

Conquest of a Worldwide Human Disease: Particle-Induced Periprosthetic Osteolysis

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Abstract [TOP](#)

It is rare in the long history of human disease to encounter a completely unique disease. In the 21st century, when it does occur, the disease commonly is man-made, as is true for periprosthetic osteolysis. However, it also is rare to unravel the mysteries of a biologic process as complex as periprosthetic osteolysis in slightly longer than one generation and even less common to create the means for the worldwide prevention of an entire disease. Such is the story of periprosthetic osteolysis. The adventure from the iatrogenic creation of the disease to the identification of its pathology, to the understanding of its molecular biology and, subsequently, to its prevention, during a period of four decades, is a fascinating story of medical detective work.

Particle-induced periprosthetic osteolysis is a unique disease. It never had been seen previously in recorded history. It is the dominant long-term complication of total hip arthroplasty (THA).^{16,17} The osteolysis is secondary to particulate debris generated through wear of the ultra-high molecular weight polyethylene (PE) at the articular surface of the total hip replacement (THR). During a 44-year interval, this unique disease has emerged, been identified, been explained, and, currently, possibly been prevented.

The history of the unraveling and prevention of this worldwide, unique, severe disease is a fascinating story of the integration of surgical innovation, molecular biology, and material science.

Not only is periprosthetic osteolysis the dominant long-term complication of THA, it is the major cause of loosening of acetabular components, the major reason for the revision of acetabular components, a major contributor to loosening of femoral components, and the most important process related to pathologic fractures of the femur and the acetabulum after THA.

Beginning approximately 5 years after surgery, the incidence of this disease increases progressively and has affected more than 40% of patients in some series.^{7,19,30} It is the major factor limiting the durability of THA, the dominant cause of clinical failure, and the leading cause for the need for reoperation.

In its severe forms, the manifestations can be alarming. Its severity seriously can complicate revision surgery. The severe forms also have compelled the development of far more complex and inherently less successful reconstructive surgical techniques.

Recognizing a New Disease [TOP](#)

Because the inciting cause has been shown to be the prolonged, continuing liberation of micron and submicron particulate debris within the human body, this iatrogenic disease is unique, occurring only during the last 50 years. It is unique because this mechanism of the disease required a process for the prolonged generation of micron and submicron particles within the human body. That requirement depended on the invention and widespread adoption of THA.

However, because no such mechanism for the generation of micron and submicron particles within the human body had ever existed before, the periprosthetic osteolysis, which characterizes this disease, came as a surprise. There is no antecedent manifestation of this disease.

For that reason, the early examples of periprosthetic osteolysis often were overlooked, commonly misunderstood, and inappropriately characterized. The pioneering work of Sir John Charnley came very close to an understanding of this disease, particularly with his recognition of particulate debris and the macrophages in the tissues associated with what we now call periprosthetic osteolysis.⁴ However, his experience with infection after THR was so common in the early days that his thought was shaped by that experience. He thought that periprosthetic osteolysis represented infection, a septic process, but with the puzzling feature that no bacteria could be recovered.⁵

Similarly, McKee and Watson-Ferrar²¹ thought that the erosion of bone that they observed was simply the result of motion of the components, and not caused by a reaction to the plastic.

Because of the obscure and unprecedented nature of this disease, it was 14 years after the first THR had been done that the true nature of the disease effectively was identified. In 1976, Willert²⁷ and Willert and Semlitsch²⁸ published their concepts of the migration of the particulate debris into the periprosthetic effective joint space. That same year, four cases of periprosthetic osteolysis were reported¹⁸ in which the initial consideration of the leading diagnostic possibility was metastatic malignancy or myeloma. In all four cases the histology was characterized by sheets of macrophages without any evidence of malignancy.

The manifestations of the disease, as reflected in radiographic changes, are varied. The most dramatic form of bone loss in the pelvis is a large focal erosive process, the so-called balloon osteolysis, but subsequent studies²⁷ also showed that the common linear radiolucent zone that developed at the interface between the bone cement and the adjacent bone also was periprosthetic osteolysis with a similar histologic appearance. Equally so on the femoral side, there may be massive endosteal erosion and compromise of the structural integrity of the femur, but there may be relatively subtle linear enlargement of the interface between cement and bone or between a metal prosthesis and bone. Also, less commonly, there may be subperiosteal erosion, reducing the external thickness and strength of the femoral cortex. The structural integrity of the greater trochanter or lesser trochanter may be compromised, leading to spontaneous pathologic fracture of the trochanter. Many of these manifestations are precursors of loosening of the acetabular or femoral component.

The Nature of the Disease [TOP](#)

Central to the understanding of the nature of periprosthetic osteolysis was an initial observation in 1983^{9,10} that the so-called fibrous membrane, which commonly was removed at revision surgery and discarded, had not only the cellular characteristics of macrophages and fibroblasts, but also had the capacity to generate prostaglandin E2 (PGE2) and collagenase. We also showed at that time that this tissue had the capacity to resorb bone when placed on rat calvaria and that this capacity could be partially, but not completely, inhibited by nonsteroidal antibiotic drugs (NSAIDs).

These seminal observations opened the gates for the subsequent and far more detailed investigation of the synthetic capacity of the cellular constituents of this membrane. At that time, transforming growth factor beta (TGF-beta), interleukin-1 (IL-1), IL-6, tumor necrosis factor alpha (TNF-alpha), and

many of the other cytokines and enzymes now recognized as important components in the mechanism leading to osteoclastic stimulation and periprosthetic osteolysis, had not yet been discovered.

Thereafter followed a rapid increase in investigations that have now, in large measure, identified the highly complex and intertwined cellular interactions, cytokines, and enzymes that result from the ingestion of the small particles by macrophages. These interactions included the subsequent activation of other cell lines, including fibroblasts and, ultimately, osteoclasts. This multifaceted elaboration of the molecular biology associated with particulate periprosthetic disease has been a triumph of the investigative capacity of orthopaedic surgeons, rheumatologists, and molecular biologists, leading to a substantial understanding of the mechanism of this disease.[2](#)

Prevention of Periprosthetic Osteolysis [TOP](#)

Because periprosthetic osteolysis is a disease of a prolonged generation of multiple small particles within the body, the prevention of this condition hinges on improved articulations. The articulations must be able to permit the 1-million to 2-million cycle activity at the hip per year under loads commonly at three times body weight (but occasionally as high as six times body weight) to take place without the generation of particles, or with the generation of so few particles that the disease does not become manifested. That goal has been achieved. Beginning more than four decades ago, in terms of metal-on-metal articulations,[1,21](#) and more than three decades ago, in terms of ceramic-on-ceramic articulations[13,14](#) and highly cross-linked PEs,[10,13,24,29](#) innovations in improving the articular surface were initiated. All three approaches have shown that these three alternate bearing-surface combinations are distinctly superior to the original ultra-high molecular weight PE in terms of the prevalence of osteolysis after THA.

Building on the long-term success of the early metal-on-metal, ceramic-on-ceramic, and highly cross-linked PE articulations, material scientists now have improved each one of these three materials based on current in vitro and in vivo studies. With the metal-on-metal articulations, the composition of the metal alloys has been optimized, and extensive studies have improved the understanding of the appropriate clearance.[1](#) With the ceramic-on-ceramic articulations, major advances have been made in reducing the grain size, increasing the resistance to burst fractures, and optimizing other material properties of the ceramics.[15](#) With the PEs, detailed studies of cross-linking have now optimized the radiation dose at approximately 10 Mrad and provided new methods for the elimination of the residual free radicals that eliminate the problem of oxidation.[22,23](#)

In each of these efforts to improve the behavior of the articular surfaces, some false starts have been encountered that actually made the outcome worse, rather than better.[3,6](#) However, with the continued critical analysis of the outcomes, these false avenues in pursuit of progress have been and currently are being discarded. The best of these three alternate bearings have wear rates in the range of 5 to 15 μm per year.[8,9,20,25](#)

Current Status [TOP](#)

Superimposed on the excellent long-term results of the three alternate bearing surfaces when used in their earlier forms are the excellent intermediate clinical results of the more contemporary versions of each alternate bearing surface.[1,3,8](#)

It is a reasonable extrapolation of data to suggest that the use of these three contemporary, alternate bearing surfaces extensively will reduce or possibly nearly eliminate the risk of periprosthetic osteolysis in the patient population receiving them. For many reasons, including familiarity, adaptability, forgiveness, and cost, the highly cross-linked, subsequently melted, ultra-high molecular weight PEs have a dominant position in the incidence of the use of alternate bearing surfaces worldwide.

During a period of four decades, an entirely new disease was created as a by-product of the ingenuity of the pioneers who created THA. The invention of THA also unwittingly simultaneously created

periprosthetic osteolysis. That devastating complication, which is a manifestation of the adverse effect of micron and submicron particulate debris, subsequently became the number one long-term complication of THA. Through the insightful investigations of a cadre of clinical and basic researchers, the disease first was identified as a separate phenomenon, but without explanation. Subsequently, the nature of the biologic process became more clearly identified. These studies established that the initiating event was the ingestion of the small particles into the macrophage. That observation forced the necessity for improved articulations and fostered the development of the three alternate bearing surfaces. All three of these surfaces have shown the capacity to markedly reduce or nearly eliminate periprosthetic osteolysis in studies covering more than two decades of in vivo use of THA. Those successes prompted the further refinement by contemporary material scientists for the optimization of each of these bearing surfaces. The use of alternate bearing surfaces now dominates much of THA. The use of highly cross-linked, subsequently melted, ultra-high molecular weight PE predominates in the incidence of use of these new alternate bearing surfaces. These events have led to a set of circumstances with a high probability of major reduction or near elimination of a unique worldwide human disease. This is a fascinating, compelling, and important story of the conquest of a unique worldwide human disease without previous precedent in the entire human experience.

References [TOP](#)

1. Amstutz HC, Campbell P, McKellop H, et al: Metal-on-metal total hip replacement workshop consensus document. *Clin Orthop* 329(Suppl):S297-S303, 1996.
[\[Medline Link\]](#) [\[Fulltext Link\]](#) [\[CrossRef\]](#) [\[Context Link\]](#)
2. Archibeck MJ, Jacobs JJ, Roebuck KA, Glant TT: The basic science of periprosthetic osteolysis. *Instr Course Lect* 50:185-195, 2001.
[\[Context Link\]](#)
3. Bierbaum BE, Narius J, Kuesis D, Morrison JC, Ward D: Ceramic-on-ceramic bearings in total hip arthroplasty. *Clin Orthop* 405:158-163, 2002.
[\[Context Link\]](#)
4. Charnley J: *Low Friction Arthroplasty. Theory and Practice*. Berlin, Springer-Verlag 25-40, 1979.
[\[Context Link\]](#)
5. Charnley J, Follacci F, Hammond B: The long-term reaction of bone to self-curing acrylic cement. *J Bone Joint Surg* 50B:822-829, 1968.
[\[Context Link\]](#)
6. Chmell M, Poss R, Thomas WH, Sledge CB: Early failure of Hylamer acetabular inserts due to eccentric wear. *J Arthroplasty* 11:351-353, 1996.
[\[Medline Link\]](#) [\[CrossRef\]](#) [\[Context Link\]](#)
7. Clohisy JC, Harris WH: The Harris-Galante uncemented femoral component in primary total hip replacement at 10 years. *J Arthroplasty* 14:915-917, 1999.
[\[Medline Link\]](#) [\[CrossRef\]](#) [\[Context Link\]](#)
8. Digas G, Karrholm J, Thanner J, Malchau H, Herberts P: Highly cross-linked polyethylene in total hip arthroplasty: Clinical performance in cemented and uncemented sockets. *Clin Orthop* 429:6-16, 2004.
[\[Context Link\]](#)
9. Dorr LD, Wan Z, Longjohn DB, Dubois B, Murken R: Total hip arthroplasty with use of the metasul metal-on-metal articulation. Four- to seven-year results. *J Bone Joint Surg* 82:789-798, 2000.
[\[Context Link\]](#)
10. du Plessis TA, Grobbelaar CJ, Marais F: The improvement of polyethylene prostheses through radiation crosslinking. *Int J Radiat Biol Relat Stud Phys Chem Med* 9:647-652, 1977.
[\[Context Link\]](#)
11. Goldring S, Jasty M, Roelke M, et al: Formation of a synovial-like membrane at the bone-cement interface. Its role in bone resorption and implant loosening after total hip replacement. *Arthritis Rheum* 29:836-842, 1986.
[\[Medline Link\]](#)
12. Goldring S, Schiller A, Roelke M, et al: The synovial-like membrane at the bone-cement interface in loose total hip replacements and its proposed role in bone lysis. *J Bone Joint Surg* 65A:575-584, 1983.
[\[Medline Link\]](#)
13. Grobbelaar CJ, Weger FA, Spirakis A, et al: Clinical experience with gamma irradiation-crosslinked polyethylene - A 14 to 20 year follow-up report. *South African Bone and Joint Surgery* XI:140-147, 1999.
[\[Context Link\]](#)
14. Hamadouche M, Boutinck P, Daussance J, Bolander ME, Sedel L: Alumina-on alumina total hip arthroplasty. *J Bone Joint Surg* 84A:69-77, 2002.
[\[Medline Link\]](#) [\[Context Link\]](#)

15. Hamadouche M, Sedel L: Ceramics in orthopaedics. *J Bone Joint Surg* 82B:1095-1099, 2000.
[\[Context Link\]](#)
16. Harris WH: Osteolysis and particle disease in hip replacement. A review. *Acta Orthop Scand* 65:113-123, 1994.
[\[Medline Link\]](#) [\[Context Link\]](#)
17. Harris WH: The problem is osteolysis. *J Biomed Mater Res* 31:19-26, 1996.
[\[Context Link\]](#)
18. Harris WH, Schiller AL, Scholler JM, Freiberg RA, Scott R: Extensive localized bone resorption in the femur following total hip replacement. *J Bone Joint Surg* 58A:612-618, 1976.
[\[Medline Link\]](#) [\[Context Link\]](#)
19. Hellman EJ, Capello WN, Feinberg JR: Omnifit cementless total hip arthroplasty. A 10-year average followup. *Clin Orthop* 364:164-174, 1999.
[\[Fulltext Link\]](#) [\[CrossRef\]](#) [\[Context Link\]](#)
20. Jazrawi LM, Bogner E, Della Valle CJ, et al: Wear rates of ceramic-on-ceramic bearing surfaces in total hip implants: A 12-year follow-up study. *J Arthroplasty* 14:781-787, 1999.
[\[Medline Link\]](#) [\[CrossRef\]](#) [\[Context Link\]](#)
21. McKee GK, Watson-Farrar J: Replacement of arthritic hips by the McKee- Farrar prosthesis. *J Bone Joint Surg* 48B:245-259, 1966.
[\[Context Link\]](#)
22. McKellop H: Development of an extremely wear-resistant ultra high molecular weight polyethylene for total hip replacements. *J Orthop Res* 17:157-167, 1999.
[\[Medline Link\]](#) [\[CrossRef\]](#) [\[Context Link\]](#)
23. Muratoglu OK, Bragdon CR, O'Connor DO, Jasty M, Harris WH: A novel method of cross-linking ultra-high-molecular-weight polyethylene to improve wear, reduce oxidation, and retain mechanical properties. Recipient of the 1999 HAP Paul Award. *J Arthroplasty* 16:149-160, 2001.
[\[Medline Link\]](#) [\[Context Link\]](#)
24. Oonishi H, Takayama Y: The Low Wear of Cross-linked Polyethylene Socket in Total Hip Prostheses. In *Encyclopedic Handbook of Biomaterials and Bioengineering Part A: Materials*. New York. Marcel Dekker 2:1852-1867, 1995.
[\[Context Link\]](#)
25. Rieker CB, Kottig P, Schon R, Windler M, Wyss UP: Clinical Tribological Performance of 144 Metal-on-metal Hip Articulations. In Ricker W, Wyss U (eds). *Metasul: A Metal-on-Metal Bearing*. Bern, Switzerland: Hans Huber 83-91, 1999.
[\[Context Link\]](#)
26. Schmalzried TP, Kwong LM, Jasty M, et al: The mechanism of loosening of cemented acetabular components in total hip arthroplasty. Analysis of specimens retrieved at autopsy. *Clin Orthop* 274:60-78, 1992.
[\[Medline Link\]](#)
27. Willert HG, Semlitsch M: Tissue reactions to plastic and metallic wear products of joint endoprostheses. In *Total Hip Prosthesis*. New York: Springer-Verlag, Berlin Heidelberg 1976.
[\[Context Link\]](#)
28. Willert HG: Reactions of the articular capsule to wear products of artificial joint prostheses. *J Biomed Mater Res* 11:157-164, 1977.
[\[Context Link\]](#)
29. Wroblewski BM: Low-friction arthroplasty of the hip using alumina ceramic and cross-linked polyethylene. A ten-year follow-up report. *J Bone Joint Surg* 81B:54-55, 1999.
[\[Context Link\]](#)
30. Zicat B, Engh C, Gokcen E: Patterns of osteolysis around total hip components inserted with and without cement. *J Bone Joint Surg* 77A:432-439, 1995.
[\[Medline Link\]](#) [\[Context Link\]](#)