# Cemented versus cementless hip arthroplasty

## A review of prosthetic biocompatibility

Seppo Santavirta[1], Anthony Gristina[2] and Yrjö T. Konttinen[3]

The fibrous interface tissue between hip prostheses and surrounding bone is often morphologically and functionally synovial-like. The fibroblast is the major cell type; but also giant cells and macrophages are present, and their numbers are increased in the occasional adverse-type host reaction to the prosthesis. Adverse lytic reactions are often associated with methylmethacrylate debris, whereas in cementless cases, polyethylene and metallic (titanium) wear debris seem to cause adverse reactions. Osteoblasts, osteoclasts, and mesenchymal collagenase secreted by fibroblasts and macrophages play an important role in the process of prosthetic loosening. Methylmethacrylate is immunologically relatively inert, while it induces inflammatory mononuclear-cell migration. Both cemented and cementless prostheses cause a foreign-body type host response, including adaptive and reactive processes. This response includes the formation of fibroblast-like B-type lining cells, which are able to synthesize and secrete hyaluronate.

Material surfaces of hip arthroplasty components also provide a unique environmental niche to which staphylococcal strains adhere and colonize. Antibiotic resistance is related to the material colonized rather than to the presence of an exopolysaccharide barrier; organisms bound to polyethylene and methylmethacrylate are more resistant than organisms that are bound to stainless steel.

An understanding of prosthetic biocompatibility requires an appreciation of tissue cell, bacterial cell and host defense-system response to biomaterials. The site of implantation is a stage on which the "players" (bacteria, host cells, and organic moieties) interact and compete, and before which the host is a "responsive audience."

[1]Orthopedic Hospital of the Invalid Foundation, Tenholantie 10, SF-00280 Helsinki, Finland; [2]The Musculoskeletal Sciences Research Institute, Herndon, Virginia, U.S.A.; and [3]Hospital for Joint Diseases, Orthopaedic Institute, New York, N.Y., U.S.A.
Tel +358–0 47481. Fax +358–0 418224
Submitted 91-06-10. Accepted 91-10-23

The clinical success of the original low-friction total hip replacement (THR) concept or its related modifications is well established (Charnley 1961, Charnley 1979), but at the same time a substantial number of failures can be attributed to loosening at the THR-bone interface (Linder et al. 1983, Jones and Hungerford 1987). Under cyclic-loading conditions, there is always some degree of foreign-body reaction to the THR prosthesis (Draenert 1981, Goldring et al. 1983, Linder and Hansson 1983, Maguire et al. 1987, Bos et al. 1990, Pazzaglia 1990, Santavirta et al. 1990a). There is increasing concern as regards the biocompatibility of the THR cemented with methylmethacrylate, and the use of cementless prostheses has become common in the hope of avoiding adverse tissue reactions that have been thought to be caused by methylmethacrylate cement and its wear debris.

## Implant reactions

Long-term clinical results of cemented THRs, with high-density polyethylene for the socket, have highlighted the increasing frequency of component loosening. The adverse effects of mechanical loosening have been emphasized, and for many years it was thought that the polyethylene and methylmethacrylate wear debris would be benign in nature (Wroblewski 1979, 1987, Editorial, Lancet 1990).

Charnley et al. (1968) observed bone lysis around the cemented THR stem and hypothesized that it was due to a chronic nonsuppurative infection, whereas recent research has shown that lytic reactions are occasionally seen around seemingly well-fixed THR prostheses and in the definite absence of an infection (Tallroth et al. 1988, Antti-Poika et al. 1990). Ultimately, neither clinical nor radiographic studies are completely accurate in determining the adequacy of fixation of the prosthesis. A great deal of controversy remains regarding the long-term changes that occur around the cemented prosthesis and what causes it to become loose (Jasty et al. 1990).

Tumor-like bone resorption after a THR has been reported (Harris et al. 1976, Schulitz and Dustman 1976). A number of femoral components loosen in association with lysis of the proximal femur (Carlsson et al. 1983). Tallroth et al. (1988) were the first to report a follow-up study on noninfectious bone lysis around stems of cemented THR prostheses as a reflection of an adverse tissue reaction to the prosthesis-cement complex. This aggressive granulomatous reaction was also found in cases where the prosthesis was thought to be well fixed at revision by both the surgeon and the radiologist. The rapidity of growth of granulomas varies and is unpredictable; some double their size in a few months, whereas others grow slowly; however, the average doubling time is about 2 years. Quite recently, other workers have confirmed these findings (Huddleston 1988, Anthony et al. 1990, Maloney et al. 1990b). Clearly, implant motion is not the only cause of adverse tissue reactions around the cemented THR prosthesis, which appear in about 5 percent of the revision cases (Eskola et al. 1990, Wilson 1990). Implant micromotion may, however, also cause granulomatous lesions (Editorial Lancet 1990).

Most reports have described adverse tissue reactions in patients with cemented prostheses. Lord et al. (1988) reported cystic bone resorption in the femoral metaphysis that they thought was due to debris from polyethylene wear, and proposed that this might be a long-term problem in cementless THRs. Santavirta et al. (1990b) reported a series of patients with aggressive granulomatous lesions in cementless total hip arthroplasty, and attributed this tissue reaction mainly to plastic debris from the acetabular socket.

## Cellular biology and immunopathology

It appears that a fibrous scar tissue forms between the methylmethacrylate cement and the bone in a THR (Mears 1979, Freeman et al. 1982, Linder and Hansson 1983, Pazzaglia 1990). This interface scar tissue has been shown to be morphologically synovial-like (Goldring et al. 1983). Currently, there is no information on the distribution of interface tissue thickness or character in the different cement-bone interface zones. Charnley (1975) showed a thin layer of connective tissue in the nonload-bearing zones, which included macrophages and giant cells; and he postulated that this indicated a sound mechanical fixation of the prosthesis. Recently, Jasty et al. (1990) reported little or no fibrous tissue at the cement-bone interface and no adverse biological responses to the cement in clinically successful cases, even as late as 18 years after implantation. Apparently, the quantity and chemical quality of the host response varies according to the cementation techniques and prosthetic materials that are used. Although macrophages are not able to resorb the bone directly, osteoclasts are activated by the intense macrophage reaction, and bone undergoes progressive resorption and fibrous substitution (Pazzaglia et al. 1986, Pazzaglia and Pringle 1988, Vaes 1988). The major cell type in the interface tissue is the fibroblast. The extensive lysosomal development within macrophages suggests their potential to generate large quantities of hydrolytic enzymes. Acid-phosphatase-rich macrophages have been identified in bone recesses in the bone-cement interface tissue; Pazzaglia et al. (1986) interpreted this to indicate that macrophage reaction may precede the mechanical instability and may be the primary cause of loosening. Macrophages are stimulated by the polyethylene and methylmethacrylate wear particles (Willert et al. 1974, Pazzaglia et al. 1985). In the cytoplasm of the macrophages in cemented THRs, small particles, identified as methylmethacrylate, polyethylene, or Zirkonium-oxyd, which is the contrast medium in most methylmethacrylate cements, are commonly found (Maguire et al. 1987, Howie et al. 1988, Bos et al. 1990). In cementless titanium-based THRs, macrophages and multinucleated giant cells frequently contain titanium and polyethylene particles (Santavirta et al. 1990b, 1991b).

Immunohistopathologic analysis has shown that most of the cells in aggressive granulomatous-type host response to cemented THRs are multinucleated giant cells and C3bi-receptor and nonspecific esterase-positive monocyte-macrophages (Figure 1; Santavirta et al. 1990a). This finding suggests a foreign-body-type reaction, compatible with the rapidly progressive lytic nature of aggressive granulomatosis. There was a clear-cut difference between aggressive granulomatosis and the more common lesion accompanying prosthetic loosening: namely, the relative lack of activated fibroblasts in granulomatosis (Santavirta et al. 1990a). The aggressive form of adverse tissue reaction to the prosthesis-cement complex involves an uncoupling of the normal sequence of monocyte-macrophage-mediated clearance of foreign material and tissue debris that is normally followed by fibroblast-mediated synthesis and remodeling of the extracellular matrix (Konttinen et al. 1988).

In response to foreign or necrotic material, monocyte-macrophages clear the involved area of exogenous and endogenous substances. This is followed by invasion of the site by fibroblasts and by synthesis of extracellular matrix by activated fibroblasts (Figure 2). Our work in progress, where we analyzed the proliferative fibroblast response to the loosening of THRs using the cytofluorographic cell cycle analysis, showed that the local proliferative fibroblast response

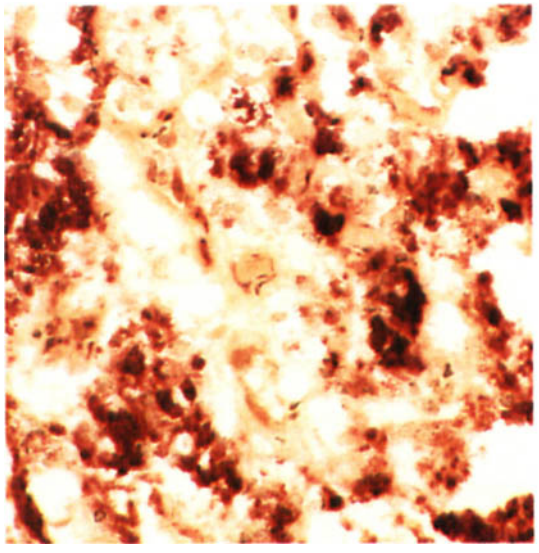

Figure 1. Numerous monocyte-macrophages (stained dark brown) in adverse interface tissue reaction against cemented THR. Grayish grains of methylmethacrylate debris (arrows) are scattered throughout the field. Besides their capacity to phagocytose, monocyte-macrophages secrete neutral proteinases, such as, collagenase. Histochemical esterase staining. ×350.

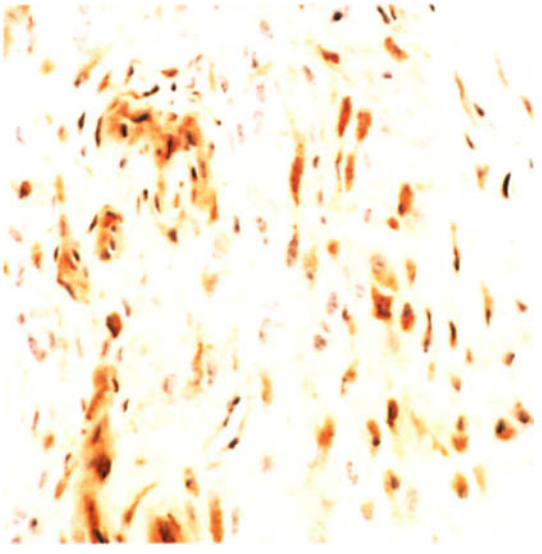

Figure 2. The fibroblast (stained dark brown) is the major cell type in the prosthesis-to-bone interface tissue. These fibroblasts often contain carboxy terminal propeptide of interstitial type-I collagen. Monoclonal pC antibody in avidin-biotin-peroxidase complex, with hematoxylin counterstain. ×350.

in general is monotonous and does not seem to depend on the type of loosening, the type of prosthesis, or the use of methylmethacrylate (Santavirta et al. 1991d). The role of osteoblasts in this process appears to be that they expose the mineral to osteoclasts and release a soluble factor that activates osteoclasts (Vaes 1988). The so-called pseudosynovium around the prosthesis-cement complex is known to contain PG-E2, collagenase, and phosphatase (Maguire et al. 1987).

Fibroblast-type mesenchymal collagenase secreted by fibroblasts and macrophages is found in the pseudosynovial tissue in THRs and is associated with prosthesis loosening in both cemented and cementless THRs (Santavirta et al. 1991c, Sorsa et al. 1991).

Tetracycline is a known inhibitor of collagenase; tetracycline prosthetic coating could prevent some part of the adverse reaction to the prosthesis. Spector et al. (1991) have investigated the effects of an anti-inflammatory agent and found decreased $PGE_2$ and IL-1 levels in the periprosthetic tissue.

Adverse tissue reactions to uncemented THRs are immunopathologically similar to the ones observed in cemented cases. Polyethylene wear debris and a reaction to titanium probably initiate the host reaction (Boss et al. 1990, Nasser et al. 1990, Maloney et al. 1990a, Santavirta et al. 1991b). Lennox et al. (1987) found considerably fewer macrophages around a press-fit cementless prosthesis than around a cemented one. Evans et al. (1974) proposed metal sensitivity as a cause of bone necrosis and loosening of the prosthesis. Titanium, which is relatively inert (Linder et al. 1988), releases wear particles under cyclic-loading conditions, and thus may cause an accelerated foreign-body reaction (Agins et al. 1988). Lalor et al. (1991) have proposed that sensitivity to titanium may cause an implant failure; monoclonal antibody labeling of periprosthetic tissues of failed total hip components showed abundant macrophages and T lymphocytes, in the absence of B lymphocytes, suggesting sensitization to titanium. Another interesting finding was the complete absence from the periprosthetic tissues of aluminum and vanadium, both present in the titanium alloy, which was possibly due to different solubilities of the metals. Aluminum is more soluble than titanium, and may be transported away from the implant site.

Hydroxyapatite has proven very promising as an orthopedic implant material; hydroxyapatite-coated prosthetic components may improve the incorporation into bone without causing an adverse reaction. Geesink (1991) has shown that radiographically there appears to be bone ingrowth into hydroxyapatite-coated titanium prostheses; preliminary clinical results are promising. However, our work in progress has shown that under clinical cyclic loading conditions there does not seem to be chemical fixation or bony ingrowth into hydroxyapatite-coated acetabular

components, and immunohistologic analysis of the interface tissue of a well-fixed acetabular component revealed the presence of macrophages and monocytes. However, in human lymphocyte cultures, we have found hydroxyapatite to be immunologically inert (Santavirta et al. 1991e).

## Methylmethacrylate

Jones and Hungerford (1987) reviewed the tissue response to methylmethacrylate and found frequent adverse reactions, which they called cement disease. Transient initial necrosis of bone and bone marrow caused by insertion of a cemented THR prosthesis includes mechanical injury, chemical trauma (resulting from leaching of monomer and additives), and thermal trauma from polymerization of the cement (Linder et al. 1983). Linder (1976) pointed out the acute toxicity of the methylmethacrylate monomer.

The immunologic response to methylmethacrylate cement in THRs has been debated. Most studies have been based on indirect evidence (Linder and Carlsson 1986).

Santavirta et al. (1991a) studied methylmethacrylate in human lymphocyte cultures using activation markers. The results suggested that methylmethacrylate is essentially immunologically inert, while it induces inflammatory mononuclear cell migration and adhesions leading to a nonspecific lymphocyte reaction. Herman et al. (1989) suggested that methylmethacrylate induces the release of bone-resorbing factors. Current research is making an effort to improve the qualities of methylmethacrylate, and growth hormone loaded cement is one of the interesting possibilities (Downes et al. 1990).

## Studies of joint fluid

The THR prosthesis is a foreign body, and the host response, including adaptive and reactive processes, is reflected at the tissue level. In successful THRs, where the prosthesis remains well fixed over a period of several years, the host response is of a benign nature, and signs of immune-inflammatory reaction remain modest. In loosened THRs, there is an influx of various immunocompetent cells in such a proportion that the CD8 subset is outnumbered by the CD4 subset by approximately one to two (Santavirta et al. 1989, 1992). This suggests that peripheral blood T lymphocytes migrate to and accumulate in the arthroplasty joint cavity. This accumulation seems to be unselective in the sense that it happens in proportions reflecting the T-cell subset composition found in normal peripheral blood. This reaction is similar in both cemented and cementless prostheses. Mangione et al. (1990) concluded that joint fluids in loose, totally replaced hips were inflammatory exudates.

When the composition of the THR joint-cavity fluid was compared in primary arthrosis with that obtained at revision operations for loosening, it was found that protein concentrations differed only slightly, which suggests similar transcapillary flow (Saari et al. 1991). The hyaluronate concentration was low in the THR pseudojoint fluid as compared with primary arthrosis, whereas the composition of the molecular-weight profile was similar. This suggests that THRs cause an adaptive tissue response and formation of fibroblast-like B-type lining cells, which are able to synthesize and secrete hyaluronate, associated with the so-called marginal lubrication.

## The interface and host defense

Tissues traumatized by the insertion of foreign materials and the abnormal fibrous interfaces described in this review are domains without competent natural tissue cell layers and basement membranes. The presence of a foreign material alters host defenses and produces a surface for bacterial colonization (Gristina et al. 1985, 1987b). Antibacterial incompetence is caused by macrophage exhaustion secondary to oxidative preemption by adsorbed particles of methylmethacrylate, high-density polyethylene, and metallic debris (Gristina et al. 1976, 1987a, 1989). Foreign-body implant surfaces are susceptible to and are readily colonized by bacteria if random exposure or contact occurs (Gristina et al. 1987b, Naylor et al. 1990). The process of colonization is driven by the natural tendency of bacteria to adhere to inanimate surfaces and to damaged tissues in nature. In healthy tissues, transient bacterial colonization is usually eliminated by the normal host defense mechanism unless (1) the inoculum size exceeds threshold levels (threshold levels are lowered by foreign bodies), (2) the host defense is impaired (host defense is impaired by foreign bodies), and (3) tissues are traumatized (cell surfaces are damaged and membranes are disrupted by mechanical forces).

An understanding of the pathogenesis of infection also includes an appreciation of tissue cell and defense-mechanism response to implanted materials (Gristina et al. 1985, 1987a). Such materials cause local and systemic perturbations in host defenses. The first step in infection of biomaterials and damaged tissues is bacterial adhesion to those receptive surfaces.

## Integration

Tissue integration, if it truly exists to some degree, is the adhesion (chemical bonding) of tissue cells to foreign materials. Integration to foreign materials, has, however, not been programmed in tissue cells by natural evolution. Tissue integration and bacterial adhesion are biochemically parallel, may be competitive, and and mutually exclusive. Surfaces homeostatically colonized by healthy tissue cells tend to be resistant to infection by virtue of competent basement membranes and eukaryotic extracellular polysaccharides (Gristina et al. 1987b).

The fate of an implanted material is a virtual race for the surface between bacteria, tissue cells, and matrix molecules (Gristina et al. 1987a). Adhesive-integrative processes for bacteria or tissue cells, respectively, are based on similar mechanisms and are competitive.

## Infection

Bacteria in natural environments usually colonize surfaces rather than remain in floating or planktonic form. Surgery may allow microorganisms to colonize a material almost instantaneously, ultimately resulting in infection and preventing tissue integration. Tissue cell integration, however, is an exquisite process requiring optimal conditions. Bacteria have readily adapted to rapidly colonize all inanimate substrate. The colonization potential of synthetic materials is high (Costerton et al. 1987, Gristina et al. 1987b, Naylor et al. 1990). Healthy cells may satisfy binding sites on foreign materials and form a layer somewhat resistant to bacterial colonization by virtue of extracellular exopolysaccharides and basement membranes of tissue cells, as well as presenting a cell surface environment for the normal host defense response.

The ability of antibiotics to kill coagulase-negative staphylococci is clinically important, as studies have shown that staphylococci are major colonizers of surgical biomaterials, including heart valves, intravascular catheters, and orthopedic implants (Dankert et al. 1986, Gristina et al 1987a). Prosthetic infections are generally resistant to antibiotic therapy and always require removal of the implant before true eradication of the infection is possible.

Both coagulase-positive and coagulase-negative staphylococci have been reported as causes of biomaterial-centered infections, with a tendency of coagulase-negative bacteria to be associated with polymer-sited infections (Naylor et al. 1990). In vitro studies have indicated preferential colonization of polymer surfaces by coagulase-negative staphylococci and of metal surfaces by coagulase-positive staphylococci, although both metal and polymer surfaces are readily colonized by both types. Recent studies indicate that resistance to antibiotics is increased for both coagulase-positive and coagulase-negative species adherent to biomaterial surfaces (Gristina et al. 1989, Naylor et al. 1990).

## Antibiotic resistance

Mechanisms of antibiotic resistance have not been well characterized. A biofilm barrier effect has been proposed. Organisms grown in suspension are susceptible to lower concentrations of antibiotics than when they are surface-adherent, biofilm-enclosed (Gristina et al. 1987b, Gristina et al. 1989).

The MBCs (Minimum Bacteriocidal Concentration) of nafcillin, vancomycin, gentamicin, and daptomycin (LY146032) were determined for three clinical isolates of coagulase-negative staphylococci grown in suspension and adherent to THR biomaterials. Strains studied were the slime-producing strain *Staphylococcus epidermidis* RP-12 (ATCC 35983), *S. hyicus* Se-360, and the non-slime-producing strain *S. hominis* SP-2 (ATCC). All three strains were allowed to colonize surgical-grade disks of stainless steel, polymethylmethacrylate, and ultra-high-molecular-weight polyethylene for 24 hours, and the disks were then exposed to various concentrations of antibiotics for 24 hours. Surviving adherent bacteria were quantitated (Gristina et al. 1989). Antibiotic resistance was unrelated to the presence of bacterial exopolysaccharides or a biofilm (Gristina et al. 1989). The resistance of biomaterial-adherent strains RP-12 (slime-producing) and SP-2 (non-slime-producing) was much greater than for these strains when tested in suspension cultures.

Biomaterial specificity of effect on resistance was indicated by strain SP-2 susceptibility to nafcillin when adherent to polyethylene and by resistance to nafcillin when adherent to stainless steel or polymethylmethacrylate. All the organisms examined were most resistant when adherent to polymethylmethacrylate (Gristina et al. 1989, Naylor et al. 1990).

The data on bacterial binding to biomaterials revealed several other interesting findings: (1) exopolysaccharide-producing organisms attached more bacteria per unit surface area than the non-slime-producing organisms did, suggesting a role for slime in quantitative bacterial adherence; and (2) there was greater binding to polymethylmethacrylate per unit than to stainless steel or polyethylene, indicating a possible biomaterial specificity for quantitative bacterial adherence to that biomaterial.

Our studies and those of Nichols et al. (1988, 1989), suggest that the surface colonization and the antibiotic resistance are species-related and substratum- (biomaterial) directed and, to a degree, may be altered by substrate-induced phenotypic changes rather than by a barrier effect of exopolysaccharides.

## Acknowledgements

The authors wish to thank the Sigrid Juselius Foundation, the Finnish Academy, and the Paulo Foundation for financial support.

## References

Agins H J, Alcock N W, Bansal M, Salvati E A, Wilson P D Jr, Pellicci P M, Bullough P G. Metallic wear in failed titanium-alloy total hip replacements. A histological and quantitative analysis. *J Bone Joint Surg* (Am) 1988; 70 (3): 347–56.

Anthony P P, Gie G A, Howie C R, Ling R S. Localised endosteal bone lysis in relation to the femoral components of cemented total hip arthroplasties. *J Bone Joint Surg* (Br) 1990; 72 (6): 971–9.

Antti-Poika I, Josefsson G, Konttinen Y, Lidgren L, Santavirta S, Sanzen L. Hip arthroplasty infection. Current concepts. *Acta Orthop Scand* 1990; 61 (2): 163–9.

Bos I, Lindner B, Seydel U, Johannisson R, Dörre E, Henssge J, Löhrs U. Untersuchungen über die Lockerungsursache bei zementierten Hüftgelenkendoprothesen. Licht und elektronenmikroskopische Untersuchung und Laser Mikrosonden Massenanalyse. *Z Orthop* 1990; 128 (1): 73–82.

Boss J H, Shajrawi I, Soudry M, Mendes D G. Histological features of the interface membrane of failed isoelastic cementless prostheses. *Int Orthop* 1990; 14 (4): 399–403.

Carlsson A S, Gentz C F, Linder L. Localized bone resorption in the femur in mechanical failure of cemented total hip arthroplasties. *Acta Orthop Scand* 1983; 54 (3): 396–402.

Charnley J. Arthroplasty of the hip: A new operation. *Lancet* 1961; 1: 1129–32.

Charnley J, Follacci F M, Hammond B T. The long-term reaction of bone to self curing acrylic cement. *J Bone Joint Surg* (Br) 1968; 50 (4): 822–9.

Charnley J. The reaction of bone to self-curing acrylic cement. A long term histological study in man. *J Bone Joint Surg* (Br) 1970; 52 (2): 340–53.

Charnley J. Proceedings: The histology of loosening between acrylic cement and bone. *J Bone Joint Surg* (Br) 1975; 57 (2): 245.

Charnley J. *Low friction arthroplasty of the hip. Theory and practice*. Springer Verlag, Berlin 1979: 25–40.

Costerton J W, Cheng K J, Geesey G G, Ladd T I, Nickel J C, Dasgupta M, Marrie T J. Bacterial biofilms in nature and disease. *Annu Rev Microbiol* 1987; 41: 435–64.

Dankert J, Hogt A H, Feigen J. Biomedical polymers: Bacterial adhesion, colonization and infection. *Crit Rev Biocompat* 1986; 2: 219–301.

Downes S, Wood D J, Malcolm A J, Ali S Y. Growth hormone in polymethylmethacrylate cement. *Clin Orthop* 1990; 252: 294–8.

Draenert K. The John Charnley Award Paper. Histomorphology of the bone to cement interface: remodeling of the cortex and revascularization of the medullary canal in animal experiments. *Hip* 1981: 71–110.

Eskola A, Santavirta S, Konttinen Y T, Hoikka V, Tallroth K, Lindholm T S. Cementless revision of aggressive granulomatous lesions in hip replacements. *J Bone Joint Surg* (Br) 1990; 72 (2): 212–6.

Evans E M. Metal sensitivity as a cause of bone necrosis and loosening of the prosthesis in total joint replacement. *J Bone Joint Surg* (Br) 1974; 56 B (4): 626–42.

Freeman M A, Bradley G W, Revell P A. Observations upon the interface between bone and polymethylmethacrylate cement. *J Bone Joint Surg* (Br) 1982; 64 (4): 489–93.

Geesink R G. Hydroxyapatite-coated total hip prostheses. Two-year clinical and roentgenographic results of 100 cases. *Clin Orthop* 1990; 261: 39–58.

Goldring S R, Schiller A L, Roelke M, Rourke C M, O Neil D A, Harris W H. 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* (Am) 1983; 65 (5): 575–84.

Granulomatous reaction in total hip arthroplasty (editorial) (see comments). *Lancet* 1990; 335 (8683): 203–4.

Gristina A G, Rovere G D, Shoji H, Nicastro J F. An in vitro study of bacterial response to inert and reactive metals and to methyl methacrylate. *J Biomed Mater Res* 1976; 10 (2): 273–81.

Gristina A G, Oga M, Webb L X, Hobgood C D. Adherent bacterial colonization in the pathogenesis of osteomyelitis. *Science* 1985; 228 (4702): 990–3.

Gristina A G. Biomaterial-centered infection microbial ashesion versus tissue integration. *Science* 1987a; 237 (4822): 1588–95.

Gristina A G, Hobgood C D, Webb L X, Myrvik Q N. Adhesive colonization of biomaterials and antibiotic resistance. *Biomaterials* 1987b; 8 (6): 423–6.

Gristina A G, Jennings R A, Naylor P T, Myrvik Q N, Webb L X. Comparative in vitro antibiotic resistance of surface colonizing coagulase negative staphylococci. *Antimicrob Agents Chemother* 1989; 33 (6): 813–6.

Harris W H, Schiller A L, Scholler J M, Freiberg R A, Scott R. Extensive localized bone resorption in the femur following total hip replacement. *J Bone Joint Surg* (Am) 1976; 58 (5): 612–8.

Herman J H, Sowder W G, Anderson D, Appel A M, Hopson C N. Polymethylmethacrylate-induced release of bone resorbing factors. *J Bone Joint Surg* (Am) 1989; 71 (10): 1530–41.

Howie D W, Vernon-Roberts B, Oakeshott R, Manthey B. A rat model of resorption of bone at the cement-bone interface in the presence of polyethylene wear particles. *J Bone Joint Surg* (Am) 1988; 70 (2): 257–63.

Huddleston H D. Femoral lysis after cemented hip arthroplasty. *J Arthroplasty* 1988; 3 (4): 285–97.

Jasty M, Maloney W J, Bragdon C R, Haire T, Harris W H. Histomorphological studies of the long-term skeletal responses to well fixed cemented femoral components. *J Bone Joint Surg* (Am) 1990; 72 (8): 1220–9.

Jones L C, Hungerford D S. Cement disease. *Clin Orthop* 1987; 225: 192–206.

Konttinen Y T, Saari H, Santavirta S, Antti Poika I, Sorsa T, Nykänen P, Kemppinen P. Synovial fibroblasts. *Scand J Rheumatol* (Suppl 76) 1988: 95–103.

Lalor P A, Revell P A, Gray A B, Wright S, Railton G T, Freeman M A. Sensitivity to titanium. A cause of implant failure? *J Bone Joint Surg* (Br) 1991; 73 (1): 25–8.

Lennox D W, Schofield B H, McDonald D F, Riley L H Jr. A histologic comparison of aseptic loosening of cemented, press fit, and biologic ingrowth prostheses. *Clin Orthop* 1987; 225: 171–91.

Linder L. Tissue reaction to methyl methacrylate monomer. A comparative study in the rabbit's ear on the toxicity of methyl methacrylate monomer of varying composition. *Acta Orthop Scand* 1976; 47 (1): 3–10.

Linder L, Hansson H A. Ultrastructural aspects of the interface between bone and cement in man. Report of three cases. *J Bone Joint Surg* (Br) 1983; 65 (5): 646–9.

Linder L, Lindberg L, Carlsson A. Aseptic loosening of hip prostheses. A histologic and enzyme histochemical study. *Clin Orthop* 1983; 175: 93–104.

Linder L, Carlsson A S. The bone cement interface in hip arthroplasty. A histologic and enzyme study of stable components. *Acta Orthop Scand* 1986; 57 (6): 495–500.

Linder L, Carlsson A, Marsal L, Bjursten L M, Branemark P I. Clinical aspects of osseointegration in joint replacement. A histological study of titanium implants. *J Bone Joint Surg* (Br) 1988; 70 (4): 550–5.

Lord G, Marotte J H, Blanchard J P. Cementless madreporic and polarised total hip prostheses: a ten-year review of 2688 cases. *French J Orthop Surg* 1988; 2 (1): 82–92.

Maguire J K Jr, Coscia M F, Lynch M H. Foreign body reaction to polymeric debris following total hip arthroplasty. *Clin Orthop* 1987; 216: 213–23.

Maloney W J, Jasty M, Harris W H, Galante J O, Callaghan J J. Endosteal erosion in association with stable uncemented femoral components. *J Bone Joint Surg* (Am) 1990a; 72 (7): 1025–34.

Maloney W J, Jasty M, Rosenberg A, Harris W H. Bone lysis in well-fixed cemented femoral components. *J Bone Joint Surg* (Br) 1990b; 72 (6): 966–70.

Mangione P, Chauveaux D, Baquey C, Honton J L. Caracterisation chimique, biochimique, et dosage des metaux du liquide "periprothetique". *Int Orthop* 1990; 14 (4): 393–7.

Mears D C. The biological response to implanted materials. In: *Materials and orthopaedic surgery* (Ed. Mears D C) Williams & Wilkins, Baltimore 1979: 235.

Nasser S, Campbell P A, Kilgus D, Kossovsky N, Amstutz H C. Cementless total joint arthroplasty prostheses with titanium-alloy articular surfaces. A human retrieval analysis. *Clin Orthop* 1990; 261: 171–85.

Naylor P T, Myrvik Q N, Gristina A. Antibiotic resistance of biomaterial-adherent coagulase-negative and coagulase-positive staphylococci. *Clin Orthop* 1990; 261: 126–33.

Nichols W W, Dorrington S M, Slack M P, Walmsley H L. Inhibition of tobramycin diffusion by binding to alginate. *Antimicrob Agents Chemother* 1988; 32 (4): 518–23.

Nichols W W, Evans M J, Slack M P, Walmsley H L. The penetration of antibiotics into aggregates of mucoid and non-mucoid *Pseudomonas aeruginosa*. *J Gen Microbiol* 1989; 135: 1291–303.

Pazzaglia U E, Ceciliani L, Wilkinson M J, Dell Orbo C. Involvement of metal particles in loosening of metal-plastic total hip prostheses. *Arch Orthop Trauma Surg* 1985; 104 (3): 164–74.

Pazzaglia U E, Minoia C, Gualtieri G, Gualtieri I, Riccardi C, Ceciliani L. Metal ions in body fluids after arthroplasty. *Acta Orthop Scand* 1986; 57 (5): 415–8.

Pazzaglia U E, Pringle J A. The role of macrophages and giant cells in loosening of joint replacement. *Arch Orthop Trauma Surg* 1988; 107 (1): 20–6.

Pazzaglia U E. Pathology of the bone-cement interface in loosening of total hip replacement. *Arch Orthop Trauma Surg* 1990; 109 (2): 83–8.

Saari H, Santavirta S, Nordström D, Paavolainen P, Konttinen Y T. Hyaluronate in the totally replaced hip. *Finn J Orthop Traumatol* 1991; 14: 276–8.

Santavirta S, Konttinen Y T, Nordström D, Bergroth V, Antti Poika I, Eskola A. Immune inflammatory response in infected arthroplasties. *Acta Orthop Scand* 1989; 60 (1): 116–8.

Santavirta S, Konttinen Y T, Bergroth V, Eskola A, Tallroth K, Lindholm T S. Aggressive granulomatous lesions associated with hip arthroplasty. Immunopathological studies. *J Bone Joint Surg* (Am) 1990a; 72 (2): 252–8.

Santavirta S, Hoikka V, Eskola A, Konttinen Y T, Paavilainen T, Tallroth K. Aggressive granulomatous lesions in cementless total hip arthroplasty. *J Bone Joint Surg* (Br) 1990b; 72 (6): 980–4.

Santavirta S, Konttinen Y T, Bergroth V, Grönblad M. Lack of immune response to methyl methacrylate in lymphocyte cultures. *Acta Orthop Scand* 1991a; 62 (1): 29–32.

Santavirta S, Konttinen Y T, Hoikka V, Eskola A. Immunopathological response to loose cementless acetabular components. *J Bone Joint Surg* (Br) 1991b; 73 (1): 38–42.

Santavirta S, Sorsa T, Konttinen Y T, Saari H, Eskola A, Eisen A Z. Mesenchymal collagenase in the loosening of THR. *Acta Orthop Scand* (Suppl 243) 1991c; 62: 34–5.

Santavirta S, Pajamäki J, Konttinen Y T, Eskola A, Lindholm T S. Proliferative cell response to the loosening of THR. A cytofluorographic cell cycle analysis. *Arch Orthop Trauma Surg* 1991d; 111: 43–6.

Santavirta S, Nordström D, Ylinen P, Konttinen Y T, Silvernoinen T, Rokkanen P. Biocompatibility of hydroxyapatite coated hip prosthesis. *Arch Orthop Trauma Surg* 1991e; 110: 288–92.

Santavirta S, Nordström D, Saari H, Paavolainen P, Konttinen Y T. Immune inflammatory response in the loosening of totally replaced hip. *J Orthop Rheumatol* 1992 (In press).

Schulitz K P, Dustmann H O. Komplikationen der Totalendoprothese. *Arch Orthop Unfallchir* 1976; 85 (1): 33–50.

Sorsa T, Konttinen Y T, Lindy O, Saari H, Suomalainen K, Eklund K, Santavirta S. Collagenase type-specific activation pathways: relevance in rheumatoid arthritis. *Sem Arthritis Rheumat* 1991, In press.

Spector M, Shortkroff S, Hsu H P, Lane N, Sledge C B, Thornhill T S. Tissue changes around loose prostheses. A canine model to investigate the effects of an antiinflammatory agent. *Clin Orthop* 1990; 261: 140–52.

Tallroth K, Eskola A, Santavirta S, Konttinen Y T, Lindholm T S. Aggressive granulomatous lesions after hip arthroplasty. *J Bone Joint Surg* (Br) 1989; 71 (4): 571–5.

Vaes G. Cellular biology and biochemical mechanism of bone resorption. A review of recent developments on the formation, activation, and mode of action of osteoclasts. *Clin Orthop* 1988; 231: 239–71.

Willert H G, Ludwig J, Semlitsch M. Reaction of bone to methacrylate after hip arthroplasty: a long-term gross, light microscopic, and scanning electron microscopic study. *J Bone Joint Surg* (Am) 1974; 56 (7): 1368–82.

Wilson W J. Complications of hip arthroplasty. *Curr Opinion Orthop* 1990; 1: 44–54.

Wroblewski B M. Wear of high-density polyethylene on bone and cartilage. *J Bone Joint Surg* (Br) 1979; 61 (4): 498–500.

Wroblewski B M, Lynch M, Atkinson J R, Dowson D, Isaac G H. External wear of the polyethylene socket in cemented total hip arthroplasty. *J Bone Joint Surg* (Br) 1987; 69 (1): 61–3.