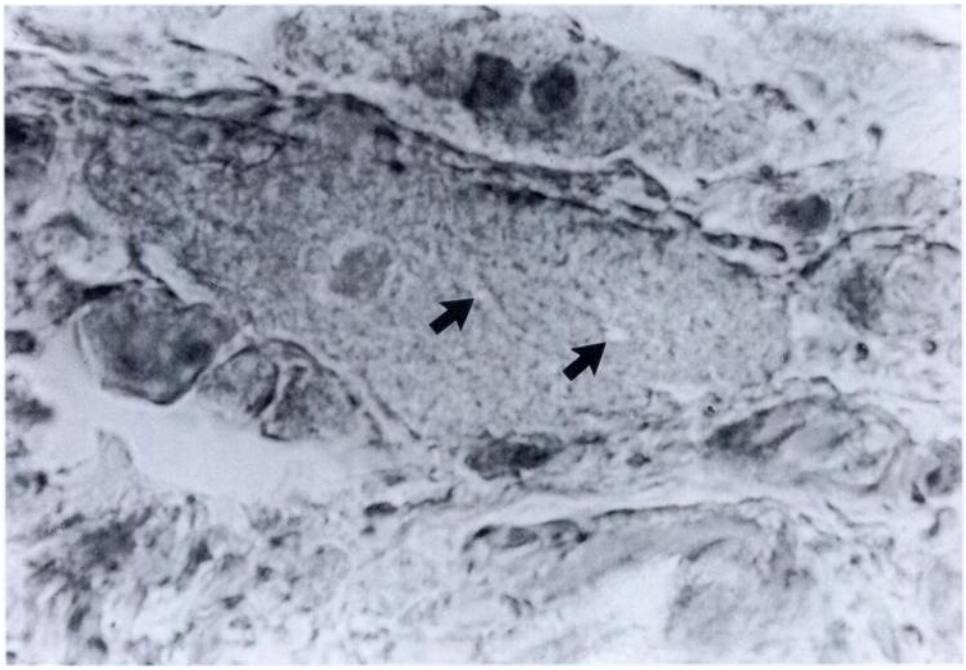

FIG. 4-D

In this photomicrograph viewed under polarized light and with oil immersion and high magnification (hematoxylin and eosin, × 1000), the macrophages are shown to be filled with multiple small polyethylene particles. Only a few of the larger intracellular particles (arrows) are visible on this black-and-white reproduction.

TABLE III
HISTOLOGICAL FINDINGS

Case	Location of Section	Bone Loss	Particulate (Extracellular/Intracellular)*			Ratio of Macrophages to Fibroblasts†	Active Bone Resorption
			Metal	Polyethylene	Polymethyl-methacrylate		
1	Femur	Linear	2/3	0/1	—	Low	No
2	Femur	Linear	0/2	1/2	—	Low	No
3	Femur	Linear	1/2	2/2	—	Low	No
4	Femur	Linear	0/1	1/2	—	Intermed.	No
5	Femur	Linear	0/2	1/2	—	High	No
6	Prox. femur	Lytic	3/2	1/2	—	Intermed.	Yes
	Dist. femur	Lytic	0/1	1/2	—	Intermed.	Yes
7	Dist. femur	Linear/lytic	0/1	0/2	—	Intermed.	No
	Dist. femur	Lytic	2/0	0/2	—	Intermed.	No
8	Dist. femur	Lytic	0/1	1/2	—	High	No
	Acetab. rim	Linear	0/0	1/1	—	High	No
9	Dist. femur	Lytic	0/1	1/2	—	High	No
	Dist. femur	Lytic	0/1	0/1	—	Intermed.	No
	Prox. femur	Lytic	0/1	1/2	—	Intermed.	No
	Calcar	Lytic	0/1	1/2	—	Intermed.	No
10	Dist. femur	Linear/lytic	0/1	1/3	—	Intermed.	No
	Dist. femur	Linear/lytic	1/2	1/3	—	Intermed.	No
	Prox. femur	Linear/lytic	0/1	0/3	—	Intermed.	No
	Calcar	Lytic	0/1	2/3	—	High	No
	Mid. femur	Linear/lytic	0/1	1/2	—	High	Yes
	Fem. shoulder	Linear/lytic	0/1	2/2	—	Intermed.	No
	Acetab. lysis	Lytic	1/2	1/3	—	High	Yes
	Screw-hole	Lytic	0/1	2/2	—	High	No
	Acetab. rim	Linear	0/1	1/2	—	Low	Yes
11	Femur	Linear	0/1	1/3	—	Low	No
12	Med. acetab.	Linear	0/1	0/1	—	Low	No
	Med. acetab.	Linear	0/1	0/1	—	Low	No
	Acetab. lining	Linear	0/1	0/2	—	Low	No
	Acetab. lining	Linear	0/0	0/1	—	Low	No
	Acetab. lining	Linear	0/0	2/2	—	Intermed.	No
13	Mid. femur	Linear	0/2	1/2	—	Intermed.	No
14	Femur	None	1/1	0/0	—	Very low	No
15	Femur	Lytic	1/2	1/2	—	High	Yes
16	Femur	Lytic	1/2	1/2	—	High	Yes
17	Femur	Lytic	1/2	1/2	—	High	Yes
18	Femur	Lytic	1/1	1/1	2/2	High	Yes
19	Femur	Lytic	1/1	1/1	2/2	High	Yes
20	Femur	Lytic	0/1	1/2	2/2	High	Yes
21	Dist. femur	Lytic	0/1	1/2	2/2	Intermed.	Yes
22	Femur	Lytic	0/0	1/2	1/1	High	Yes
23	Femur	Lytic	0/0	0/1	1/1	High	Yes
24	Calcar	Lytic	0/1	1/2	—	High	Yes
25	Acetab.	Linear	0/0	1/2	0/0	Low	Yes
26	Acetab.	Linear	0/0	1/2	0/0	Low	Yes
27	Acetab.	Linear	0/0	1/2	0/0	Low	Yes
28	Acetab.	Linear	0/0	1/2	1/1	Low	Yes
29	Acetab.	Linear	0/0	1/2	1/1	Low	Yes
30	Acetab.	Linear	0/0	1/2	1/1	Low	Yes
31	Prox. femur	Linear	0/0	1/2	0/0	High	Yes
32	Prox. femur	Linear	0/0	1/2	0/0	High	Yes
33	Prox. femur	Linear	0/0	1/2	1/1	High	Yes
	Prox. femur	Lytic	0/0	1/2	1/1	High	Yes
34	Prox. femur	Linear	0/0	1/2	0/0	High	Yes
	Femur	Lytic	0/0	1/2	0/0	High	Yes
35	Greater troch.	Lytic	0/1	2/2	—	High	Yes
	Acetab.	Lytic	0/1	1/2	—	High	Yes

*0 = no particles were seen, 1 = particles were present in a limited amount or distribution and were not readily apparent, 2 = particles were a general feature, and 3 = the amount of particles was striking and dominated.
†Low = 1:20, intermediate = 20:20, and high = 20:1.

Particulate polymethylmethacrylate could be identified in specimens from ten of the sixteen hips with cement. Even here, particulate polyethylene was found far from the articular surfaces, in association with bone loss next to both loose and mechanically stable implants (Fig. 2). In one striking example, particulate polyethylene was found in an area of bone resorption that extended ten centimeters inferior to the distal tip of the solidly fixed cement-plug (Fig. 3).

Particulate debris invariably was accompanied by macrophages. Most particles were intracellular in macrophages, and different species of particles (polyethylene, metal, and polymethylmethacrylate) could be seen within the same macrophage. Within the range of sizes of

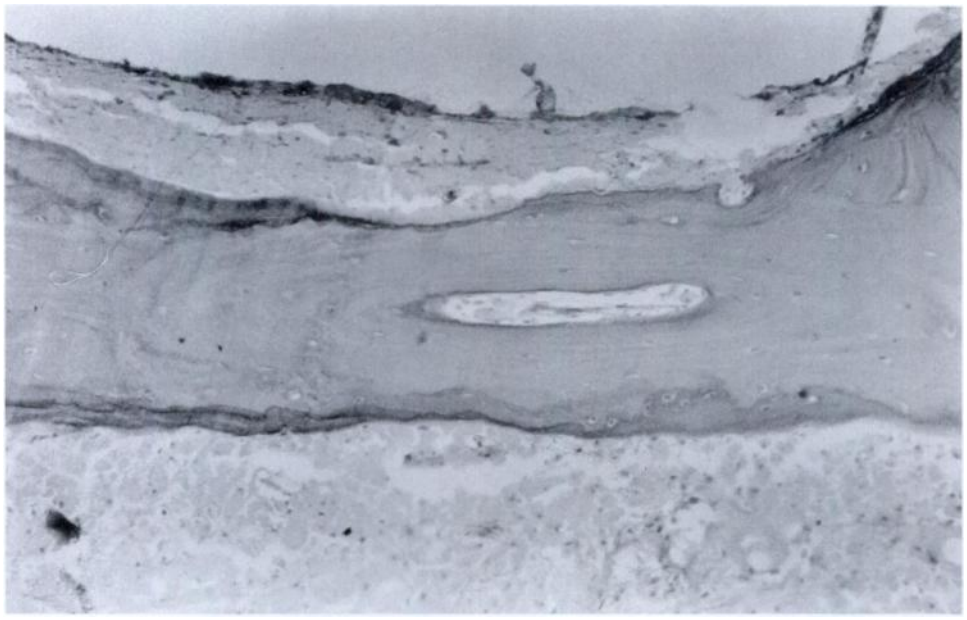

FIG. 5

Area of bone resorption in the region of the femoral neck from a mechanically stable specimen that was obtained at autopsy. There is a high concentration of foamy macrophages (hematoxylin and eosin, × 100).

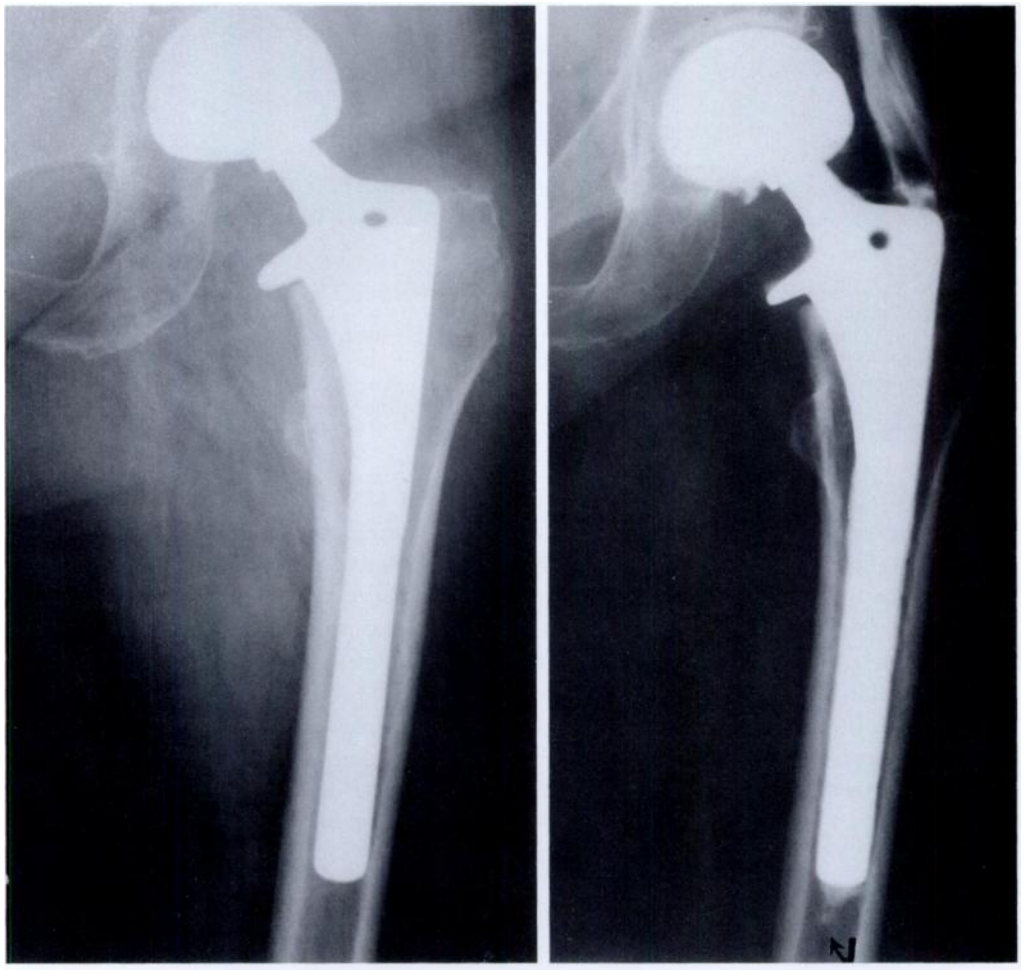

FIG. 6-A

FIG. 6-B

Figs. 6-A and 6-B: Case 14. Demonstration of the effective joint space. The patient complained of pain in the groin and lengthening of the extremity on the side that had been operated on.

Fig. 6-A: Anteroposterior radiograph of the hip five months after bipolar arthroplasty. There is no radiographic evidence of bone loss.

Fig. 6-B: Anteroposterior projection of an arthrogram made five months after bipolar arthroplasty. There is tracking of the contrast medium along the stem, with pooling at the tip of the stem (arrow). At the operation, the femoral component was found to be well fixed by extensive ingrowth of bone; this was confirmed histologically.

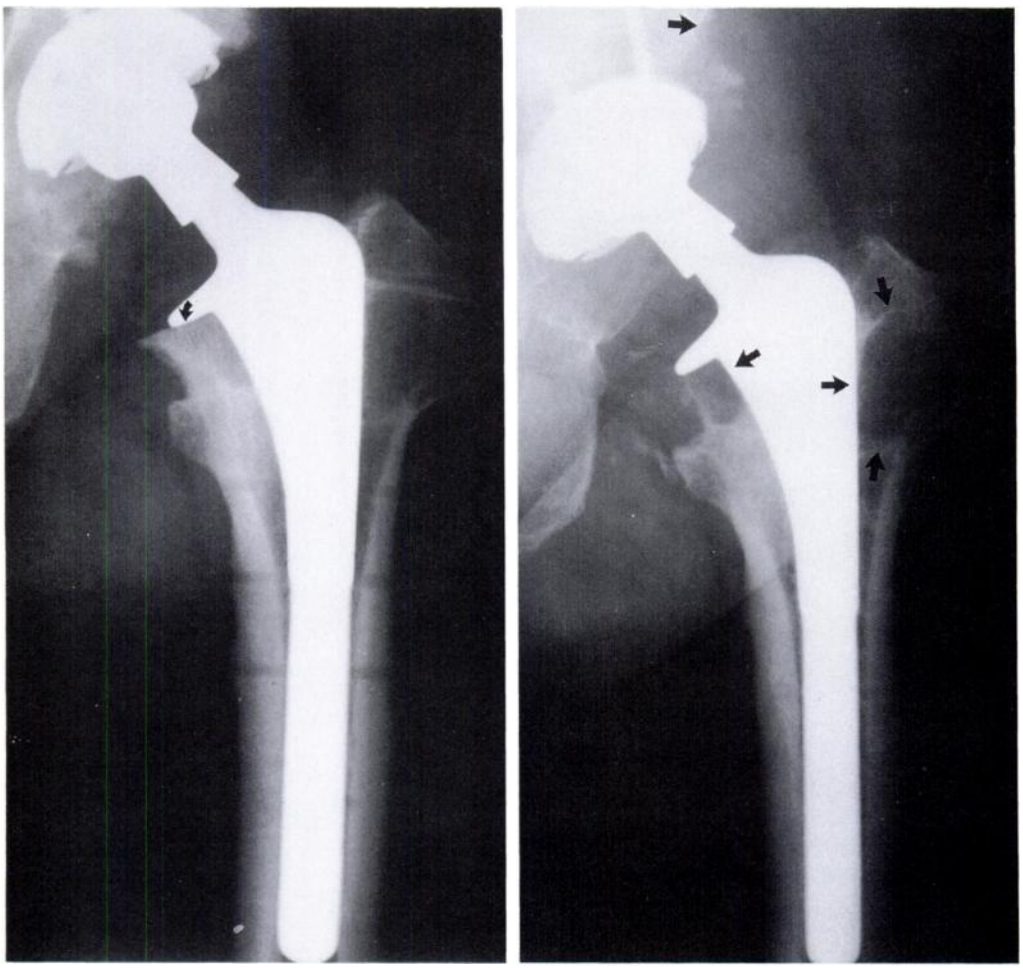

FIG. 7-A FIG. 7-B

Figs. 7-A, 7-B, and 7-C: Case 35. Anteroposterior radiographs of the hip of a fifty-two-year-old man who had a primary uncemented total hip replacement after an intertrochanteric osteotomy for osteoarthrosis.

Fig. 7-A: There is excellent contact between the collar of the prosthesis and the femoral neck (arrow) and good filling of the diaphysis by the prosthesis on this radiograph, made soon after the operation.

Fig. 7-B: After eighty-two months, there was extensive resorption of the femoral neck and evidence of osteolysis in the greater trochanter and superolateral acetabulum (arrows). The channel left by the removed blade-plate probably created a route for preferential flow of joint fluid and wear debris into the greater trochanter. The position of the femoral head within the acetabulum is eccentric, indicating extensive wear of the polyethylene liner.

particles that could be detected by light microscopy, there was a strong and direct relationship between the number of macrophages in a field and the number of particles.

We observed a spectrum in the concentration of macrophages: from a relative paucity (ratio of macrophages to fibroblasts, 1:20) to sheets of macrophages (ratio of 20:1). When present, giant cells contained the same species of particles as did the macrophages in that same region. Lymphocytes were present focally in several specimens; the meaning of this sporadic finding was unclear. Acute inflammation was not seen[31].

Particulate debris and macrophages were present not only in the interface between bone and metal or between bone and cement; they frequently invaded marrow and the intertrabecular spaces of cancellous bone. Particulate debris also was found in the periprosthetic soft tissues. Linear aggregates of macrophages that were filled with particulate polyethylene often were seen in a well developed connective-tissue stroma of numerous fibroblasts and organized collagen. These aggregates of debris-laden phagocytic cells were not readily identified within the predominantly fibrous stroma and could easily be overlooked; the region would then be interpreted as being purely fibrous tissue.

Specimens in which the over-all concentration of macrophages was high were usually in areas where aggressive localized bone resorption was visible on radiographs; the sections in which there were relatively few macrophages and a predominance of fibroblasts generally showed a linear or more diffuse pattern of resorption (Figs. 4-A through 4-D).

The specimens in which the histological sections included bone that was being actively resorbed were particularly valuable. In all twenty-nine such sections, there were histological similarities regardless of the

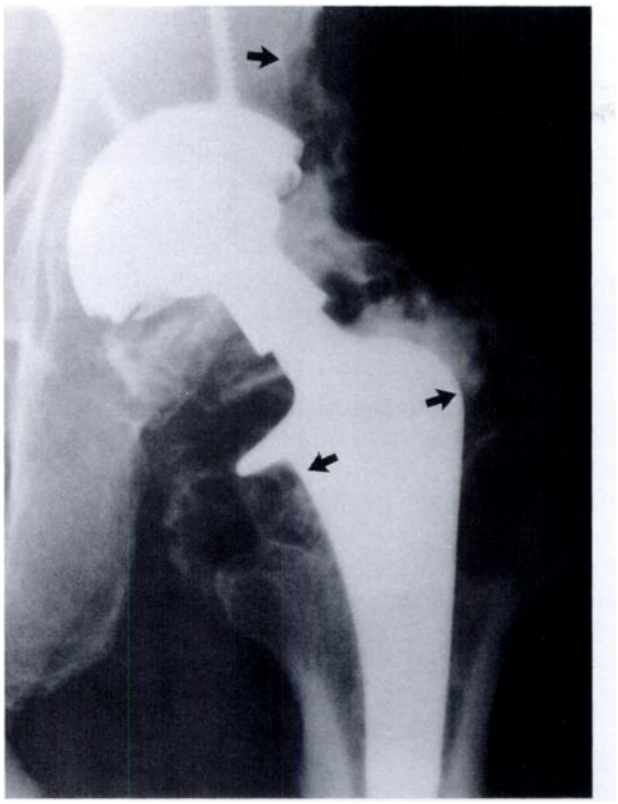

FIG. 7-C

An arthrogram reveals contrast medium in the region of loss of bone from the femoral neck, around the shoulder of the prosthesis into the greater trochanter, and proximally into the superolateral acetabulum (arrows). Histological examination of tissue from all three sites was similar: concentrations of foamy macrophages and rare giant cells were found in association with active bone resorption. These inflammatory cells were filled with various-sized particles of polyethylene; particles of metal were rare.

type of fixation, the gross radiographic appearance of the bone loss, or the anatomical origin of the specimen. Regardless of the predominant stroma of the specimen, focal concentrations of macrophages were observed in direct association with the areas of bone resorption (Fig. 5). The cytoplasm of these macrophages was always filled with particulate debris. Although several species of particulate debris could be identified in nearly every such specimen, particulate polyethylene was identified in association with the bone resorption in every specimen, regardless of the type of fixation or the presence or absence of mechanical stability; in some regions of resorption, polyethylene was the only type of particle that was seen. Although in some specimens the bone destruction was clearly mediated by osteoclasts, in other specimens relatively few osteoclasts were identified. Occasionally, bone formation was also observed in areas adjacent to the resorptive areas.

Among the twelve arthrograms of hips that had no cement (Table II), the most striking finding was that in two hips (Cases 7 and 14) in which torque-testing had shown that the prosthesis was rigidly fixed and histological examination revealed ingrowth of bone, the contrast medium flowed rapidly and extensively in the bone-metal interface. In Case 7, there was both linear and lytic bone loss, and in Case 14, in which the bipolar component was revised after only six months, there was no apparent bone loss on radiographs (Figs. 6-A and 6-B).

Discussion

Now that technical advances have reduced the rates of infection and loosening of components after total hip replacement[9,32], the problem of periprosthetic loss of bone has become the major focus of attention. Although periprosthetic loss of bone and loss of mechanical stability often are associated, such bone loss clearly can occur without loosening of an implant[21,22,28,29].

Two fundamental questions remain unanswered: what initiates the loss of bone, and what factors determine whether the loss of bone is diffuse or more localized? Our findings prompted us to propose the following sequence of events in response to these questions.

Polyethylene wear debris and other particles are dispersed in the joint fluid. The true limits of the effective joint space are determined by how intimate the contact is between the prosthesis and bone and how this contact varies within a given reconstruction. This variability determines the access routes for the joint fluid and particulate debris, to and along the prosthetic-bone interfaces and through the soft tissues and bone as well. Joint fluid flows according to pressure gradients and simply follows the path of least resistance. In this sense, these areas that the joint fluid reaches become part of the joint space — hence our term effective joint space. The linear aggregates of macrophages that we saw running like a stream through connective-tissue stroma may also represent channels or routes through the periprosthetic soft tissues for particulate debris.

When small particles are present in sufficient numbers, phagocytosis can result in the activation of macrophages and in the direct resorption of the bone by macrophages[1,4,15,33,34,38]. In this manner, the local concentration of particles determines the degree of the inflammatory response and hence, the degree of resorption. As bone is resorbed, a bigger sink is produced, encouraging even more flow (preferential flow) into that area, delivering more particles and causing more bone resorption. When sufficient bone has been resorbed, an osteolytic area can be seen on radiographs (Figs. 7-A, 7-B, and 7-C). We postulate that if the joint fluid and its particles are distributed more evenly in an interface, there will be slower resorption of bone, accompanied by a fibroblastic response, resulting in the radiographic appearance of linear (diffuse) bone loss.

An intact barrier at the interface of metal and cement or of cement and bone may retard periprosthetic bone

loss; the integrity of such a barrier may depend to some extent on the design of the component. Anthony et al.[3] published a report on four cases of localized femoral endosteal lysis of bone in which the area of lysis was shown, at revision, to be directly related to a region in which there was a local defect in the cement-mantle. In a prosthesis such as the one in that study (Exeter; Howmedica International, Shannon, Ireland), which was specifically designed to prevent bonding between the metal implant and the cement-mantle, debris can migrate in this space and reach the endosteal surface through defects in the mantle. A similar mechanism may be at work about stems that have been designed to be bonded to the cement-mantle but in which the bonding either is incomplete or has broken down after years of service and exposure to joint fluid.

The mechanisms by which joint fluid and particulate debris are transported around the effective joint space are under investigation. Accumulating evidence suggests a role for variations in pressure of joint fluid. Hendrix et al.[13] reported large variations in the pressure of intracapsular fluid around total hip replacements during activities of daily living. Anthony et al.[3] reported fluid pressures in an area of osteolysis of as much as 198 millimeters of mercury (26.4 kilopascals). Our studies indicated that pressures of intracapsular fluid are a function of contractions of muscle and position of the joint. Additionally, the peak intracapsular pressures do not coincide with loading of the joint. We believe that this non-phasic relationship is an important force that actively drives joint fluid and particulate debris through the effective joint space and fuels progressive bone loss[42].

The concept of preferential flow may also explain why uncemented femoral implants in which the porous coating is limited to the proximal part of the prosthesis more often have osteolysis around the distal part of the stem compared with implants in which the porous coating is more extensive[29].

Joint fluid and particulate debris may flow in both directions: not only can wear debris migrate into the periprosthetic space, but particles of metal and cement from the implant can be transported to the articular surfaces. The implications of this concept for hips that have accelerated wear from three-body mechanisms are profound.

Because they are completely intra-articular, the femoral sides of surface replacements are important clinical models of the effective joint space[5,12,17-19,35]. Howie et al.[19], reporting the histological findings in a large series of femoral resurfacing components retrieved at operation, found small particles of polyethylene in association with macrophages and active bone resorption adjacent to regions of intimate cement-bone contact before there was gross evidence of loosening. They concluded that wear particles migrate along cement-bone interfaces of implants that are both macroscopically and microscopically solid, and they emphasized the role of wear particles in this type of prosthetic loosening. Nasser et al.[35] reported aggressive cavitary osteolysis in the femoral neck and head in the presence of stable uncemented femoral surface replacements. These lesions contained sheets of macrophages filled with particulate debris from both the metal alloy and the polyethylene bearing surfaces. Bone was resorbed along a front in contact with the granulomatous tissue that filled the cystic lesions. The results of our analysis of surface replacement specimens are in complete agreement with the findings of Howie et al.[19] and Nasser et al.[35].

Additional evidence for the important role of the effective joint space in periprosthetic bone loss is provided by the analysis of the acetabular specimens that were retrieved at autopsy[43]. This study demonstrated that the process of late aseptic loosening of a cemented acetabular component is the result of progressive, three-dimensional resorption of the bone that is immediately adjacent to the cement, beginning circumferentially at the intra-articular margin and progressing toward the dome of the implant. The process appears to be caused by small particles of polyethylene migrating along the cement-bone interface; bone resorption occurs as a result of the inflammatory macrophage response to the particulate polyethylene. This suggests that the initiating mechanism of late aseptic loosening of a cemented acetabular component can be biological rather than mechanical. Similar histological findings have been described in the membranes from around loose uncemented acetabular components[38].

It was previously reported that the mechanism of loosening of cemented femoral components is mechanical in nature and that the initial events involve the loss of apposition between the prosthesis and cement (debonding) and fractures of the cement[30]. In the present study, we analyzed regions of the proximal part of the femoral cement-bone interface around several of these same cemented femoral components that had been retrieved at autopsy and compared the histological findings with those involved in the mechanism of loosening of cemented acetabular components. The histological appearance was identical: debris-laden macrophages were seen in association with regions of active bone resorption. This suggests that a similar biological process of periprosthetic bone resorption does occur in a roughly centrifugal fashion on both sides of the joint[24]. Because of the difference in the shape of the femoral and acetabular components, the effect of this type of resorption on the mechanical stability of these components is different. Two centimeters of circumferential bone resorption in the proximal part of the femoral cement-bone interface adjacent to the articulation of the hip does not generally result in loosening of a femoral implant because of the extent of the femoral cement-bone interface that remains intact. If two centimeters of the acetabular cement-bone interface adjacent to the articulation is disrupted by bone resorption, however, so much of the

acetabular interface will be disrupted that stability will be jeopardized.

The deleterious effects of polyethylene wear debris in cemented hip implants have been extensively documented[16,18,24,31,37,43,45,46]. Willert and Semlitsch[45] suggested that the foreign-body reaction to particulate debris may result in loosening due to deterioration of contiguous bone anchors by the soft-tissue membrane. In an experimental animal model, resorption of bone around the perimeter of an intra-articular plug of polymethylmethacrylate has been demonstrated in the presence of particulate polyethylene and in the absence of mechanical load[20].

There were obvious differences, in the specimens in our study, in the relative amounts of macrophages, fibroblasts, and connective-tissue stroma. The most important difference between specimens from areas of localized lysis and those from areas of more diffuse linear resorption was in the proportions of the cellular constituents and matrix. In specimens from radiographically identified areas of osteolysis there was usually a predominance of macrophages throughout, with little connective-tissue stroma, but in specimens from areas of diffuse and linear loss, there was usually a predominance of fibroblasts and a variable amount of organized collagenous stroma with relatively few macrophages. There were distinct similarities, however, in the regions of active bone resorption, regardless of the radiographic distinction between diffuse and localized bone loss; localized collections of debris-laden macrophages were always seen in association with localized areas of bone resorption.

We noted a diffuse intracellular birefringence in the cytoplasm of the phagocytic cells when they were viewed at high magnification under polarized light. This observation has been made in specimens only when there were highly conforming bearing surfaces of polyethylene[41]. We have examined tissues from a broad range of other implants, including femoral intramedullary rods, titanium-alloy intercalary prostheses, cemented and uncemented Moore hemiarthroplasty components, titanium-alloy uncemented hemiresurfacing components, uncemented total hip implants that had ceramic femoral and acetabular bearing surfaces, McKee-Farrar total hip replacements, and total knee replacements, but the fine diffuse birefringence appears to be unique to systems with a highly conforming polyethylene bearing surface. We postulate that this background birefringence is caused by particles of polyethylene that are too small to be resolved clearly by light microscopy. The analysis of selected sections by transmission electron microscopy confirmed the presence of particles less than one micrometer in size within the macrophages, and these small particles appeared to be polyethylene (Fig. 1). Quantitative analysis by photon correlation spectroscopy has shown that most of the particulates in tissue that has been retrieved from total hip replacements in which there are bearing surfaces of polyethylene are less than one micrometer in size[26].

Activation of macrophages is a function of both the number and the type of particles[34]. This concept has important implications for wear-testing: the spectrum of sizes and the total number of debris particles that are generated may be at least as important as the total volume of material that is lost from the bearing surfaces over a given number of cycles. Regardless of the relative biological activity of a specific material in particulate form, if particles of that material are present in sufficient numbers and are phagocytized in sufficient amounts, macrophages will be activated. Small-particle disease therefore appears to be especially problematic, because of the high numbers and tremendous migratory potential of small particles. As has been demonstrated, particulate polyethylene can migrate in the effective joint space far from the articular surfaces.

Several of the cases of osteolysis in this comparative review have been previously reported[21,22,28,29,43]. In the early analysis of osteolysis around the cemented components, particulate polymethylmethacrylate was identified but the presence of the very small, submicrometer particles of polyethylene was not appreciated[11,22]. The identification of submicrometer particulate polyethylene in specimens from areas of bone resorption around uncemented implants led us to re-examine our specimens from cemented implants in hips that had aggressive localized bone loss. With this new perspective, submicrometer particles of polyethylene were identified as a common denominator in osteolysis associated with both cemented and uncemented implants.

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References

1. **Adams, D. O.,** and **Hamilton, T. A.:** The cell biology of macrophage activation. *Ann. Rev. Immunol.*, 2: 283-318, 1984.
2. **Agins, H. J.; Alcock, N. W.; Bansal, Manjula; Salvati, E. A.; Wilson, P. D., Jr.; Pellicci, P. M.;** and **Bullough, P. G.:** Metallic wear in failed titanium-alloy total hip replacements. A histological and quantitative analysis. *J. Bone and Joint Surg.*, 70-A: 347-356, March 1988.
3. **Anthony, P. P.; Gie, G. A.; Howie, C. R.;** and **Ling, R. S. M.:** Localised endosteal bone lysis in relation to the femoral components of cemented total hip arthroplasties. *J. Bone and Joint Surg.*, 72-B(6): 971-979, 1990.
4. **Athanasou, N. A.; Quinn, J.;** and **Bulstrode, C. J. K.:** Resorption of bone by inflammatory cells derived from the joint capsule of hip arthroplasties. *J. Bone and Joint Surg.*, 74-B(1): 57-62, 1992.
5. **Bell, R. S.; Schatzker, J.; Fornasier, V. L.;** and **Goodman, S. B.:** A study of implant failure in the Wagner resurfacing arthroplasty. *J. Bone and Joint Surg.*, 67-A: 1165-1175, Oct. 1985.

6. **Black, J.; Sherk, H.; Bonini, J.; Rostoker, W. R.; Schajowicz, F.;** and **Galante, J. O.:** Metallosis associated with a stable titanium-alloy femoral component in total hip replacement. A case report. *J. Bone and Joint Surg.*, 72-A: 126-130, Jan. 1990.
7. **Burke, D. W.; O'Connor, D. O.; Zalenski, E. B.; Jasty, Murali;** and **Harris, W. H.:** Micromotion of cemented and uncemented femoral components. *J. Bone and Joint Surg.*, 73-B(1): 33-37, 1991.
8. **Charnley, John:** *Low Friction Arthroplasty of the Hip. Theory and Practice.* New York, Springer, 1979.
9. **Engh, C. A.; Bobyn, J. D.;** and **Glassman, A. H.:** Porous-coated hip replacement. The factors governing bone ingrowth, stress shielding, and clinical results. *J. Bone and Joint Surg.*, 69-B(1): 45-55, 1987.
10. **Finlay, J. B.; Bourne, R. B.; Landsberg, R. P. D.;** and **Andreae, Peter:** Pelvic stresses in vitro II. A study of the efficacy of metal-backed acetabular prostheses. *J. Biomech.*, 19: 715-725, 1986.
11. **Harris, W. H.; Schiller, A. L.; Scholler, J.-M.; Freiberg, R. A.;** and **Scott, Richard:** Extensive localized bone resorption in the femur following total hip replacement. *J. Bone and Joint Surg.*, 58-A: 612-618, July 1976.
12. **Head, W. C.:** Wagner surface replacement arthroplasty of the hip. Analysis of fourteen failures in forty-one hips. *J. Bone and Joint Surg.*, 63-A: 420-427, March 1981.
13. **Hendrix, R. W.; Wixon, R. L.; Rana, N. A.;** and **Rogers, L. F.:** Arthrography after total hip arthroplasty: a modified technique used in the diagnosis of pain. *Radiology*, 148: 647-652, 1983.
14. **Hodgkinson, J. P.; Shelley, P.;** and **Wroblewski, B. M.:** The correlation between the roentgenographic appearance and operative findings at the bone-cement junction of the socket in Charnley low friction arthroplasties. *Clin. Orthop.*, 228: 105-109, 1988.
15. **Holtrop, M. E.; Cox, K. A.;** and **Glowacki, Julie:** Cells of the mononuclear phagocytic system resorb implanted bone matrix: a histologic and ultrastructural study. *Calcif. Tissue Internat.*, 34: 488-494, 1982.
16. **Howie, D. W.:** Tissue response in relation to type of wear particles around failed hip arthroplasties. *J. Arthroplasty*, 5: 337-348, 1990.
17. **Howie, D. W.; Cain, C. M. J.;** and **Cornish, B. L.:** Pseudo-abscess of the psoas bursa in failed double-cup arthroplasty of the hip. *J. Bone and Joint Surg.*, 73-B(1): 29-32, 1991.
18. **Howie, D. W.; Cornish, B. L.;** and **Vernon-Roberts, Barrie:** Resurfacing hip arthroplasty. Classification of loosening and the role of prosthesis wear particles. *Clin. Orthop.*, 255: 144-159, 1990.
19. **Howie, D. W.; Campbell, David; McGee, Margaret;** and **Cornish, B. L.:** Wagner resurfacing hip arthroplasty. The results of one hundred consecutive arthroplasties after eight to ten years. *J. Bone and Joint Surg.*, 72-A: 708-714, June 1990.
20. **Howie, D. W.; Vernon-Roberts, B.; Oakeshott, R.;** and **Manthey, B.:** A rat model of resorption of bone at the cement-bone interface in the presence of polyethylene wear particles. *J. Bone and Joint Surg.*, 70-A: 257-263, Feb. 1988.
21. **Jasty, Murali; Haire, Teresa;** and **Tanzer, Michael:** Femoral osteolysis: a generic problem with cementless and cemented femoral components. *Orthop. Trans.*, 15: 758-759, 1991.
22. **Jasty, M. J.; Floyd, W. E., III; Schiller, A. L.; Goldring, S. R.;** and **Harris, W. H.:** Localized osteolysis in stable, non-septic total hip replacement. *J. Bone and Joint Surg.*, 68-A: 912-919, July 1986.
23. **Johanson, N. A.; Callaghan, J. J.; Salvati, E. A.;** and **Merkow, R. L.:** 14-year follow-up study of a patient with massive calcar resorption. A case report. *Clin. Orthop.*, 213: 189-196, 1986.
24. **Johnston, R. C.,** and **Crowninshield, R. D.:** Roentgenologic results of total hip arthroplasty. A ten-year follow-up study. *Clin. Orthop.*, 181: 92-98, 1983.
25. **Jones, L. C.,** and **Hungerford, D. S.:** Cement disease. *Clin. Orthop.*, 225: 192-206, 1987.
26. **Kossovsky, N.; Liao, K.; Gelman, A.; Campbell, P. A.; Amstutz, H. C.; Finerman, G. A. M.; Nasser, S.;** and **Thomas, B. I.:** Photon correlation spectroscopy analysis of submicrometre particulate fraction in human synovial tissues recovered at arthroplasty or revision. In *Particulate Debris from Medical Implants*, pp. 68-74. Edited by K. R. St. John. Philadelphia, ASTM, 1992.
27. **Lennox, D. W.; Schofield, B. H.; McDonald, D. F.;** and **Riley, L. H., Jr.:** A histologic comparison of aseptic loosening of cemented, press-fit, and biologic ingrowth prostheses. *Clin. Orthop.*, 225: 171-191, 1987.
28. **Maloney, W. J.; Jasty, Murali; Rosenberg, Andrew;** and **Harris, W. H.:** Bone lysis in well-fixed cemented femoral components. *J. Bone and Joint Surg.*, 72-B(6): 966-970, 1990.
29. **Maloney, W. J.; Jasty, Murali; Harris, W. H.; Galante, J. O.;** and **Callaghan, J. J.:** Endosteal erosion in association with stable uncemented femoral components. *J. Bone and Joint Surg.*, 72-A: 1025-1034, Aug. 1990.
30. **Maloney, W. J.; Jasty, Murali; Burke, D. W.; O'Connor, D. O.; Zalenski, E. B.; Bragdon, Charles;** and **Harris, W. H.:** Biomechanical and histologic investigation of cemented total hip arthroplasties. A study of autopsy-retrieved femurs after in vivo cycling. *Clin. Orthop.*, 249: 129-140, 1989.
31. **Mirra, J. M.; Marder, R. A.;** and **Amstutz, H. C.:** The pathology of failed total joint arthroplasty. *Clin. Orthop.*, 170: 175-183, 1982.
32. **Mulroy, R. D., Jr.,** and **Harris, W. H.:** The effect of improved cementing techniques on component loosening in total hip replacement. An 11-year radiographic review. *J. Bone and Joint Surg.*, 72-B(5): 757-760, 1990.
33. **Mundy, G. R.; Altman, A. J.; Gondek, M. D.;** and **Bandelin, J. G.:** Direct resorption of bone by human monocytes. *Science*, 196: 1109-1111, 1977.
34. **Murray, D. W.,** and **Rushton, N.:** Macrophages stimulate bone resorption when they phagocytose particles. *J. Bone and Joint Surg.*, 72-B(6): 988-992, 1990.
35. **Nasser, Sam; Campbell, P. A.; Kilgus, Douglas; Kossovsky, Nir;** and **Amstutz, H. C.:** Cementless total joint arthroplasty prostheses with titanium-alloy articular surfaces. A human retrieval analysis. *Clin. Orthop.*, 261: 171-185, 1990.
36. **O'Neill, D. A.,** and **Harris, W. H.:** Failed total hip replacement: assessment by plain radiographs, arthrograms and aspiration of the hip joint. *J. Bone and Joint Surg.*, 66-A: 540-546, April 1984.
37. **Pazzaglia, Ugo,** and **Byers, P. D.:** Fractured femoral shaft through an osteolytic lesion resulting from the reaction to a prosthesis. A case report. *J. Bone and Joint Surg.*, 66-B(3): 337-339, 1984.
38. **Santavirta, Seppo; Konttinen, Y. T.; Hoikka, Veijo;** and **Eskola, Antti:** Immunopathological response to loose cementless acetabular components. *J. Bone and Joint Surg.*, 73-B(1): 38-42, 1991.
39. **Santavirta, Seppo; Hoikka, Veijo; Eskola, Antti; Konttinen, Y. T.; Paavilainen, Timo;** and **Tallroth, Kaj:** Aggressive granulomatous lesions in cementless total hip arthroplasty. *J. Bone and Joint Surg.*, 72-B(6): 980-984, 1990.
40. **Santavirta, Seppo; Konttinen, Y. T.; Bergroth, Ville; Eskola, Antti; Tallroth, Kaj;** and **Lindholm, T. S.:** Aggressive granulomatous lesions associated with hip arthroplasty. Immunopathological studies. *J. Bone and Joint Surg.*, 72-A: 252-258, Feb. 1990.

41. **Schmalzried, T. P.:** Light microscopic identification of high density polyethylene (HDP) wear debris using oil red O staining. *Trans. Orthop. Res. Soc.*, 17: 346, 1992.
42. **Schmalzried, T. P.,** and **Harris, W. H.:** Periprosthetic bone loss in total hip replacement: the role of high density polyethylene (HDP) wear debris and the concept of effect joint space. *Trans. Orthop. Res. Soc.*, 17: 46, 1992.
43. **Schmalzried, T. P.; Kwong, L. M.; Jasty, Murali; Sedlacek, R. C.; Haire, T. C.; O'Connor, D. O.; Bragdon, C. R.; Kabo, J. M.; Malcolm, A. J.;** and **Harris, W. H.:** The mechanism of loosening of cemented acetabular components in total hip arthroplasty. Analysis of specimens retrieved at autopsy. *Clin. Orthop.*, 274: 60-78, 1992.
44. **Tallroth, Kaj; Eskola, Antti; Santavirta, Seppo; Konttinen, Y. T.;** and **Lindholm, T. S.:** Aggressive granulomatous lesions after hip arthroplasty. *J. Bone and Joint Surg.*, 71-B(4): 571-575, 1989.
45. **Willert, H.-G.,** and **Semlitsch, M.:** Reactions of the articular capsule to wear products of artificial joint prostheses. *J. Biomed. Mater. Res.*, 11: 157-164, 1977.
46. **Willert, H.-G.; Bertram, Hendrik;** and **Buchhorn, G. H.:** Osteolysis in alloarthroplasty of the hip. The role of ultra-high molecular weight polyethylene wear particles. *Clin. Orthop.*, 258: 95-107, 1990.