A controlled experimental model of revision implants

Part I. Development

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ABSTRACT – We investigated the roles of particulate matter with unstable implant, in engendering the aggressive tissue response associated with implant loosening in humans. This study serves as a basis for establishing a controlled animal model to reproduce the conditions present after implant loosening. The model includes a 6 mm polymethylmethacrylate (PMMA) cylinder concentrically pistoning 500 μm under load in a 0.75-mm circumferential gap, inserted into canine medial femoral condyles for 8 weeks. We evaluated two size concentrations of polyethylene: type A particulate polyethylene (0.5–12 μm), and type B particulate polyethylene (0.5–50 μm; 85% < 12 μm). The following three treatment groups were investigated in 28 unstable implants in 14 dogs: (1) without polyethylene (control), (2) with type A polyethylene, and (3) with type B polyethylene. We found an aggressive periprosthetic membrane, similar to that seen at revision in humans, only in the unstable implant with polyethylene. The features of this membrane included macrophages with intracellular polyethylene, a dense fibrous membrane with a synovial-like lining layer, and a sclerotic neocortex. The size distribution of the polyethylene did not alter the tissue response. An unstable implant without polyethylene resulted in a benign, quiescent membrane with loose fibrous connective tissue. The model creates a revision cavity analogous to that seen in revision joint arthroplasty, and merits further studies of revision joint replacement.

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To study methods of improving outcomes of revision joint replacement, our aim was to develop a controlled experimental model of the revision joint replacement setting, where the model engenders a tissue response like that seen at revision surgery in humans. The tissue response we wished to replicate consists of a dense fibrous membrane with a synovial-like lining adjacent to the implant, the presence of macrophages with intracellular polyethylene, and a sclerotic bony shell (Goldring et al. 1983, 1986, Bos et al. 1990, Thornhill et al. 1990, Galante et al. 1991, Clarke et al. 1992, Friedman et al. 1993). To generate this response, we used our implant model that is known to develop a fibrous membrane when its interface is subjected to controlled displacement relative to the bone (Søballe 1993). We used this model to study the following hypothesis: an instability-induced fibrous membrane that develops in the presence of particulate polyethylene produces histological characteristics in the bone and membrane representative of the interface in aseptically-loosened human implants. Unstable implants without particulate polyethylene served as controls.

Methods

Implant description

This loaded implant is a controlled motion device that has been previously described in detail and used in numerous studies (Figure 1) (Søballe 1993). The device consists of a 6 mm diameter test implant which pistons 500 ± 15 microns in a 7.5 mm overdrilled hole in the medial femoral condyle of a dog. In this study, the implant is a molded polymethylmethacrylate (PMMA) bone cement sleeve (the

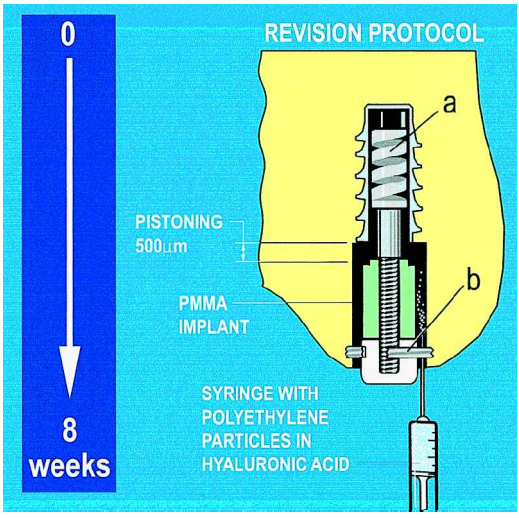


Figure 1. Loaded implant for applying a controlled axial motion of 500 microns to a 6.0 mm diameter cylinder PMMA implant pistoning in a 0.75 mm circumferential bony gap in the canine knee during flexion and weight bearing: a: spring which ensures relative motion between implant and bone; b: centralizing guide to constrain motion in an axial direction.

PMMA is not pressurized or otherwise attached to the bone). It is threaded onto a post attached to a spring (the spring generates 10 Newtons of resistive force at 500 microns displacement). The polyethylene cap on the distal end protrudes slightly above the articular cartilage, to provide the input force during knee loading. The magnitude of implant motion during activity is controlled by a precisely machined restricting shoulder, and the axial direction of motion is controlled by a centralizing ring serving as a bearing.

Particulate polyethylene

We added particulate material to the pistoning implant interface, to mimic conditions associated with aseptic loosening. We used particulate polyethylene (PE) in our model because polyethylene particles are the most ubiquitous particles (being present in 75% of human membranes analyzed (Eftekhar et al. 1985)), and have been implicated most frequently in aseptic loosening. We studied two heterogeneous size distributions of PE particles (types A and B) to determine the sensitivity of the tissue response in this model to particle size distribution. The particle-size distributions, while of a slightly larger size (and different material composition and shape) than that reported in human retrievals, were intended to resemble typical sizes that could be found in human retrievals (Lee et al. 1992, Shanbhag et al. 1994, Kobayashi et al. 1997). Since our aim with this study was not to perform an exhaustive characterization of the tissue that forms in response to various size ranges of PE, we did not include additional treatment groups.

Treatment groups for unstable loaded PMMA implants (28 implants in 14 dogs)

Type of PE	PE particle size range	Number of implants
None	–	4 with hyaluronic acid
None	–	8 without hyaluronic acid
A	0.5–12 μm	8
B	0.5–50 μm	8

To assess the sensitivity of the model to the particular size mix of polyethylene particles, we investigated two size-distributions delivered in hyaluronic acid in 16 unstable implants, and compared to control groups of 8 implants having neither hyaluronic acid nor polyethylene, and 4 unstable implants having the hyaluronic acid, without particulate polyethylene (Table). Note that the group of implants with hyaluronic acid was smaller (4 implants) in order to conserve animal resources while determining if there was a substantial effect due to the hyaluronic acid carrier used for the groups with particles.

Type A was high-density polyethylene (Brooks et al. 2000), with a mean diameter of 4.7 (0.5–12) μm, which was oval/spherical, as documented by a laser scatter method and a filtered scanning electron microscope method (Danish Technological Institute, Centre for Surface Analysis, Copenhagen, Denmark). The oval/spherical shape represents a typical shape of in vivo particles (Emmanual et al. 1992) (Shamrock Technologies, from Smith & Nephew Richards, Inc., Memphis, TN).

Type B polyethylene was a combination of 85% (by concentration) of the high-density polyethylene having a mean diameter of 4.7 (0.5–12) μm, mixed with 15% of an ultra-high molecular weight polyethylene resin, having a mean diameter of 30 (10–50) μm, spherical; Hoechst Celanese Corporation, Houston, TX).

The particles were gamma sterilized, and suspended via manual mixing in 0.27% sterile syn-

thetic hyaluronic acid (LifeCore Biomedical, Minneapolis, MN) before injection. 5.0×10^7 particles were injected in 0.1 mL hyaluronic acid in the gap around each implant. This amount of particles was chosen to provide a potent stimulus to provoke a florid response, and to correspond to levels used in analogous studies (Goodman et al. 1994a, Brooks et al. 2000).

Operative procedure

Over a 2.1 mm guide wire, a cannulated hand step-drill created a deep cavity (6 mm diameter by 10 mm long) and a superficial cavity (7.5 mm diameter by 10 mm long), with the most superficial part being tapped. PE particles were mixed under sterile conditions with hyaluronic acid and injected into the implant cavity. The PMMA test implant and polyethylene cap were screwed onto the distal portion of the threaded piston, and implant displacement and proper functioning were verified intraoperatively with a custom spring gauge. Soft tissues were closed routinely, and anteroposterior and lateral radiographs were taken immediately. After a postoperative recuperation period averaging 3 days, the dogs were allowed unlimited cage activity, and had 2 hours per day of free exercise. Their hind-limb function was assessed and noted daily, to ensure they were regularly loading their implants. The time period for observation was 8 weeks. This protocol was approved by our institution's Animal Care and Use Committee, and was performed in their AALAC-approved animal care facility.

Data collection and analysis techniques

Anteroposterior and lateral radiographs were taken after killing the animals. The knees were surgically exposed, and bacterial cultures were taken from the joint. The distal femur was removed and frozen at –20 °C.

To prepare histological sections, the femur was cut into 3 mm sections perpendicular to the implant using a guide wire inserted in the cannula of the implant, and a water-cooled diamond band saw (EXAKT, Norderstadt, Germany). The middle section was decalcified and cut into 5 μm slices, and stained with hematoxylin and eosin.

Cells participating in the tissue response were identified, by subjecting HE-stained sections of each implant to semi-quantitative analysis, blinded as to treatment group. The slides were systematically evaluated for the salient characteristics of periprosthetic membranes. These include macrophages, fibroblasts, osteoclasts and lymphocytes, with a scale of: none (0), mild (+), moderate (++), marked (+++). Characteristics of the periprosthetic gap tissue (loose or dense connective tissue), and presence of osteoid and new bone were quantified.

The distribution of the bone was measured, with respect to its proximity to the implant, and the formation of a sclerotic endosteal bone rim (SEBR). A SEBR rim was defined as a circumferential condensation of trabeculae, with fewer than five radial interruptions. The location of the rim, at or beyond the original drill hole, was recorded. To verify that the polyethylene particles had been retained in the peri-implant space, polarized microscopy was used.

Results

Control group

Unstable implants with neither polyethylene nor hyaluronic acid. During processing after retrieval, 1 implant was damaged. In all 7 remaining implants, the gaps had been filled with loose fibrous tissue (Figure 2). The cut trabecular bone surface in the original drill-hole had remodeled to a partially interrupted circumferential neocortex in 2/7 implants. On histological examination, the fibrous membrane consisted of loosely spaced mature spindle-shaped fibroblasts, characteristic of a reparative response with no inflammation. There was no neutrophilic, macrophage/histiocytic or lymphocytic response. Abundant vascularity was seen. The interstitium of the marrow space in the surrounding bone was acellular. Each of the implants showed a similar response. A quiescent membrane was generated, without the characteristics of the aggressive membrane seen in human retrievals.

Unstable implants without polyethylene and with hyaluronic acid. Similar histologic findings of mainly loose fibrous connective tissue were associated with the 8 unstable implants having neither hyaluronic acid nor particulate PE, and for the 4

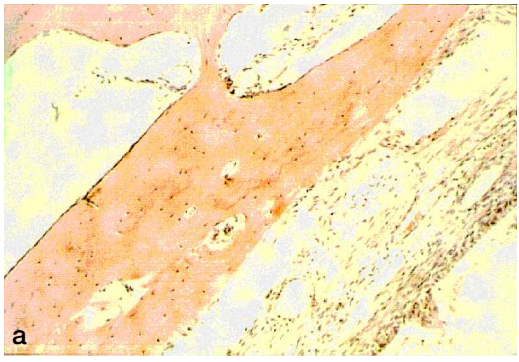
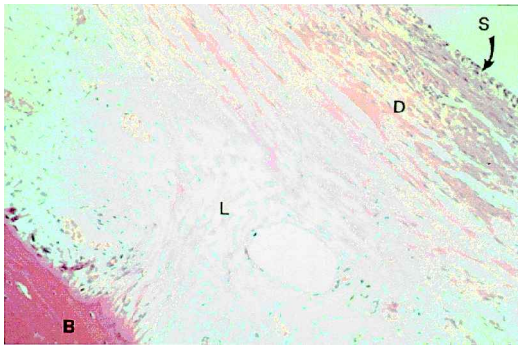
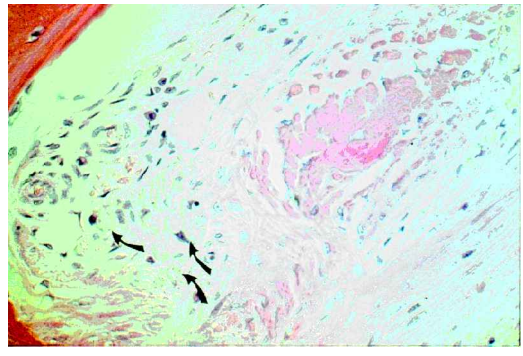


Figure 2. Typical histologic sections (HE) of unstable implant without particulate polyethylene (control group), showing loose connective tissue in gap (a: ×4, b: ×40).

Figure 3. Typical histologic sections (HE) of unstable implants with Type A particulate polyethylene.



Dense connective tissue in the gap, with synovial-like lining cells, and macrophages with ingested intracellular polyethylene (×10).



Close-up of membrane showing ingested polyethylene (×40).

unstable implants with hyaluronic acid, but having no particulate PE.

Treatment groups

Unstable implants with type A particulate polyethylene (4.7 (0.5–12) μm). On retrieval, in all 8 implants the gaps had been filled with dense fibrous tissue. The PE particles remained in the gap and adjacent bone, and in 4/8 implants the cut trabecular bone surface in the original drill-hole had remodeled to a partially interrupted circumferential endosteal bone rim (SEBR). Histologically, dense sheets of macrophages and histiocytes were present (+++), with intracellular polyethylene particles (++) (Figure 3). The membrane had synovial-like cells at the surface interfacing with the implant (+++), and was composed of dense sheets of spindle-shaped fibroblasts (+++). Polyethylene particles, identified with polarized microscopy, were seen to remain in the membrane surrounding the implant. Polyethylene was also observed in the adjacent bone. No foreign body giant cells were present (0). Rare lymphocytes and cartilage formation (+), and rare osteoclasts (+) were found. Each of the 8 implants showed a similar response.

Unstable implants with type B particulate polyethylene (0.5–50 μm). On retrieval, in all 8 implants the gaps had been filled with dense fibrous tissue (Figure 4). The bone in the original drill-hole had remodeled to a partially interrupted circumferential SEBR in 7/8 implants (Figure 5). On histological examination, the same findings were seen with type B particles as with type A. That is, dense sheets of macrophages and histiocytes were present (+++), with intra- and extracellular polyethylene particles (++). The membrane had synovial-like cells at the surface interfacing with the implant (+++), and was composed of spindle-shaped fibro-

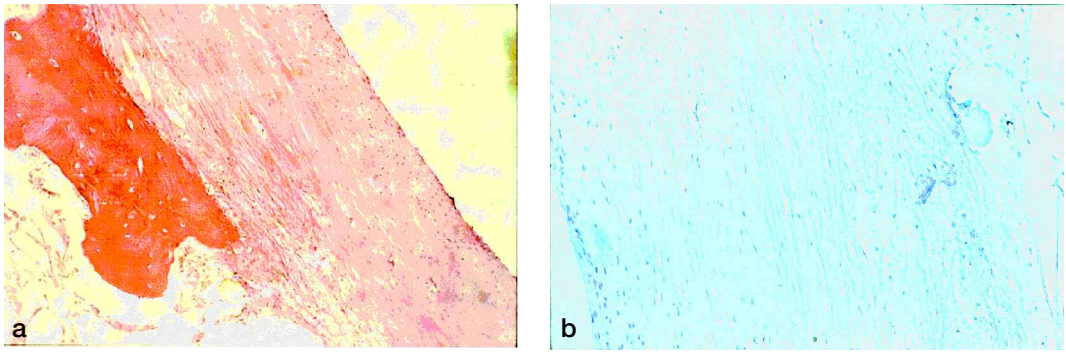


Figure 4. Typical histologic sections (HE) of unstable implants with Type B particulate polyethylene showing dense connective tissue in the gap, with synovial-like lining cells, and macrophages with ingested intracellular polyethylene (a: ×4, b: ×20).

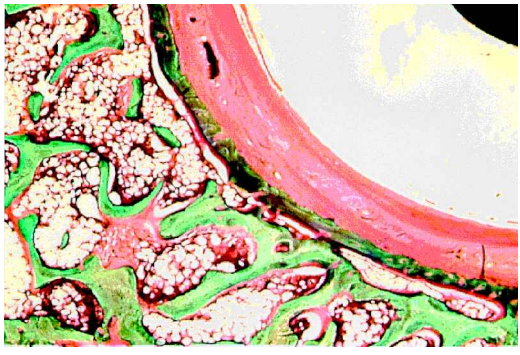


Figure 5. Ground section (basic fuchsin and light green) of unstable implant with Type B particulate, 50 micron thickness (2× magnification) showing a dense fibrous membrane (red) and sclerotic endosteal bone rim (SEBR, light green). PMMA implant has been dissolved during processing.

blasts (+++). Polyethylene particles remained in the membrane surrounding the implant, and were also seen in the adjacent bone. As with type A particles, no foreign body giant cells were seen (0). Each of the eight implants showed a similar response.

Discussion

Various factors can provoke the cascade of events leading to revision for aseptic loosening. In addition to patient-specific factors, the main factors include mechanical instability of the implant, and the presence of particulate material (Kozinn et al. 1986, Lennox et al. 1987, Pazzaglia 1990, Horowitz et al. 1993, Maloney et al. 1993, Gonzalez et al. 1996, Schmalzried and Callaghan 1999). Since the goal of this study was to produce a tissue response like that encountered in human revisions, we chose our model of an unstable implant in the presence of particulate polyethylene.

In humans, tissue surrounding aseptically-loosened implants has been well characterized, and has the chief feature of a fibrous, synovial-like membrane (Willert et al. 1974, 1990, Mirra et al. 1982, Goldring et al. 1983, 1986, Athanasou et al. 1992). This membrane consists of macrophages (Harris et al. 1976, Goldring et al. 1983, 1986, Lennox et al. 1987, Jasty et al. 1990, Pazzaglia 1990, Athanasou et al. 1992, Xu et al. 1997) and histiocytes in sheets (Goldring et al. 1986, Johanson et al. 1987, Lennox et al. 1987, Jasty et al. 1990, Athanasou et al. 1992, Kim et al. 1993, Goodman et al. 1997). Foreign body giant cells (Goldring et al. 1983, Eftekhar et al. 1985, Lennox et al. 1987, Willert et al. 1990, Athanasou et al. 1992) and lymphocytes (Eftekhar et al. 1985, Lennox et al. 1987, Cook et al. 1991, Salter et al. 1992) are also seen. Fibroblasts are abundant and often spindle-shaped (Pazzaglia and Pringle 1988, Galante et al. 1991, Athanasou et al. 1992). A synovial layer is adjacent to the implant, with macrophages in deeper layers (Goldring et al. 1983). A neocortex of dense, circumferentially oriented trabeculae, with peripheral loss of trabecular density, is also commonly seen (Jasty et al. 1990, Kwong et al. 1992).

Around uncemented implants, particulate material is usually present in the membrane (Johanson et al. 1987), the smaller particles (less than 2–5 microns) being internal to macrophages and histiocytes, while larger particles are walled off (Athanasou et al. 1992). Polymethylmethacrylate (PMMA)

particles have been seen in 80% of the membranes of cemented implants (Eftekhar et al. 1985), and polyethylene in 75% (Eftekhar et al. 1985); polyethylene and PMMA particles correlate well with loosening (Mirra et al. 1982). Metal particles are also seen in 15%–50% of the membranes (Eftekhar et al. 1985). Neutrophils (Lennox et al. 1987), mast cells (Lennox et al. 1987), callus (Jasty et al. 1990) and osteoclasts (Jasty et al. 1990) have also been reported in the bone and membrane surrounding aseptically-loosened implants (Willert et al. 1974, 1990).

This aggressive fibrous tissue and bony response was replicated in our unstable implants with both experimental size ranges of PE. The formation of a fibrous membrane in response to motion was not unexpected, since it has been found in all previous studies with this micromotion device, and since motion is known to affect tissue response (Eftekhar et al. 1985, Lennox et al. 1987, Ko et al. 1992, Goodman et al. 1993, 1994b, Goodman1994, Kärrholm et al. 1994, Giori et al. 1995, Aspenberg and Herbertsson 1996, Bragdon et al. 1996, Jasty et al. 1997, Nelissen et al. 1998, Szmukler-Moncler et al. 1998). Mechanical instability (relative motion between the implant and the bone) influences a tissue response by a direct effect on cells, and by stimulating the extracellular matrix to activate cells which produce cytokines and/or prostaglandin E2 (PGE_2) (Rodan et al. 1975, Eftekhar et al. 1985, Lennox et al. 1987). Motion can also induce formation of a synovium or bursa, which then produces inflammatory mediators and stimulates osteoclast proliferation and differentiation (Eftekhar et al. 1985, Lennox et al. 1987, Spector et al. 1990, Horowitz et al. 1996).

The enhancement of the aggressive inflammatory response by the particles of PE was also not unexpected, since the role of particulate material in inducing this aggressive tissue response leading to prosthesis failure has been the focus of much recent research (both in vitro and in vivo, as regards the effects of particle size, material, quantity, shape, and surface characteristics (Kozinn et al. 1986, Lennox et al. 1987, Pazzaglia 1990, Gonzalez et al. 1996, Schmalzried and Callaghan 1999, Lohman et al. 2000). The reproducibility of our model was increased by its low sensitivity to particle size distribution and type (consistent tissue response was generated for either of the two heterogeneous size distributions of polyethylene particles).

Foreign body giant cells were not seen in any of our treatment groups, although they often occur around loosened cemented implants. We suspected that the phagocytosable size of the type A particles (0.5–12 μm) was responsible for the lack of foreign body giant cells. However, they were also lacking in the presence of type B particles (0.5–50 μm), when large particles were seen to be contained in the membrane without a foreign body giant cell adjacent to or engulfing the large particle. Foreign body giant cells are generally regarded as being more benign, and no direct or indirect osteolytic function has been ascribed to them. Thus, their absence in these membranes should not change the membrane's biologic function, or utility as an analog for a loosened implant.

Our study considered only one type of material (polyethylene), at a single concentration. However, these were chosen to be in the range encountered clinically. While it is recognized that high-density polyethylene has a lower molecular weight than ultra-high molecular weight polyethylene, and is denser, these high density particles have been used to represent adequately ultra-high molecular weight polyethylene in other experimental studies on the effects of particles. Since the focus of this study was to document a controlled model of revision implants, an exhaustive set of particle-related factors influencing tissue response was not evaluated (e.g., particle material, shape and concentration).

On the basis of our findings, type B particle distribution was chosen for our further studies of revision implants, since it may represent a more clinically relevant mix of particle sizes, and it elicited the formation of a sclerotic endosteal bone rim (SEBR) in 7/8 implants (compared with 4/8 for type A). While it is generally held that in vivo the most incendiary particles are the smallest, submicron size, larger particles are also often present in retrieved tissues. We felt it was important to include a larger size mix in our model.

In conclusion, an aggressive fibrous membrane consistently formed around the unstable implants in this model (0.75 mm gap, 500 μm motion and polyethylene: 50% < 1 μm, range 0.5–50 μm; 5.0×10^7 particles/implant, at 8 weeks). The typical three-layered membrane consisted of a syno-

vial lining adjacent to the implant, dense connective tissue, including macrophages with intracellular polyethylene, and a sclerotic SEBR rim. This response is analogous to that seen during revision joint replacement arthroplasty in humans. When particles were not present, the unstable implant produced a more benign, loose fibrous membrane, without the inflammatory characteristics observed in the presence of particles.

This model will be used in future studies to assess the efficacy of treatments for improving the results of revision joint replacement. To allow controlled comparison to the primary setting, the analogous primary implant with the identical implant geometry and loading conditions is inserted at the time of the revision operation into the contralateral, previously unoperated limb. Application of this model to primary and revision titanium implants is reported in Part II (Bechtold et al. 2001).

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